STATISTICAL ANALYSIS PLAN

Study: PD0055

Product: Minzasolmin (UCB0599)

A DOSE-BLINDED EXTENSION STUDY TO EVALUATE THE LONG-TERM EFFICACY, SAFETY, AND TOLERABILITY OF UCB0599 IN STUDY PARTICIPANTS WITH PARKINSON'S DISEASE

PHASE 2

SHORT TITLE:

An extension study to evaluate the long-term efficacy and safety of minzasolmin (UCB0599) in study participants with Parkinson's disease

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VERSION HISTORY

SAP Version	Approval Date
Original SAP	06 Dec 2022
Amendment 1	15 Aug 2023
Amendment 2	26 Jun 2025

Amendment 2 (26 Jun 2025)

Overall Rationale for the Amendment

To align with protocol amendment 3, clarify some of the ICE handling strategies and account for the early termination of the study.

Section # and Name	Description of Change	Brief Rationale
Global	Updates made throughout to change 'Compliance' to 'IMP Compliance' where applicable.	As we also discuss ST washout compliance in this SAP, text updated to make it clear which compliance we are referring to.
	UCB0599 was changed to "minzasolmin (UCB0599)" throughout.	To introduce the international nonproprietary name for UCB0599, in line with protocol amendment 3.
	References to 'baseline' have been clarified as either PD0053 or PD0055 baseline.	To add clarity throughout the SAP of which baseline to use.
	References to 'EOT' have been changed to 'EOT/ET'.	To align with the Schedule of Activities in the Protocol.
	Removed all text regarding participants switching on to best dose.	Due to the early termination of the study, this is no longer applicable.

Section # and Name	Description of Change	Brief Rationale
	Adjustments for disease duration has been removed from ANOVA models.	To simplify these analyses.
	Changed plots with error bars to use SEM in place of SD.	To improve the interpretability of the plots produced.
	Plots for some efficacy endpoints were removed.	To reduce the complexity of analysis at the end of the study.
Section 1, Introduction	Reference to PD0055 protocol updated to Amendment 3, dated 18th September 2023.	To refer to the latest Protocol.
	Text added to clarify which study data will be used in Listings, Tables and Figures.	To add clarity to which visits are to be included in the outputs.
Section 1.1, Objectives and estimands/endpoints	Table 1.1 updated to align with Protocol objectives table.	To align with Protocol Amendment 3.
	Sentence added to objectives text: "In addition, suitability of using Digital Health Technology as a non-invasive method to collect data on signs and symptoms of PD is explored."	To align with Protocol Amendment 3.
	Note added regarding changes to objectives that have occurred due to early study termination.	To explain that the objectives/estimands/endpoints described are based on the protocol but changes have been made throughout the SAP.

Section # and Name	Description of Change	Brief Rationale
	Sentence added to explain that Exploratory Objective II will no longer be implemented.	Due to the early termination of the study, this is no longer applicable.
Section 1.2, Intercurrent events	In the tables of ICEs: "Important ICE-like protocol deviations related to investigational treatment" updated to "Important ICE-like protocol deviations".	To correct this title, not all ICE-like protocol deviations will be treatment related.
	Under the hypothetical strategy, added that the 'copy increments in reference' version of RBI will be used and removed consideration of alternative imputation approaches.	To clarify the type of RBI approach which will be implemented.
	Added that an initial step will be performed where true non-monotonic missing data will be imputed using multiple imputation prior to implementing other ICE strategies.	When there are intermittent missing data in clinical trials, the MAR assumption is often reasonable because the intermittent missing is often caused by missing visit, missing visit time window, or data collection issues that are unlikely related to the missing data.
	Table 1.2 updated in line with changes to ICE strategies.	For consistency with approaches used in PD0053.
Section 1.2.5, Death or serious injury	The following sentence was added to this section: "In practice, these events will be identified as serious adverse events that result in persistent or significant disability/incapacity or death.".	To help identify these events.
Section 1.2.6, Study termination and loss to follow-up	Removed paragraph regarding cause of study termination.	To account for the early termination of the study.

Section # and Name	Description of Change	Brief Rationale
	Added statement to clarify the strategy used in the case of early study termination.	
Section 1.3, Study Design	Study overview figures removed, references to these figures updated throughout to refer to the versions in the protocol. Paragraph summarizing sample size calculations removed. Paragraph added to summarize the reason for early termination of PD0055.	To avoid needing to update these figures in multiple sources. To account for the early termination of the study. To account for the early termination of the study.
Section 3, Sample Size Determination	Sentence added to clarify the number of participants predicted to complete the Month 18 visit.	To account for the early termination of the study.
Section 4, Populations for Analysis	Introduced and defined a Full Analysis Set for PD0055.	To define an analysis set in which participants who did not meet key inclusion/exclusion criteria are excluded for use in the analysis of the efficacy endpoints.
Section 5.1, General considerations	Footnote added to Table 5.1 (Visit labelling) about PD0055 V1 coinciding with PD0053 V14.	To clarify that all data collected at these visits, whether they coincide or not, will be labelled as 'Month 16' in the TFLs.
Section 5.1.1, Date imputation	Rules for calculating duration of Parkinson's Disease updated to use the middle of the month/year rather than the beginning of the month/year when dates are partial.	Update to our analysis approach, assume a central date rather than assuming that the participant had the longest possible disease duration.

Section # and Name	Description of Change	Brief Rationale
	Rule added for determining ST initiation/end date to be used in analyses when partial dates are captured.	Add in the assumption to be made when day is missing from ST initiation/end date, so that ICE strategies can be correctly applied in these cases and LEDD can be calculated.
Section 5.1.2.1.3, Study periods	Removed paragraph defining total duration of the study per participant. Statement regarding the Sponsor potentially extending treatment duration removed. Updated the early termination section to be early termination of a participants treatment or early termination of the study.	To account for the early termination of the study. To account for the early termination of the study. To account for the early termination of the study.
Section 5.1.2.1.4, Mapping of assessments performed after early termination	Rules changed regarding the mapping of assessments so that results are included in summary tables.	To account for the early termination of the study and maximize the amount of data to be used in the summaries.
Section 5.1.2.2, Protocol deviations	Removal of any references to unblinding. Updated the text to say that only one DEM would be conducted throughout the study.	To account for the early termination of the study. To account for the early termination of the study.
Section 5.1.2.4, Center pooling strategy	Sentence added to state that data for some endpoints will be summarized by geographical region.	Added to account for the possibility that treatment assignment will not

Section # and Name	Description of Change	Brief Rationale
		necessarily be balanced across countries or sites.
Section 5.1.2.6, Multicenter studies	Removed statement that summaries will be presented by number of participants in each country.	To reduce complexity of analysis at the end of the study.
Section 5.2, Participant dispositions	Addition of a table to summarize the P0055 EOT/ET visits.	To account for the early termination of the study.
Section 5.3, Efficacy estimands and endpoints	ST initiation timing categories updated so that the final category includes early terminators. Removed statement to include LEDD and WOQ-9 data up to Month 30. Added statement to say that a variance-covariance matrix structure may be reviewed if convergence problems are encountered. Added note to say that ICE summary tables will be produced by visit and treatment group, overall and by gender. Categories to be used in Figures for ST initiation timing have been updated.	To add details on how early terminators should be handled in figures presented by ST initiation timing category. To account for the early termination of the study. To add clarity on methods for the cases when convergence issues arise. For consistency with outputs produced for PD0053. To account for the early termination of the study.
Section 5.3.1.1, Definition of endpoint	Removal of descriptive statistics by ST status.	To reduce complexity of analysis at the end of the study.

Section # and Name	Description of Change	Brief Rationale
	Added clarification that descriptive statistics will be presented at all available (scheduled or mapped) visits.	To account for the early termination of the study.
	Addition of annualized change from baseline.	To allow comparisons with PD0053.
	Addition of mapping rules for DaT-SPECT assessments completed in PD0055.	To account for the early termination of the study and maximize the amount of data for use in the statistical analyses.
Section 5.3.1.2, Main analytical approach	Sentence added to clarify the visits that will be included.	To account for the early termination of the study.
	Introduced an additional summary table to be produced by gender.	To investigate gender effect within the primary analysis.
Section 5.3.1.3, Sensitivity analyses	Removed paragraph to say that a LMEM for ANCOVA will be done.	To reduce complexity of analysis at the end of the study.
Section 5.3.1.4, Supporting analyses	Updated section to state 'not applicable'.	To account for the early termination of the study.
Section 5.3.2.1, Definition of endpoint	Added clarification that cumulative LEDD will be calculated at all available (scheduled or mapped) visits.	To account for the early termination of the study.
	Text added to state that continuous summary statistics will be presented by geographical regions.	To account for the possibility that treatment assignment will not necessarily be balanced across countries or sites.
Section 5.3.2.2, Main analytical approach	Added sentence to clarify the participant data that should be used in the ANOVA.	To account for the early termination of the study.

Section # and Name	Description of Change	Brief Rationale
Section 5.3.2.3, Sensitivity analyses	Specified that LEDD at 24 months will be used.	To account for the early termination of the study.
Section 5.3.3.3, Exploratory endpoints: Clinical Outcome Assessments	Listing of MDS-NMS non-motor fluctuations subscale data removed.	Subscale removed from the TFLs, it is the main MDS-NMS questionnaire that is of interest in PD0055.
	MDS-UPDRS section updated to include ePD subscore and for mean change from PD0053 baseline to be plotted.	For consistency with outputs produced for PD0053.
	Section added for UPSIT, an assessment that was added to the protocol schedule of assessments in amendment 3.	To align with protocol amendment 3.
	Summary tables for exploratory endpoints updated to remove summarizing by gender.	To reduce complexity of analysis at the end of the study.
Section 5.4.2, Adverse events	Updated paragraph explaining AEs which should be summarized to clarify that AEs which are unresolved from PD0053 should be included.	Add clarity for the programming team.
Section 5.4.3.1, Clinical safety laboratory assessments	Text added for handling clinical safety laboratory retest results.	Add clarity for the programming team.
	Deletion of Section 5.4.3.1.2 Individual participant changes of laboratory values.	Due to a different central lab being used in PD0055 compared to PD0053.
Section 5.4.3.1.1, Laboratory values over time	Updated section such that changes from baseline will not be summarized.	Due to a different central lab being used in PD0055 compared to PD0053.

Section # and Name	Description of Change	Brief Rationale
Section 5.4.3.2.1, Vital sign values over time	Updated section to clarify that both changes from PD0053 baseline and PD0055 baseline will be summarized.	Add clarity for the programming team.
Section 5.6, Subgroup analyses	"using RBI approach" removed from all subgroup analyses.	RBI is used for treatment-related study termination as default, so this does not need to be specified again.
Section 5.8, Planned analysis at 18 months	Updated as section is no longer applicable.	Due to the early termination of the study.
Section 6.1.1.2, Baseline disease characteristics	Added text to state that baseline disease characteristics will be done by gender.	To show any difference in disease characteristics at baseline between genders.
Section 6.1.8, Compliance	Listing and summary of compliance data updated to also present compliance calculated under the assumption that no overdosing has occurred.	Additional compliance calculations were added that assume any discrepancies between planned and actual dosing are due to drug accountability issues and do not necessarily represent participants taking more than the planned doses.
Section 6.2, Changes to protocol-planned analysis	Updated section to detail changes.	To describe any changes to planned analyses between Protocol Amendment 3 and SAP Amendment 2
Section 6.4, Appendix 4: UPSIT percentile reference tables	New section.	To provide reference tables for determining percentiles based on UPSIT score.
Section 7, References	Three new references added: (Liu and Pang, 2016), (Brumm et all, 2023) and (Yuan, 2014).	References added for new papers discussed in Section 1.2 and 5.3.3.

Amendment 1 (15 August 2023)

Overall Rationale for the Amendment

Ensure SAP covers all visits that will be summarized in the PD0055 TFLs. Make updates to align with protocol amendment 1 and protocol amendment 2 that have been approved after the original SAP approval.

Section # and Name	Description of Change	Brief Rationale
Global	The SAP was updated to remove the term "individual" in the context of switching to the best dose upon Phase 3 dose selection, to clarify that all participants will be switched to the best dose.	Align with protocol amendment 1.
Section 1.3, Study Design	Sentence removed: "However, in case of safety concerns with respect to the [redacted] dose at the time the first participant is planned to transition into PD0055, the dose to switch both placebo and UCB0599 [redacted] participants to may be revised to be UCB0599 [redacted] instead."	To align with protocol amendment 1, this statement is no longer applicable.
Section 3, Sample Size Determination	Sentence removed: "However, estimates of power may be provided as part of the quantitative decision making at a program/product level."	Not relevant for this document, applicable on a program/product level.
Section 5.1, General Considerations	Table 5.1 updated to include additional visits (PD0053 screening part 1 and Day 10, PD0055 V4a, V5a and V5b).	PD0053 visit labels added so that this data from PD0053 can be summarized correctly in the PD0055 TFLs. PD0055 visits added to reflect updates made in protocol amendment 2, where the monitoring of liver function tests was increased.

LIST OF ABBREVIATIONS

ADaM	Analysis Data Model
ADRG	ADaM data reviewers guide
AE	Adverse Event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALQ	above limit of quantification
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ASPS	All Study Participants Set
AST	aspartate aminotransferase
ASYN	alpha-synuclein
BID	twice per day
BLQ	below limit of quantification
BMI	body mass index
BP	blood pressure
CBD	Corticobasal degeneration
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
COVID-19	Coronavirus Disease-2019
CRO	Contract Research Organization
CSF	cerebrospinal fluid
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
DaT-SPECT	Dopamine Transporter Imaging with Single Photon Emission Computed Tomography
DEM	data evaluation meeting
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EMA	European Medicines Agency

EOT	End of Treatment
EQ-5D-5L	Euro Quality of life 5-Dimensions 5-Level
EQ-VAS	EQ visual analogue scale
ET	Early Termination
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
H&Y	Hoehn and Yahr
HLT	high level term
ICC	intra-class correlation coefficient
id	Idem
ICF	Informed Consent Form
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICE	intercurrent event
IMP	investigational medicinal product
IPD	important protocol deviation
IQR	Inter quartile range
IRB	Institutional Review Board
LBD	Lewy bodies
LEDD	Levodopa Equivalent Daily Dose
LLOQ	lower limit of quantification
LMEM	linear mixed effects model
MAO-B	Monoamine oxidase-B
MAR	missing at random
MDS-NMS	Movement Disorder Society Non-motor symptom scale
MDS-UPDRS	Movement Disorder Society Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
ML	maximum likelihood
MNAR	missing not at random
MoCA	Montreal Cognitive Assessments
MSA	Multiple system atrophy
PCS	potentially clinically significant

PD	Parkinson's disease
PDILI	potential-drug induced liver injury
PRO	patient reported outcome
PSP	Progressive supranuclear palsy
PT	preferred term
QoL	Quality of Life
QTcF	QT corrected for heart rate using Fridericia's formula
RBI	reference-based imputation
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SBR	specific binding ratio
SD	standard deviation
SEM	standard error of the mean
SFU	Safety Follow-up
SMC	Safety Monitoring Committee
SMQ	Standardized MedDRA Query
SOC	system organ class
SoC	Standard of Care
SS	Safety Set
ST	symptomatic treatment
TEAE	treatment-emergent adverse event
TEMA	treatment-emergent markedly abnormal
TFL	tables, figures and listings
TMF	Trial Master File
ULN	upper limit of normal
UPSIT	University of Pennsylvania Smell Identification Test
WHODD	World Health Organization Drug Dictionary
WO	wearing-off
WOQ-9	Wearing-off Questionnaire-9

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide all information that is necessary to perform the final statistical analysis of study PD0055. It also defines the summary tables, figures and listings (TFLs) to be included in the PD0055 end-of-study clinical study report (CSR), according to the protocol. Listings will contain only data from PD0055 and PD0053 Baseline/Screening (when relevant). Summary tables and figures will include data from PD0053 and PD0055 as specified in this SAP.

This SAP is based on Protocol Amendment 3 dated 18th September 2023. If a future protocol amendment necessitates a substantial change to the statistical analysis of the study data, this SAP will be amended accordingly. In addition, if analysis definitions must be modified or updated prior to database lock, a SAP amendment will be required. If, after database lock, additional analyses are required to supplement the planned analyses described in this SAP, these changes will be described in the CSR together with the associated rationale. Other minor changes to non-key analyses will also be documented in the CSR.

The content of this SAP is compatible with the International Council for Harmonization (ICH)/Food and Drug Administration (FDA) E9 Guidance documents (Phillips et al, 2003).

UCB is the sponsor and Parexel is the Contract Research Organization (CRO) for this study.

1.1 Objectives and estimands/endpoints

This section includes the objectives, endpoints and estimands as described in Protocol Amendment 3. Due to the early termination of the study, changes will be made to some of the objectives and endpoints/estimands: details are provided in the respective subsections of Section 5. These changes from the protocol are summarized in Section 6.2.

The primary objective of PD0055 is to estimate the pharmacodynamic effects of minzasolmin (UCB0599) on brain pathophysiology in Early-start versus Delayed-start participants originally diagnosed with new onset PD. The Delayed-start participants will receive the equivalent of half the cumulative dose of minzasolmin (UCB0599) compared with the Early-start participants; they will also initiate minzasolmin (UCB0599) at a later phase with respect to their PD diagnosis.

The Dopamine Transporter Imaging with Single Photon Emission Computed Tomography (DaT-SPECT) whole striatum specific binding ratio (SBR) signal was selected as the biomarker endpoint of choice to measure the impact of minzasolmin (UCB0599) on the integrity of dopaminergic nerves terminals (Figure 1-2 in Section 1.2 of the protocol). The biomarker DaT-SPECT is the best-established in vivo method to monitor dopaminergic neurodegeneration. It has been reported in the literature that DaT-SPECT results are not impacted (or are only marginally impacted) by using ST (Ikeda et al, 2019). In parallel, levels of ASYN in the cerebrospinal fluid (CSF) will be used as exploratory endpoints to evaluate the impact of minzasolmin (UCB0599) on ASYN metabolism in the brain.

The secondary efficacy objective of PD0055 is to estimate the pharmacodynamic effects of minzasolmin (UCB0599) on the need for ST in participants originally diagnosed with new onset PD, taking advantage of the Early-start versus Delayed-start arms design. The cumulative Levodopa Equivalent Daily Dose (LEDD) and the Wearing-off Questionnaire-9 (WOQ-9) were

selected as clinical outcomes of choice to measure the impact of minzasolmin (UCB0599) on the ST burden and the wearing-off (WO) of dopaminergic treatment.

The secondary safety objective of the study is to assess the safety and tolerability of UCB0599 in participants originally diagnosed with new-onset PD and will include recording of incidences of TEAEs, SAEs, and TEAEs leading to withdrawal from the study.

Exploratory objective I of the study (methodology) is to identify clinical endpoints able to detect the pharmacodynamic effects of minzasolmin (UCB0599) on the clinical course of Parkinson's disease after initiation of ST in Early-start versus Delayed-start participants originally diagnosed with new onset PD. To address this objective, motor and nonmotor outcomes were selected based on research work at UCB to develop new endpoints which would be most relevant to PD patients and be a suitable sensitive endpoint in longitudinal clinical studies performed in the early PD population under ST (levodopa). In addition, suitability of using Digital Health Technology as a non-invasive method to collect data on signs and symptoms of PD is explored.

Exploratory objective II of the study (effectiveness) is to estimate the pharmacodynamic effects of minzasolmin (UCB0599) versus SoC on the Quality of Life (QoL) and clinical course of PD in participants 3 years post PD diagnosis and beyond, using external benchmark/reference data (where available). The results from this objective will allow the strengthening of the patient value stemming from impact on key motor outcomes through (potentially) showing an impact also on QoL outcomes. Research with national payers indicates that this combination would be particularly impactful in demonstrating patient value. Exploratory objective II will no longer be implemented due to the early termination of the study.

Exploratory objective III of the study (efficacy: dose comparison) is to estimate the pharmacodynamic effects of minzasolmin (UCB0599) [redacted] versus minzasolmin (UCB0599) [redacted] on the clinical course of PD, need for ST and brain pathophysiology in participants originally diagnosed with new onset PD. The results obtained from this objective may inform any dose-response modeling and may confirm any difference seen in efficacy in PD0053.

Finally, the exploratory objective IV of the study will be to re-assess the initial PD clinical diagnosis in order to identify participants with atypical parkinsonian disorders. This will allow the exclusion of participants who are no longer believed to have a clinical diagnosis of PD from primary analyses in PD0053 and PD0055 (sensitivity analyses).

The primary and secondary efficacy objectives of the study, as well as the exploratory methodology objective (I), will make use of the Delayed-start arm (Figure 1-2 in Section 1.2 of the protocol). The exploratory efficacy objective (III) will make use of the Low-dose arm (Figure 1-3 in Section 1.2 of the protocol). Finally, the exploratory effectiveness objective (II) will make use of the external benchmark reference data (Figure 1-4 in Section 1.2 of the protocol).

The analyses to be performed for the primary and secondary efficacy objectives, as well as for the exploratory objectives I (methodology) and III (efficacy: dose comparison) will use data from the first 18 months of the study; while analyses to be performed for the exploratory objective II (effectiveness) and the safety analyses will make use of all available study data.

Table 1–1: Study objectives

Objectives	Endpoints
Primary Efficacy Objective	
To estimate the pharmacodynamic effects of minzasolmin (UCB0599) on brain pathophysiology in Early-start versus Delayed-start participants originally diagnosed with new onset PD	**Primary Efficacy Endpoint** • Baseline [a]-adjusted DaT-SPECT whole striatum SBR at PD0055 Month 18 **Exploratory Efficacy Endpoints** • DaT-SPECT striatal sub-regions SBR • CSF total ASYN • CSF ASYN oligomers/seeding capacity
Secondary Efficacy Objective	
To estimate the pharmacodynamic effects of minzasolmin (UCB0599) on the need for ST in Early-start versus Delayed-start participants originally diagnosed with new onset PD	**Secondary Efficacy Endpoint** • Cumulative LEDD at PD0055 Month 18 **Exploratory Efficacy Endpoints** • WOQ-9
Secondary Safety Objective	
To assess the safety and tolerability of minzasolmin (UCB0599) in participants originally diagnosed with new onset PD	**Secondary Safety Endpoints** • Incidence of TEAEs • Incidence of SAEs • Incidence of TEAEs leading to withdrawal from study
Exploratory Objectives	
I. Methodology: To identify clinical endpoints able to detect the pharmacodynamic effects of minzasolmin (UCB0599) on the clinical course of Parkinson's disease after initiation of ST in Early-start versus Delayed-start participants originally diagnosed with new onset PD	**Exploratory Endpoints (Clinical Outcomes)** • MoCA • MDS-NMS (or selected items) • MDS-UPDRS Parts I-III sum score • MDS-UPDRS Part I subscale (or selected items) • MDS-UPDRS Part II subscale (or selected items) • MDS-UPDRS Part III subscale (or selected items) • Modified H&Y • FATIGUE-PRO

Table 1–1: Study objectives

Objectives	Endpoints
	• Early PD Function Slowness PRO • Early PD Mobility PRO **Exploratory Endpoints (Other)** • Koneksa Neuroscience Toolkit
II. Effectiveness: To estimate the pharmacodynamic effects of minzasolmin (UCB0599) versus SoC on the QoL and clinical course of PD in participants 3 years post PD diagnosis and beyond, using external benchmark/reference data (where available)	**Exploratory Endpoints (Clinical Outcomes)** • EQ-5D-5L • LEDD • MoCA • MDS-UPDRS Parts I-III sum score • MDS-UPDRS Part IV • MDS-UPDRS Part I subscale (or selected items) • MDS-UPDRS Part II subscale (or selected items) • MDS-UPDRS Part III subscale (or selected items) • Modified H&Y
III. Efficacy: To estimate the pharmacodynamic effects of minzasolmin (UCB0599) [redacted] versus minzasolmin (UCB0599) [redacted] on the clinical course of PD, need for ST and brain pathophysiology in participants originally diagnosed with new onset PD	**Exploratory Endpoints (Clinical Outcomes)** • LEDD • WOQ-9 • MoCA • MDS-NMS (or selected items) • MDS-UPDRS Parts I-III sum score • MDS-UPDRS Part I subscale (or selected items) • MDS-UPDRS Part II subscale (or selected items) • MDS-UPDRS Part III subscale (or selected items) • Modified H&Y • FATIGUE-PRO • Early PD Function Slowness PRO • Early PD Mobility PRO

Table 1–1: Study objectives

Objectives	Endpoints
	Exploratory Endpoints Biomarkers • DaT-SPECT whole striatum SBR (and striatal sub-regions SBR) • CSF total ASYN • CSF ASYN oligomers/seeding capacity
IV. Atypical Parkinsonism: Revision of PD clinical diagnosis; identification of participants with Atypical Parkinsonian Disorders [b] at PD0055 Baseline Visit and at PD0055 Month 18	**Exploratory Assessments** • Re-confirmed PD diagnosis status

ASYN=alpha-synuclein; CSF=cerebrospinal fluid; DaT-SPECT=Dopamine Transporter Imaging with Single Photon Emission Computed Tomography; EQ-5D-5L=Euro Quality of life 5-Dimensions 5-Level; H&Y=Hoehn and Yahr; LEDD=Levodopa Equivalent Daily Dose; MDS-NMS=Movement Disorder Society Non-Motor Rating Scale; MDS-UPDRS=Movement Disorder Society Unified Parkinson's Disease Rating Scale; MoCA=Montreal Cognitive Assessment; PRO=patient-reported outcome; PD=Parkinson's disease; QoL=Quality of Life; SAE=serious adverse event; SBR=specific binding ratio; SoC=standard of care; ST=symptomatic treatment; TEAE=treatment-emergent adverse event; WOQ-9=Wearing-off Questionnaire-9

[a] Baseline will refer to PD0053 Baseline Visit data (or Screening Visit data where applicable).

[b] Most frequent Atypical Parkinsonian Disorders are:

- Progressive supranuclear palsy (PSP): Tau
- Corticobasal degeneration (CBD): Tau (alpha-syn)
- Multiple system atrophy (MSA): Alpha-syn deposition in glial cells/oligodendrocytes
- Dementia with Lewy bodies (LBD): Alpha-syn deposition in cortical neurons

Sensitivity and supportive analyses are not included in Table 1.1, these will be discussed in Section 5.3.

For all endpoints/estimands, the target population will be the entire study population.

1.2 Intercurrent events

The table below covers all planned primary and secondary efficacy analyses, except for sensitivity analyses.

The strategies/approaches for handling ICEs will be as follows:

- *Treatment Policy*: all (pre ICE and post ICE) data will be included in the analysis, regardless of whether the participant remains on the assigned investigational treatment or discontinued. This approach will reflect the treatment effect regardless of the ICE.
- *Hypothetical*: data will be modified to mirror its value had an ICE not happened (under some hypothetical conditions). One such hypothetical condition is that the ICE occurred completely at random. In this case, all post-ICE data are set to missing (removed) and imputed under the assumption of missing at random (MAR). This strategy can be applied to ICEs which are considered uninformative with respect to the effect of interest, ie, treatment efficacy. As a default approach, this strategy will be applied to any occurrence

of an ICE affecting the existence of measurements and maximum likelihood (ML) imputation will be used (Schafer and Graham, 2002).

- *Composite*: ICE data will be incorporated into the endpoint being analyzed. This approach will reflect the treatment effect in the presence of the ICE.

Intermittent missing data will be assumed to be MAR: in clinical trials, the MAR assumption is often reasonable because the intermittent missing is often caused by missing visit, missing visit time window, or data collection issues that are unlikely related to the missing data (Liu & Pang, 2016).

Table 1–2: Overview of handling strategies for ICEs, ICE-like protocol deviations and study termination or loss to follow-up

	DaT-SPECT whole striatum SBR over 36 Months from PD0053 baseline	**Cumulative LEDD over 24 months from PD0053 baseline**
Estimand	**Primary**	**Secondary**
	Regardless of ST initiation / type / dose	**ST initiation / type / dose as integral part**
ICE & ICE-like protocol deviations		
ST initiation (Non-MAO-B Inhibitors) [a]	Treatment policy (Include post ICE data)	Composite (ICE data incorporated into endpoint)
ST initiation (MAO-B Inhibitor) [ab]	Hypothetical (Set to missing & impute impacted visit data – MAR/ML)	
Treatment discontinuation (Lack of efficacy or AE)	Treatment policy (Include post ICE data)	id
Treatment discontinuation (Other causes)	Treatment policy (Include post ICE data)	id
Important ICE-like protocol deviations		
with long-term impact [c]	Hypothetical (set to missing & impute all post ICE visit data – MAR/ML)	Hypothetical (set to missing & ignore – use data from completers)
with short-term impact [c]	Hypothetical (set to missing & impute single post-ICE visit data – MAR/ML)	Treatment policy (Include post ICE data)

Table 1–2: Overview of handling strategies for ICEs, ICE-like protocol deviations and study termination or loss to follow-up

	DaT-SPECT whole striatum SBR over 36 Months from PD0053 baseline	**Cumulative LEDD over 24 months from PD0053 baseline**
Estimand	**Primary**	**Secondary**
	Regardless of ST initiation / type / dose	**ST initiation / type / dose as integral part**
COVID-19-related ICEs without Treatment discontinuation or Study termination	Treatment policy (Include post ICE data)	id
Death or serious injury (all causes)	Hypothetical (Actual missing: impute all post ICE data – MAR/ML)	Hypothetical (set to missing & ignore – use data from completers)
Study termination and loss to follow-up		
Missed visit(s) (intermittent)[d]	Actual missing: impute single visit data – MAR/ML	Actual missing: ignore
Study Termination – Any Reason	Actual missing: impute all post termination visit data – MAR/ML	Actual missing: ignore

AE=adverse event; COVID-19=Coronavirus Disease-2019; DaT-SPECT=Dopamine Transporter Imaging with Single Photon Emission Computerized Tomography; ICE=intercurrent event; id=idem, "the same" across rows; LEDD=Levodopa Equivalent Daily Dose; NA=Not applicable; WOQ-9=Wearing-Off Questionnaire - 9; SBR=specific binding ratio; SAP=statistical analysis plan; ST=symptomatic treatment

[a]See Section 5.3.2 for how to determine which type of ST a medication is.

[b]If non-compliant with the washout period, see Section 1.2.1.

[c]The category that each protocol deviation falls into will defined outside of the SAP, in the protocol deviation specifications or a separate document. Only important protocol deviations can be ICEs, but not all important protocol deviations will be defined as ICEs.

[d]This does not apply to missing baseline data. Baseline data will not be imputed.

Note: Where missing data will be imputed under a MAR assumption, whether in the case of either intermittent missing or longitudinal missing (study termination or loss to follow-up), a ML approach will be used for all LMEM-based modelling.

1.2.1 Symptomatic treatment initiation

The main ICE affecting the interpretation of measurements will be initiation of ST as well as any change in type or dose throughout PD0053 and PD0055.

DaT-SPECT

In this study, it will be assumed that DaT-SPECT signal is not affected by initiation or dose of levodopa (reviewed in Ikeda et al, 2019). Initiation of levodopa, dopamine agonists, and COMT inhibitors as well as change in dose or type will be considered NOT to impact the effect of interest for DaT-SPECT, and the post ICE data will be included in the main estimand analysis 'regardless of ST initiation/type/dose' ("Treatment policy" strategy – see details in Table 1.2). Monoamine oxidase-B inhibitors (MAO-B) will not be allowed in this study (see Section 6.5.2 and Section 6.5.3 of the protocol).

If a participant was to take an MAO-B inhibitor, then a washout Period of 50 hours (or 5 half-lives) must be completed prior to performing the DaT-SPECT measurement. If washout was not respected, post ICE DaT-SPECT data will be removed ("Hypothetical" handling strategy) and missing data will be imputed assuming missing at random (MAR) in the primary analysis, using maximum likelihood (ML) imputation (Schafer and Graham, 2002). MAO-B inhibitors are not allowed per protocol, so taking MAO-B is considered a protocol deviation which is also considered an ICE, and therefore also covered in Section 1.2.3.

Missing data due to scan not having taken place at the participant's or Investigator's discretion will be also treated as MAR and imputed in the same way as above.

Cumulative LEDD

Initiation of, type, dose, and/or change in ST will be considered to be an integral part of the calculation of the LEDD outcome; therefore, a "Composite" handling strategy will be applied where the post-ICE data form an integral part of the outcome.

1.2.2 Treatment discontinuation and treatment-related ICE-like protocol deviations

Participant-led or Investigator-led treatment discontinuation may be related to assigned investigational treatment (due to lack of efficacy / AEs) or unrelated (including COVID-19 pandemic).

Treatment discontinuation will not be considered to impact the effect of interest, and the post-ICE data will be included in the analyses ('Treatment policy' strategy).

Minor treatment-related protocol deviations such as treatment non-compliance (missing a dose or taking a dose at a different time of the day) or minor drug administration error will not be considered to impact the effect of interest, and the post-ICE data will be included in the analyses ('Treatment policy' strategy).

1.2.3 Other ICE-like Protocol deviations

Some protocol deviations can be defined as ICEs. The protocol deviations specification document will clearly define the protocol deviations that are ICEs and the type of impact they will have.

For important protocol deviations considered to impact the effect of interest on the long-term, the deviation will be considered uninformative with respect to the treatment of interest and the post-

ICE data will be removed from the analyses for all following visits and the post ICE missing data will be imputed ("Hypothetical" handling strategy) assuming (MAR) and using ML imputation.

For important protocol deviations considered to only impact the effect of interest in the short-term, e.g. a single visit, the deviation will be considered uninformative with respect to the treatment of interest and data for the impacted visit(s) will be removed from the impacted analyses and the post ICE missing data will be imputed ("Hypothetical" handling strategy) assuming (MAR) and using ML imputation.

Further details on protocol deviations are given in Section 5.1.2.2.

1.2.4 Confirmed or suspected COVID-19 and COVID-19 vaccination

Confirmed or suspected cases of COVID-19 will not be considered to impact the effect of interest, and the post-ICE data will be included in the analyses ('Treatment policy' strategy). This is assuming that the participant remains in the study.

This strategy only applies to confirmed or suspected COVID-19. Other ICEs or protocol deviations related to COVID-19 (treatment or study discontinuation) should be handled using the approaches outlined in the sections above.

Study participants are permitted to receive the COVID-19 vaccine at any point in the study. A treatment policy strategy will be used for this ICE where post-vaccination data is kept as part of the analyses.

1.2.5 Death or serious injury

Local injuries, eg, to head for DaT-SPECT, to arms/hands/legs/feet for clinical outcomes, and/or systemic acute conditions such as a stroke or an accident-related coma, may prevent the taking of measurements. Death due to PD is unlikely, as participants have been selected in the early stage of the disease, although an accident may be the consequence of PD symptoms.

Both PD-related and non-PD-related serious injury or death will be considered uninformative with respect to the effect of interest, the ICE ignored, and the post ICE data imputed in the analyses ("Hypothetical" handling strategy) assuming MAR and applying ML imputation. In practice, these events will be identified as serious adverse events that result in persistent or significant disability/incapacity or death.

1.2.6 Study termination and loss to follow-up

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. If a study participant withdraws or is withdrawn, he or she should be encouraged to perform the End-of-Treatment (EOT)/ Early Termination (ET) Visit and the Safety Follow up Visit approximately 30 days after last dose of IMP.

Regardless of the cause for a participant's termination, study termination will be considered uninformative with respect to the effect of interest, and the post ICE data will be imputed ("Hypothetical" handling strategy) assuming MAR and using ML imputation.

The same strategy will be applied in the case of early study termination.

1.3 Study design

PD0055, a dose-blinded, Phase 2, extension study of PD0053, will evaluate the long-term efficacy, safety, and tolerability of minzasolmin (UCB0599) in study participants who were diagnosed with new onset PD when entering PD0053, the proof-of-concept study. Study participants will be allowed to receive ST (ie, they will either continue ST from PD0053 or they will be free to request the initiation of ST in collaboration with the study physician) and will receive IMP for 30 months or longer. Parkinson's disease clinical diagnosis will be reviewed at the PD0055 Baseline Visit and at PD0055 Month 18 (ie, 36 months post PD0053 Screening).

Participants who have been treated with minzasolmin (UCB0599) [redacted] during PD0053 will continue to receive minzasolmin (UCB0599) [redacted] in extension study PD0055. Participants who have been treated with minzasolmin (UCB0599) [redacted] during PD0053 will continue to receive minzasolmin (UCB0599) [redacted] in PD0055. Participants who received placebo during PD0053 will receive minzasolmin (UCB0599) [redacted] in PD0055.

Throughout the study, data will be reviewed on an ongoing basis by a DMC and a SMC. Refer to Section 5.9 for details on specific data review and timings.

A study overview of PD0055 is provided in Figure 1-1 in Section 1.2 of the protocol. The study will comprise 3 embedded designs. The active arm will be considered to be minzasolmin (UCB0599) [redacted] Two comparator arms will be used to provide further insight into the efficacy/effectiveness of minzasolmin (UCB0599):

- Delayed-start arm ([redacted]) (Figure 1-2 in Section 1.2 of the protocol)
- Low-dose arm ([redacted]) (Figure 1-3 in Section 1.2 of the protocol)

In addition, external benchmark/reference data (where available) may be used to contextualize the efficacy of minzasolmin (UCB0599) (selected endpoints only) beyond 18 months post PD0055 Baseline visit (Figure 1-4 in Section 1.2 of the protocol). All analyses for this exploratory objective will be detailed in an exploratory SAP and will be performed outside of the CSR planned analyses.

PD0055 includes a Screening Period of up to 60 days (overlapping with the Treatment Period of PD0053) followed by a planned Treatment Period of 30 months or longer and an SFU Visit 30 days after the last dose. Study participants who completed the Treatment Period of PD0053 are eligible for enrollment in PD0055.

PD0055 was terminated early as PD0053 (ORCHESTRA), the proof-of-concept study of minzasolmin did not meet its primary or secondary clinical endpoints. Study participants were asked to complete an End of Treatment (EOT)/ Early Termination (ET) and SFU visit (30 days after the last dose).

2 STATISTICAL HYPOTHESES

No formal statistical hypothesis testing is planned for this study, analyses will be focusing on estimation.

3 SAMPLE SIZE DETERMINATION

No formal sample size estimation will be provided as the sample size for this study will be determined according to the number of participants completing the Treatment Period of PD0053, meeting the eligibility requirements for PD0055 and consenting to participate in PD0055.

A total of 493 participants were dosed in PD0053. Of the 431 participants who completed PD0053, 428 transitioned into PD0055. Assuming that 15% of PD0055 participants who were randomized to placebo in PD0053 drop out within the first few months of rolling over into PD0055 due to AEs upon initiating minzasolmin (UCB0599) [redacted] (ie, around 20 participants not completing their Month 3 visit), and that another 5% of participants across all treatment arms drop out or are lost to follow up in any given year, around 374 participants were be expected to reach PD0055 Month 18. Due to the early termination of the study, less participants than originally predicted are expected to complete the PD0055 Month 18 visit.

4 POPULATIONS FOR ANALYSIS

The following analysis sets will be used:

- All Study Participants Set (ASPS): All study participants who were randomized into PD0053 and who sign the ICF for PD0055.
- Safety Set (SS): All study participants who were randomized in PD0053 and who receive at least a partial dose of PD0055 IMP. The SS will be used for disposition, demographic, safety, and pharmacodynamic analyses.

Safety, disposition and demographic analyses will be based on treatment actually received in PD0055.

- Full Analysis Set (FAS): All study participants who were randomized into PD0053, who sign the ICF for PD0055, who receive at least a partial dose of PD0055 IMP, and have at least 1 assessment post PD0055 baseline. This is any non-missing post-baseline assessment, including unscheduled assessments. This analysis set will exclude participants who did not meet PD0053 key inclusion/exclusion criteria, including age and disease duration at time of informed consent/baseline, Hoehn and Yahr stage at screening, evidence of dopamine transporter deficit (from screening DaT-SPECT) and ST status at screening (see Section 6.5 for details).

The FAS will be used for all efficacy analyses, and analyses will be conducted based on treatment assigned in PD0055 with ICEs and other protocol deviations to be handled according to the approach specified for each estimand (see Sections 1.2).

For a given endpoint, the analysis models will exclude any participant with a missing assessment at PD0053 baseline/screening for that particular endpoint.

5 STATISTICAL ANALYSES

5.1 General considerations

All tables, figures and listings (TFLs), including statistical evaluation, will be produced by Parexel using SAS version 9.4 or higher (SAS Institute, Cary, North Carolina, USA). Analysis data will adhere to Clinical Data Interchange Standards Consortium (CDISC) guidance documents for Analysis Data Model (ADaM) and follow the UCB interpretation.

TFLs will be presented by treatment group and visit where applicable. Listings of all documented and calculated data will be presented by treatment group, study participant and visit. Data collected at unscheduled visits will be included in listings but not in any summary tables unless explicitly stated otherwise.

Visit labelling

Since PD0055 is the extension study of PD0053, and since the majority of summaries/analyses will include PD0053 data, all visits will be labelled using PD0053 Screening/Baseline as reference. The following visits labels will be used for PD0055 visits:

Table 5–1: Visit Labelling

PD0055 Visit	PD0053 Visit	TFL Label (relative to PD0053 Baseline)
	V1, Day -42 to -23	PD0053 Screening Part 1
	V2, Day -21 to -14	PD0053 Screening Part 2
	V3, Day 0	Day 0 (PD0053 Baseline Visit)
	V4, Day 10	Day 10
	V5, Month 1	Month 1
	V6, Month 2	Month 2
	V7, Month 3	Month 3
	V8, Month 4	Month 4
	V9, Month 6	Month 6
	V10, Month 8	Month 8
	V11, Month 10	Month 10
	V12, Month 12	Month 12

Table 5–1: Visit Labelling

PD0055 Visit	PD0053 Visit	TFL Label (relative to PD0053 Baseline)
	V13, Month 14	Month 14
V1, Screening	V14, Month 16	Month 16[a]
V2, PD0055 Baseline Visit	V15, Month 18 EOT	Month 18[b]
V3, Phone Call		PD0055 Day 10 (Phone call)
V4, Month 1		Month 19
V4a, Month 2		Month 20
V5, Month 3		Month 21
V5a, Month 4		Month 22
V5b, Month 5		Month 23
V6, Month 6		Month 24
V7, Month 12		Month 30
V8, Month 18		Month 36
V9, Month 24		Month 42
V10, Month 30		Month 48
SFU		PD0055 SFU

[a]PD0055 V1 may coincide with PD0053 V14. All data collected at either PD0055 V1 or PD0053 V14 will be labelled as 'Month 16'.

[b]If PD0055 V2 is conducted more than 2 weeks after V15 (month 18) of PD0053, or if any assessments are not performed at V15 (month 18) in PD0053, these will be repeated during PD0055 V2. All data collected at either PD0053 V15 or PD0055 V2 will be labelled as 'Month 18', but data collected in the PD0055 database will be flagged in data listings. All repeat assessments will be included in listings. For descriptive summaries and analyses, data collected in PD0053 for month 18 should be used unless it is not available.

For any PD0053 visit data to be included in summary tables or analyses, the same visit labels as described for PD0053 will be used.

Continuous variables

Unless stated otherwise, summary statistics will be presented for continuous variables including number of participants (n), mean, standard deviation (SD), median, minimum and maximum. When summarizing efficacy endpoints, the inter quartile range (IQR) will also be included.
In listings, if the data is coming directly from the CRF it should be presented exactly as captured. For derived variables, data should be reported using 1 decimal place more than the values which they are calculated from.

Categorical variables

Categorical variables will be summarized using frequency counts and percentages. Unless otherwise stated, the denominator for the percentage calculations will be based on the number of study participants in the respective analysis set, treatment group and visit (as applicable) with non-missing data.

Unless otherwise noted, all percentages will be displayed to 1 decimal place. No percentage will be displayed for zero counts, and no decimal will be presented when the percentage is 100%.

Estimands

Estimands will be described as a function of their attributes: (1) the population of interest, (2) the treatment effect of interest, (3) the participant-level variable (or endpoint) of interest, (4) the specification of how ICEs are reflected in the scientific question of interest, and (5) the population-level summary for the variable/endpoint. (See Table 1.1 and 1.2 for the estimands and ICE handling strategies to be used in this study).

Age Categories

Where age categories are being used, the following categories will be defined (in years):

- 40 to less than 50;
- 50 to less than 60;
- 60 to less than 70;
- 70+ years.

5.1.1 Date imputation

Partial dates may be imputed for the following reasons:

- Classification of adverse events (AEs) as treatment emergent
- Classification of medications as prior or concomitant
- Calculation of duration of exposure
- Calculation of duration of AEs
- Calculation of Parkinson's disease duration

Imputed dates will not be shown in the listings; all dates will be displayed as reported in the database.

The following rules will be applied for partial AE and concomitant medication start dates when classifying as treatment-emergent or prior/concomitant:

- If only the month and year are specified and the month and year of the first dose of IMP (first dose in PD0053) is not the same as the month and year of the start date then the 1st of the month will be used, or the date of PD0053 Screening visit 1 if this is later (if the latter imputation results in an end date that is earlier than the start date, then the 1st of the month will be used).
- If only the month and year are specified and the month and year of the first dose of IMP in PD0053 is the same as the month and year of the start date, then the date of the first dose of IMP in PD0053 will be used. If this results in an imputed start date that is after the specified end date, then the 1st of the month will be used, or the date of PD0053 Screening visit 1 if this is later (if the latter imputation results in an end date that is earlier than the start date, then the 1st of the month will be used).
- If only the year is specified, and the year of the first dose of IMP in PD0053 is not the same as the year of the start date then January 01 will be used.
- If only the year is specified, and the year of the first dose of IMP in PD0053 is the same as the year of the start date, then the date of the first dose of IMP in PD0053 will be used. If this results in an imputed start date that is after the specified end date, then January 01, or the date of PD0053 Screening visit 1 if this is later will be used (if the latter imputation results in an end date that is earlier than the start date, then January 01 will be used). If the imputed date is the date of first dose of IMP in PD0053 then the event will be regarded as treatment emergent or the medication as concomitant.
- If the start date is completely unknown, the start date will not be imputed.

The following rules will be applied to partial AE and concomitant medication stop dates when classifying as treatment-emergent or prior/concomitant:

- If only the month and year are specified, then the last day of the month will be used.
- If only the year is specified, then December 31 of the known year will be used.
- If the stop date is completely unknown, the stop date will not be imputed.

Missing or partially missing dates will be imputed as described in the table below for the calculation of duration of each AE.

Table 5–2: Calculation rules for duration of adverse events

Data availability	Onset date/time	Outcome date/time	Calculation rules
Complete data	D1	D2	Duration = D2 – D1 + 1
Start date missing	--	D2	Duration = D2 – D0 + 1 For a study participant in the SS, D0 is the date of first administration of IMP in PD0055, for screen failures, D0 is the date of their PD0055 Screening Visit.

Table 5–2: Calculation rules for duration of adverse events

Data availability	Onset date/time	Outcome date/time	Calculation rules
End date missing	D1	--	If the stop date is missing, duration will not be calculated.

Rules for calculating duration of exposure (minzasolmin (UCB0599) or placebo)

For partial study medication stop dates, the last day of the month will be used if only day is missing. If the start date is missing or more than just the day is missing for the medication stop date, exposure duration will not be calculated. If partial dates are recorded for date of first and last dose of study medication this should be queried prior to applying any imputation rules.

Rules for calculating duration of Parkinson's Disease at PD0055 Baseline

Partial date of diagnosis dates will be imputed with the 15th of the month if only day is missing, if both day and month are missing the date will be imputed with 30th June (ie, the middle of the year).

Rules for determining start/end date of ST

Partial ST initiation dates will be imputed with the 15th of the month (if only day is missing) for the purposes of analyzing ST data (determining when ST started for ICE handling, and for calculating LEDD). If the imputed date is after the date of last contact with the study participant, then the date of last contact will be used instead. If an end date is imputed to be prior to the start date, then the date of last contact will be used instead. This imputation rule will also apply to partial ST end dates. If month and/or year is missing, no imputation will be performed. If partial ST dates are recorded, these should be queried prior to applying any imputation rules.

5.1.2 General study level definitions

5.1.2.1 Analysis time points

5.1.2.1.1 Relative day

The relative day of an event will be derived with the date of first dose of minzasolmin (UCB0599) as reference. For participants taking placebo in the feeder study, this will be their date of first study medication in PD0055. For participants taking minzasolmin (UCB0599) in the feeder study, this will be their date of first study medication in PD0053.

Relative day for an event or measurement occurring before the date of first minzasolmin (UCB0599) dose will be calculated as follows:

$$Relative\ Day = Event\ Date - Date\ of\ First\ UCB0599\ Dose$$

The relative day for an event or measurement occurring on the date of first minzasolmin (UCB0599) dose is day 1. The relative day for an event or measurement occurring on or after the first dose and before the date of the last dose will be calculated as follows:

$$Relative\ Day = (Event\ Date - Date\ of\ first\ UCB0599\ Dose) + 1$$

For events or measurements occurring after the date of last dose of study medication (within the SFU period), relative day will be prefixed with '+' in the data listings and will be calculated as follows:

$$Relative\ Day = +\ (Event\ Date - Date\ of\ Last\ UCB0599\ Dose)$$

There is no relative Day 0. Relative day will not be calculated for partial dates. In such cases, relative day should be presented as "--" in the relevant data listing.

For use in disposition and PD0055 baseline characteristics summaries, we will also define Study Day as follows:

For events occurring before the first dose in PD0055:

$$Study\ Day = Event\ Date - Date\ of\ First\ Dose\ of\ Study\ medication\ in\ PD0055$$

For events occurring on or after the first dose in PD0055:

$$Study\ Day = (Event\ Date - Date\ of\ first\ Dose\ of\ Study\ Medication\ in\ PD0055) + 1$$

For events occurring after the date of last dose in PD0055:

$$Study\ Day = +\ (Event\ Date - Date\ of\ Last\ Dose\ of\ Study\ Medication\ in\ PD0055)$$

Here, study medication refers to either minzasolmin (UCB0599) or placebo.

5.1.2.1.2 End date of the treatment period

The end date of the treatment period will be either the date of the month 30 EOT visit (visit 10) for participants who complete the treatment period, or the date of the EOT/ET visit for participants who discontinue the study during the treatment period (same procedures as visit 10 for completers). If a study participant does not have an EOT/ET visit then the date of the last scheduled or unscheduled visit during the treatment period or the date of last known dose of study medication (whichever is later) will define the end date of the treatment period.

5.1.2.1.3 Study periods

The end of the study is defined as the date of the last visit of the last participant in the study. The following study periods are defined for this study:

PD0053 Treatment period:

All PD0055 participants will be taking part in study PD0053 before entering the PD0055 screening period. The PD0053 Treatment period ends once the participant has completed their final PD0053 visit at Month 18 (PD0053 Visit 15).

Screening period:

The screening period will last up to 60 days (overlapping with the Treatment Period of PD0053). A participant's screening visit may coincide with visit 14 (month 16) of PD0053.

Treatment period:

Participants will receive either minzasolmin (UCB0599) [redacted] or minzasolmin (UCB0599) [redacted] until they reach month 18.

Safety follow up period:

The safety follow up will last for approximately 30 days and includes 1 visit (the Safety Follow-Up (SFU) visit).

Early termination:

In case of early termination of a participant's treatment or early termination of the study, the participant will be asked to attend the End of Treatment (EOT)/ Early Termination (ET) and the SFU visit (30 days after the last dose).

5.1.2.1.4 Mapping of assessments performed after early termination

If study participants discontinue the study for any reason or if the study is terminated early, study participants will be asked to attend the End of Treatment (EOT)/ Early Termination (ET) and the SFU Visit (30 days after the last dose) and encouraged to attend these two visits as soon as possible after last dose of study drug.

The following rules will apply regarding the inclusion of data obtained at the EOT/ET visit, unless stated differently in later sections:

- If the EOT/ET visit occurs at the same time as the next scheduled visit, the results will be included with all other participants' results from that visit in summary tables;
- If the above is not true, the results will be mapped to the nearest scheduled visit, following the last scheduled visit where assessments were performed (use the earliest visit if equidistant) and the results will be included in the summary tables for that visit;
- Mapped results will be included in any statistical analyses (where applicable).

The results from these EOT/ET visits will be displayed as the mapped visit and flagged in the data listings. Early SFU visit results will not be mapped to another visit and data from early SFU visits will be listed only.

For all statistical analyses, data for participants who terminate early will be handled using the pre-specified ICE strategies (see Section 1.2 for further details). If the data is to be included in the analysis, the mapping rules above will be used.

5.1.2.1.5 Definition of baseline values

In general, for efficacy analyses, Baseline values will be determined from the latest non-missing value collected prior to the first dose of study medication in PD0053, unless otherwise stated for a specific analysis in later sections.

For some safety and efficacy analyses Baseline will be defined relative to first dose of study medication in PD0055. Here, Baseline values will be determined from the latest non-missing value collected prior to the first dose of study medication in PD0055.

For both defined Baseline values, Baseline visit assessments will be assumed to have been taken pre-dose. If pre-dose data is supposed to be collected but is not for any reason, this should be investigated before automatically using the latest screening value.

5.1.2.2 Protocol deviations

Important protocol deviations (IPDs) are deviations from the protocol which could potentially have a meaningful impact on study conduct or on either the primary or key secondary outcome(s) for an individual study participant. The criteria for identifying such protocol deviations will be defined within the IPD specifications document.

Important protocol deviations will be categorized as follows:

- Inclusion/exclusion criteria deviations
- Incorrect treatment or dose administered – some of these will be defined as treatment-related ICE (see Section 1.2)
- Procedural non-compliance – some of these will be defined as treatment-related ICE (see Section 1.2)
- Prohibited concomitant medication use - some of these will be defined as treatment-related ICE (see Section 1.2)
- Withdrawal criteria deviation

All protocol deviations will be reviewed as part of the ongoing data cleaning process. Important protocol deviations will be listed and summarized. One data evaluation meeting (DEM) will be held throughout this study, occurring just before database lock. The purpose of this DEM review will be to review all protocol deviations and check the quality of the data. The reviews will also help decide on strategies on how to handle issues in the study participants' data (eg, missing values and withdrawals – also refer to Section 1.2).

Accepted deviations from scheduled time points will be described in the appropriate documents and included in the eTMF. After the pre-analysis review, resolution of all issues, and documentation of all decisions (including inclusion into each of the analysis sets) at the final DEM, the database will be locked.

Some protocol deviations will be pre-defined as ICEs and the handling of these deviations is discussed in Section 1.2

5.1.2.3 Treatment assignment and treatment groups

Participants who have been treated with minzasolmin (UCB0599) [redacted] during PD0053 will continue to receive minzasolmin (UCB0599) [redacted] in extension study PD0055. Participants who have been treated with minzasolmin (UCB0599) [redacted] during PD0053 will continue to receive minzasolmin (UCB0599) [redacted] in PD0055. Participants who

received placebo during PD0053 will receive minzasolmin (UCB0599) [redacted] in PD0055. All listings and summaries will be presented by treatment group unless stated otherwise. Appendix 3 outlines which summaries should present an overall summary as well as data summarized by treatment group.

Table 5–3: Treatment group descriptions

Full Description	Data Display Label
Delayed-start arm (placebo in PD0053, [redacted] in PD0055)	Delayed-start UCB0599 [redacted]
Low-dose arm ([redacted] in both PD0053 and PD0055)	Early-start UCB0599 [redacted]
High-dose arm ([redacted] in both PD0053 and PD0055)	Early-start UCB0599 [redacted]
Early-start arms, all Early-start minzasolmin (UCB0599) [redacted] and Early-start minzasolmin (UCB0599) [redacted] participants	Pooled Early-start UCB0599
minzasolmin (UCB0599) pooled Low-dose arm, High-dose arm and Delayed-start arm	All participants

Since participants who do not meet the PD0055 entry criteria will already be assigned to a treatment arm (no re-randomization in PD0055) all screen failures will still be assigned to a treatment arm. It will be made clear in all listings that these participants are screen failures and these participants will only have data available from their screening visits; their safety and efficacy data will not be reported in any listings, tables or figures.

Treatment assignment for safety and disposition TFLs will be based on the treatment they predominantly received (actual treatment). For efficacy/pharmacodynamic analyses assignment will be based on randomized treatment. For all safety and efficacy analyses, it will be made clear in each TFL whether randomized or actual treatment is being used. ASPS assignment will always be based on actual treatment received.

5.1.2.4 Center pooling strategy

The data from different centers will be pooled for all analyses. Data for some endpoints will be summarized by geographical region (Europe and North America) as described in Section 5.1.2.6.

5.1.2.5 Coding dictionaries

Adverse events and medical history will be coded using the version of the Medical Dictionary for Regulatory Activities (MedDRA®) used in study PD0053. Medications will be coded according to the World Health Organization Drug Dictionary (WHODrug-Global B3 format), also using the version used in PD0053. Medical procedures will not be coded.

5.1.2.6 Multicenter studies

Since treatment assignment will not necessarily be balanced across countries or sites, no statistical analyses will be carried out to investigate center effects. However, for the primary and secondary endpoints summary statistics will be produced by geographical region (Europe and North America).

For each geographical region, summary statistics for both observed results and changes from PD0053 Baseline by visit and treatment group will be produced for the following endpoints:

- DaT-SPECT whole striatum SBR;
- Levodopa cumulative daily dose (changes from Baseline not applicable here).

In addition, in response to the COVID-19 pandemic, the number of participants who contracted COVID-19 during the study (further details given in Section 5.2) will be summarized by treatment group and visit, overall and by geographical region.

5.2 Participant dispositions

Treatment group assignment for all participant disposition summaries will be based on actual treatment received. The number of study participants who started the study, completed the study and prematurely discontinued will be presented by treatment group and overall. The reasons for discontinuation will also be summarized. This summary of disposition and discontinuation will be based on the SS. A study participant who completed the study is defined as a study participant who has a completed status in the study termination eCRF. Since the primary estimand analysis in this study will be done using the first 18 months of data for each participant, the number of completers and the number of premature discontinuations will be summarized separately up to this time (in the same summary table). Participants who discontinue early are considered to have completed month 18 if their study termination date falls in or after the month 18 visit window.

The number and percentage of study participants who discontinue due to AEs will be summarized by treatment group, based on the SS. This summary will be used for European Union Drug Regulating Authorities Clinical Trials (EudraCT) reporting. This table will also present (separately) discontinuations due to AEs prior to the month 18 visit.

The number of study participants included in each of the analysis sets will be summarized by treatment group.

Screen failure reasons will be summarized for the ASPS. A listing of study participants who did not meet study eligibility criteria will also be presented for this analysis set.

In addition, the following listings will be presented:

- Disposition of study participants (ASPS)
- Study discontinuation (SS)
- Visit dates (SS)
- Study participant analysis sets (ASPS)

The listing of disposition of study participants will include the date of informed consent, date of first and last dose of IMP in PD0055, date of premature termination and primary reason (if applicable) and date of final contact.

The listing of study discontinuation will include the reason for discontinuation and both the study day and relative day for the date of the last dose received (see Section 5.1.2.1.1 for how these are defined).

Additionally, a summary of the impact of COVID-19 (for any reason) will be produced by region and treatment group for the SS. This information will also be listed for the ASPS. Potential impacts that will be included in these summaries are missed visits or doses, visits performed out of window or through a different modality, and temporary/permanent study or drug discontinuation. Relationship to COVID-19 will also be included in these outputs, detailing whether the impact is due to confirmed infection, suspected infection or general COVID-19 related circumstances.

A summary will be created to show the number and percentage of participants who had a PD0055 EOT/ET Visit and which month this visit was remapped to (relative to PD0053 baseline).

5.3 Efficacy estimands and endpoints

For all efficacy analyses, Baseline will refer to PD0053 Baseline Visit data (or PD0053 Screening Visit data where applicable). Longitudinal analyses will include data from the PD0053 study (as applicable). All time points will be defined with the PD0053 Baseline/Screening Visits as reference (see Section 5.1.2.3 for details on visit labelling).

All efficacy listings, summaries and analyses will be presented for the FAS using randomized treatment assignment.

For all efficacy estimands/endpoints, descriptive summary tables will include data for all visits from PD0053 Baseline up until PD0055 EOT/ET, however, statistical analyses will only include data up to PD0055 month 18. For PD0053, data will be summarized for visits at which the endpoint/assessment was scheduled as per the Schedule of Activities in the protocol (excluding PD0053 safety follow-up). For PD0055, data will be summarized and listed for visits at which the endpoint/assessment was scheduled as per the Schedule of Activities in the protocol or were mapped to as per Section 5.1.2.1.4.

All analyses will be adjusted for gender (to account for stratification at PD0053 randomization), and age at PD0053 baseline. Where continuous, these covariates will be mean centered to aid interpretability (the intercept term can be interpreted as the expected value of the response when the dependent variables are set to their means).

If convergence problems are encountered, analyses will be run without adjusting for age at baseline. If convergence remains an issue after this step, the use of random effects or variance-covariance matrix structure may be reviewed.

To support the efficacy analyses presented in this section, a (cumulative) summary table presenting the number and percentage of participants with each ICE (see Section 1.2 for a full list of the ICEs defined in this study) will be produced by visit and treatment group, overall and by gender.

For all statistical models fitted to the efficacy data, diagnostic plots will be included in the statistical output documents.

Symptomatic Treatment Status

For all summary tables and listings where ST status is used or presented, the assumption is made that once a participant starts ST, they remain on ST for all study visits after their initiation date.

For summary tables that are being presented for participants who are not yet on ST, this means not yet on ST by a particular visit. This means that the number of participants contributing to the summary will differ by visit in the table, as more participants may have initiated ST by the following visit.

For plots that are displayed by ST initiation timing, the following categories will be defined for participants who started ST:

- by Month 12 (inclusive);
- between Months 12 and 24 (inclusive);
- not started by 24 months/EOT/ET (if applicable).

Additional Exploratory Analyses

Additional exploratory analyses for both the primary and secondary estimands, and for some exploratory endpoints, will be detailed in a PD0055 Exploratory Analysis Plan.

5.3.1 Primary estimand analysis: Neurodegeneration

For the primary estimand analysis, only DaT-SPECT data collected during the first 18 months of PD0055 will be considered. The primary estimand is for the primary efficacy objective, which is to estimate the pharmacodynamic effects of minzasolmin (UCB0599) on brain pathophysiology in Early-start versus Delayed-start participants originally diagnosed with new onset PD.

5.3.1.1 Definition of endpoint

The whole striatum will be calculated as the average of the specific binding ratio (SBR) data values for the four following "small" regions: left caudate small, left putamen small, right caudate small and right putamen small. The SBR will be calculated for each region with the occipital cortex as a reference region, where a lower SBR indicates worse disease. The following formula will be used to calculate this:

(Average (Small region) – Average (Occipital region))/ (Average (Occipital region))

Descriptive statistics and visualization

Descriptive statistics for observed results, changes from PD0053 Baseline and annualized change from PD0053 baseline in DaT-SPECT whole striatum SBR at PD0053 Screening/Baseline and at all available timepoints (scheduled or mapped visits) post PD0053 Baseline will be presented. Summary tables will be produced by treatment group and visit (PD0053 Screening/Baseline and at all available timepoints), overall, by gender, and by geographical regions.

Annualized change from baseline is calculated as change from baseline/actual time of visit (in years).

Plots of individual trajectories over time will also be produced. To make these plots interpretable given the large sample size, plots will be produced by treatment group (Delayed-start [redacted], Early-start [redacted] and Early-start [redacted]) and gender. Trajectories will be color coded to clearly indicate when a participant initiates ST.

In addition to these individual plots, longitudinal plots of mean observed, mean change from PD0053 and annualized change from PD0053 baseline DaT-SPECT whole striatum SBR will be produced by treatment group, overall and by gender. These plots will include error bars (±SEM) and all treatment groups will be overlaid on the same plot.

The participant-level endpoint will be DaT-SPECT whole striatum SBR up to 36 months post PD0053 Screening (PD0055 Month 18), regardless of ST initiation of, type, dose, and/or change in ST. For DaT-SPECT, Baseline is the value recorded at PD0053 Screening visit 2 (or data from a historical DaT-SPECT scan acquired within 3 months of PD0053 Screening Visit 1).

DaT-SPECT assessments performed within 2 months of PD0055 Screening Visit will be mapped to Month 18 (post PD0053 baseline). Any DaT-SPECT assessment from Month 23 post PD0053 baseline will be combined as if from a single assessment/visit and referred to as "PD0055 EOT/ET" visit.

5.3.1.2 Main analytical approach

A linear mixed effects model (LMEM) for analysis of covariance (ANCOVA) will be used to analyze the longitudinal observed data using the FAS excluding any participant with missing assessment at PD0053 screening. Treatment, time (visit, categorical) and treatment by time (interaction term between treatment and visit) will be included as fixed effects, and PD0053 Baseline DaT-SPECT whole Striatum SBR, gender, and age at PD0053 baseline will be included as covariates. Participant will be included in the model as a random effect. Visits will include screening, Month 12, Month 18 and the "PD0055 EOT/ET" visit.

The population-level summary of interest will be the PD0053 Baseline-adjusted difference in target population mean in DaT-SPECT whole Striatum SBR at the "PD0055 EOT/ET" visit regardless of ST initiation between:

- Early-start minzasolmin (UCB0599) ([redacted]) arm and 18-month Delayed-start minzasolmin (UCB0599) ([redacted]) arm; and
- Early-start minzasolmin (UCB0599) ([redacted]) arm and Early-start minzasolmin (UCB0599) ([redacted]) arm.

Details on the ICE handling for this estimand can be found in Section 1.2. It will be assumed that DaT-SPECT signal is not affected by ST initiation and the handling strategy for this ICE will be "Treatment policy" (include post ICE data).

A summary table presenting the estimates of the treatment effects at the "PD0055 EOT/ET" visit and corresponding 95% CIs from this model will be presented. These estimates will come from both the treatment effects and the treatment by time interactions from the model. Since there is only one random effect in this model, the intra-class correlation coefficient (ICC) can be calculated and interpreted as the proportion of the total variance that is accounted for by variation within participants.

A plot displaying the adjusted means and 95% CIs over time for each treatment group from this model will be produced.

A summary table will also be produced by gender using the same model as described above (removing gender as a covariate).

See Section 5.3.3.1 for the details on the descriptive summaries to be produced for the striatal sub-regions.

5.3.1.3 Sensitivity analyses

The main model (Section 5.3.1.2) will be refit pooling the early-start arms together so that we can look at the PD0053 Baseline-adjusted difference in target population mean in DaT-SPECT whole Striatum SBR at 36 months regardless of ST initiation between pooled Early-start minzasolmin (UCB0599) arms and the Delayed-start minzasolmin (UCB0599) ([redacted]) arm.

5.3.1.4 Supporting analyses

Not applicable.

5.3.2 Secondary estimand analysis: Symptomatic Treatment (ST)

For the secondary estimand analysis, only data from the first 18 months of PD0055 will be considered. This estimand is for the secondary efficacy objective, which is to estimate the pharmacodynamic effects of minzasolmin (UCB0599) on the need for ST in Early-start versus Delayed-start participants originally diagnosed with new onset PD.

5.3.2.1 Definition of endpoint

The cumulative LEDD will be calculated for each participant at all available (scheduled or mapped) visits post-PD0053 baseline. This is the sum of all the levodopa equivalent daily doses taken up to that visit (ie, if a participant is taking [redacted] of levodopa a day, their cumulative dose over 10 days would be [redacted]).

Descriptive statistics and visualization

A listing of cumulative LEDD will be produced by visit and treatment group based on the SS, only participants with nonzero data will be presented in this listing. Continuous summary statistics will be presented by visit, treatment group, overall, by gender, and by geographical regions. Summary statistics will only be calculated at Months 6, 12, 18 and all available (scheduled or mapped) PD0055 visits. For participants who have not started ST by a particular visit, their cumulative LEDD will be [redacted] and this will be included in the calculation of summary statistics. As part of the summary statistics, the number of participants who have initiated ST by each visit will be included. In addition to the summary tables, plots of both individual trajectories and separate mean (+/-SEM) longitudinal cumulative LEDD will be produced overall and by treatment group and gender.

ST options other than levodopa are only permitted in exceptional cases. For participants taking levodopa, the LEDD calculation is simple and the cumulative dose is calculated just based on the dose level, dosing regimen and duration of ST. For participants not taking levodopa, the levodopa equivalent dose will be calculated using conversion factors as detailed in the study ADRG (ADaM data reviewers guide).

When calculating the LEDD, the following points should be taken into consideration:

- All participants taking levodopa will take carbidopa (or equivalent) in combination, carbidopa intake is ignored when calculating levodopa equivalent dosing.
- MAO-B inhibitors are prohibited medications in this study, taking any of these medications would lead to a protocol deviation.
- Despite not being the recommended approach per protocol, participants may be prescribed levodopa in combination with a COMT inhibitor. The COMT inhibitor medication may be prescribed as a separate pill or part of a combination drug with levodopa. COMT inhibitor conversion factors will depend on the dosing level and regimen, the ADRG will give further details on this.

Any changes in medication (type, dose or dosing regimen) should be accounted for when calculating cumulative doses. Participants who take a ST other than levodopa/carbidopa at any point during the study will be flagged in the listing of cumulative LEDD.

The participant-level endpoint will be the cumulative LEDD at 24 months post PD0053 Baseline. No Baseline data will be available as participants were "ST-naïve" at PD0053 Baseline.

5.3.2.2 Main analytical approach

Details on the ICE handling for this estimand can be found in Section 1.2. Since the endpoint here is calculated based on ST intake, ST is not considered an ICE for this analysis.

An ANOVA will be used to analyze the cumulative LEDD data of participants who completed PD0055 Month 6 visit (either as scheduled or mapped), i.e. corresponding up to 24 months post-PD0053 baseline. Treatment will be included in the model as a categorical fixed effect, with gender, and age at PD0053 Baseline included as covariates. The population-level summary of interest will be the differences in target population mean cumulative LEDD at 24 months for the following treatment comparisons:

- Early-start minzasolmin (UCB0599) ([redacted]) arm and 18-month Delayed-start minzasolmin (UCB0599) [redacted] arm; and
- Early-start minzasolmin (UCB0599) ([redacted]) arm and Early-start minzasolmin (UCB0599) [redacted]) arm.

A summary table presenting the model estimates of these differences and corresponding 95% CIs will be presented. A plot displaying the adjusted mean and 95% CI for each treatment group will be produced.

5.3.2.3 Sensitivity analyses

As a sensitivity analysis, the model described in Section 5.3.2.2 will be refit pooling the early-start arms together so that we can look at the difference in target population mean cumulative LEDD at 24 months between pooled Early-start minzasolmin (UCB0599) arms and the Delayed-start minzasolmin (UCB0599) ([redacted]) arm.

5.3.2.4 Supporting analyses

To support the above analyses, a summary table presenting the number and percentage of participants with an LEDD (at the time of the visit) greater than [redacted] and

[redacted] per day will be produced. This summary will be produced by treatment group, visit (the same visits as described for the continuous summary of cumulative LEDD) and gender.

5.3.3 Exploratory endpoints analysis

5.3.3.1 Exploratory endpoints: Neurodegeneration

DaT-SPECT imaging: striatal sub-regions

DaT-SPECT regional SBR continuous summary statistics will be presented by visit and treatment group, for the following striatal sub-regions: left caudate small, left putamen small, right caudate small and right putamen small.

CSF total alpha-syn and CSF ASYN oligomers/seeding capacity

CSF total alpha-syn continuous summary statistics will be presented by visit and treatment group.

Analyses of CSF ASYN oligomers/seeding capacity will be covered in the Exploratory Analysis Plan.

5.3.3.2 Exploratory endpoints: ST

WOQ-9

The WOQ-9 will be measured at PD0055 Day 0, Month 6, Month 12, Month 18 and EOT/ET visits (corresponding to 18, 24, 30 and 36 months post PD0053 Baseline respectively). No Baseline data will be available as participants were "ST-naive" at PD0053 Baseline.

Data collected at an EOT/ET visit will be mapped to the nearest scheduled visit where the assessment was scheduled to be performed, following the last scheduled visit where assessments were performed.

Responses to the WOQ-9 will be used as an exploratory efficacy endpoint to identify the presence of WO (wearing-off) in study participants taking ST.

The questionnaire includes questions for 9 symptoms: Tremor, Any Slowness, Any Stiffness, Muscle cramping, Reduced dexterity, Anxiety/Panic attacks, Mood changes, Cloudy mind/Slow thinking, and Pain/Aching (Stacy et al, 2006). For each symptom, up to two questions can be asked. The first question asks whether or not a participant is experiencing the particular symptom. The second question asks whether or not the symptom improves after the next dose of ST. For each symptom, the second question is only asked if the answer to the first question is "Yes". A participant is defined as being wearing-off positive if they answer "Yes" to both questions for at least one symptom.

The responses to the WOQ-9 will be listed for each participant by treatment group and visit. The listing will include a participant's response to each question, for each symptom, as well as an indicator of whether or not the participant has been determined to be wearing-off positive.

A summary table will be produced for the responses to the WOQ-9. The table will be produced by treatment group and visit, overall and by gender. The summary table will include the number and percentage of participants who are wearing-off positive (ie, for at least one symptom).

5.3.3.3 Exploratory endpoints: Clinical Outcome Assessments

All clinical outcome assessments listings and summaries will be presented by visit and treatment group where applicable. Listings and summary tables will be produced based on the SS (randomized treatment). All data will be listed by study participant and individual item (where applicable), with a flag for ST initiation at each visit (Yes/No flag for whether they have started taking ST by that visit) included in the listing.

For all continuous endpoints, tabulated summary statistics will be produced for both observed results and changes from PD0053 Baseline.

No statistical analyses are planned for these endpoints within the CSR.

Patient reported outcomes (PROs)

Fatigue PRO

The Fatigue PRO is composed of 3 scales containing 31 items each with 5 levels: Physical fatigue (items 1-9, raw score range 0-36), Mental fatigue (items 10-20, raw score range 0-44) and Fatigability (items 21-31, raw score range 0-44). Before calculating the sum scores for each fatigue scale, the items for all these scales need to be rescaled from 1-5 to 0-4 (as for a Likert scale). This PRO will be summarized using continuous summary statistics by visit and treatment group. This summary will be repeated for the transformed score, separately for each scale, where transformed score is calculated as:

$$\frac{raw\ score}{raw\ score\ range} \times \frac{total\ number\ of\ items\ in\ the\ scale}{number\ of\ non-missing\ items\ in\ the\ scale} \times 100$$

Data collected at an EOT/ET visit will be mapped to the nearest scheduled visit where the assessment was scheduled to be performed, following the last scheduled visit where assessments were performed.

Early PD Function Slowness and Early PD Mobility PROs

The early PD function slowness PRO has 28 items each with 5 levels (0 to 4, with 4 representing "slower function") and the early PD mobility PRO consists of 23 items each with 5 levels (0 to 4, with 4 representing "worse mobility"). Data for these PROs will be listed only. The analyses of these PROs will be described in the Exploratory Analysis Plan; the results will be part of a separate exploratory report and will not be part of the CSR.

EQ-5D-5L

The EQ-5D-5L consists of the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS) (Devlin and Brooks, 2017). The EQ-5D-5L descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression scored according to 5 levels: 1- no problems, 2 - slight problems, 3 - moderate problems, 4 - severe problems and 5 - extreme problems. These levels are expressed as a 1-digit number, and the digits for the five dimensions are combined into a 5-digit combined score that describes the participants' health state (eg, 13414). The 1-digit numbers for each of the 5 dimensions will be summarized

categorically by visit and treatment group. The 5-digit health state combined score will be used in the listings.

The EQ VAS records a patient's self-rated health on a vertical visual analogue scale; it ranges from 0 to 100 (with 100 representing the "best health you can imagine" and 0 representing "The worst health you can imagine"). EQ VAS scores will be summarized using continuous descriptive statistics presented by visit and treatment group.

Data collected at an EOT/ET visit will be mapped to the nearest scheduled visit where the assessment was scheduled to be performed, following the last scheduled visit where assessments were performed.

For both sets of EQ scores/ratings, data will be summarized overall.

Other exploratory clinical outcomes

MDS-UPDRS Parts I-III sum score, Part I, II and III subscale level data and ePD subscore

For all MDS-UPDRS summaries, MDS-UPDRS Part I-III and subscales (Part I, Part II, Part III) sum scores will only be calculated if responses are available for all questionnaire items that contribute to the sum scores. If one item response is missing, for example in Part I, Part II and Part III sum scores can still be calculated but Part I and Part I-III sum scores will not be calculable. Missing responses to individual items within the questionnaire are not expected.

Questionnaire items in each part are scored using a Likert scale from 0 to 4 with an integer rating, higher scores indicate more severe status. To calculate the sum scores, the response scores to the following questionnaire items will be summed:

- Part I: items 1.1 to 1.13, sum score ranges from 0 to 52;
- Part II: items 2.1 to 2.13, sum score ranges from 0 to 52;
- Part III: items 3.1 to 3.18 (for Part III some items will be tested on both side of the body and on the upper as well as the lower limb – all responses will be summed to get the Part III total score, 33 items in total), sum score ranges from 0 to 132;
- Part I-III: items 1.1 to 1.13, 2.1 to 2.13 and 3.1 to 3.18, sum score ranges from 0 to 236.
- ePD subscore: the 15-item set, which contains all 5 Rigidity items (3.3), Finger tapping (3.4, Right/Left), Hand movements (3.5, Right/Left), Pronation-supination of the hands- (3.6, Right/Left), Toe tapping (3.7, Right/Left), and Leg agility (3.8, Right/Left). The ePD subscore will be constructed by summing the score for the 15 items.

The participant-level endpoint will be MDS-UPDRS Parts I-III sum score at each available (scheduled or mapped) visit up to PD0055 SFU.

Data collected at an EOT/ET visit will be mapped to the nearest scheduled visit where the assessment was scheduled to be performed, following the last scheduled visit where assessments were performed.

The MDS-UPDRS Part I-III sum score, up to PD0055 SFU, will be listed by treatment group, participant and visit. This listing will also include a flag for indicating whether the participant has been compliant to the 12-hour ST washout prior to the visit.

Plots of individual MDS-UPDRS Parts I-III sum scores over time, up to PD0055 SFU, by treatment group and gender will be presented, color coded to clearly indicate when a participant is and is not on ST. Actual time will be used for this plot.

Summary tables presenting the observed mean and mean change from PD0053 Baseline in MDS-UPDRS Parts I-III sum score, up to month 36 post PD0053 Baseline, by treatment group and visit, overall and by gender will be produced. The summary will be presented overall and for participants who are not yet on ST by each visit.

Plots of observed mean and mean change from PD0053 baseline MDS-UPDRS Parts I-III sum score will be produced by treatment group overall and by gender. These plots will include error bars (±SEM) and all treatment groups will be overlaid on the same plot.

Descriptive statistics and visualizations will also be produced for the MDS-UPDRS Part I, II and III subscales (separately) and ePD subscore in the same way as described for the MDS-UPDRS Part I-III sum score above.

Modified Hoehn and Yahr (H&Y)

Modified H&Y staging results will be summarized descriptively using frequency counts and percentages. The summary will be presented by treatment group and visit, overall and by gender.

Data collected at an EOT/ET visit will be mapped to the nearest scheduled visit where the assessment was scheduled to be performed, following the last scheduled visit where assessments were performed.

Movement Disorder Society -Non-Motor Scale

The MDS-NMS scale is composed of 63 items grouped in 15 domains. Continuous summary statistics will be presented for the MDS-Non-Motor Scale (MDS-NMS) total scores (total frequency and total severity scores) by treatment group, and visit; overall. The data listing for MDS-NMS will be grouped by domain, with frequency and severity results appearing side by side.

MoCA

The MoCA (Nasreddine et al, 2005) assesses different cognitive domains (visuospatial/executive, naming, memory, attention, language, abstraction, delayed recall, and orientation). Participants are assessed on a 30-point scale. A score of 26 or above is considered normal. For all listings, summaries and analyses of MoCA data the derived total score will be used rather than the total score collected in the database. When calculating the derived total score, if a participant's years of schooling is recorded as 'Unknown' the assumption will be made that the participant has 12 years or less of education.

Descriptive statistics for observed and change from PD0053 Baseline scores at each visit will be presented. Summary tables will be produced by treatment group and visit. The summary will be presented overall and by gender.

UPSIT

Olfactory impairment, eg, hyposmia, is a common finding in PD. The University of Pennsylvania Smell Identification Test (UPSIT) is a well-established 40-item olfactory test that allows for determining the absolute value of anosmia and mild, moderate, or severe hyposmia.

Site staff will perform the UPSIT with each study participant once during the Treatment Period (at Visit 4 for all participants in the process of being enrolled into PD0055 and at the next scheduled visit for those already enrolled in PD0055).

Each participant is exposed sequentially to 40 odorants. For each odorant, the participant is asked to select among 4 choices to identify the odorant presented. Scoring of the UPSIT is based on the number of odorants that are correctly identified up to a maximum total score of 40.

The UPSIT score will need to be transformed into a participant-specific percentile: this percentile is allocated according to the participant's age and sex (See Section 6.4 Appendix 4). Hyposmic status will then be determined based on this percentile, where 'Hyposmia' is defined as having a percentile less than or equal to 15%, participants with a percentile above 15% WILL be classified as having 'No Hyposmia'. Site staff will document if the underlying cause for hyposmia may be due to other underlying conditions than PD (for example, COVID-19).

A listing including the participants UPSIT score, percentile, hyposmic status and information on the underlying cause for hyposmia (for any non-PD-related hyposmia) will be presented.

Participant-specific percentiles will be categorized as follows for summary tables:

- <10%
- 10 - < 25%
- 25 - < 50%
- 50- < 75%
- ≥ 75%

A summary table will be produced presenting frequency counts and percentages for the above categories, by treatment group. In the summary table, the last two categories will also be pooled together so that our results can be compared with literature (Brumm et al, 2023). In addition to this summary, a summary will be produced presenting frequency counts and percentages for hyposmia status.

5.4 Safety analyses

Safety data will be summarized and listed by treatment group for the SS, based on treatment predominantly received (see Section 5.1.2.3).

For all summaries and listings presenting change from Baseline data, changes from both PD0053 and PD0055 Baseline will be presented/summarized. PD0053 Baseline data will therefore be included in these listings as well as all PD0055 data.

5.4.1 Extent of exposure

Exposure data will be listed for each study participant in the SS by treatment group. For participants who received placebo in PD0053, only PD0055 exposure data will be included in these outputs. Participants who received minzasolmin (UCB0599) in PD0053 will have exposure summarized across both studies. This listing will include date of first dose of minzasolmin (UCB0599), date of last dose of minzasolmin (UCB0599), total number of minzasolmin (UCB0599) capsules taken, duration of exposure and overall IMP compliance (see Section 6.1.8 for how this is calculated).

The duration of exposure to IMP (days) will be calculated as follows:

$$Duration = (Date\ of\ Last\ UCB0599\ Dose - Date\ of\ First\ UCB0599\ Dose) + 1\ day$$

Participants who have any dosing interruptions during the study (temporarily stop taking medication) will have multiple rows in this listing. Therefore, a column for "cumulative duration" will also be presented. Participants who have a dosing interruption will be flagged.

Duration of exposure and total number of capsules taken will be summarized using descriptive statistics by treatment group based on the SS and will be presented in the same summary table as study medication compliance (see Section 6.1.8).

5.4.2 Adverse events

AEs will be collected from the time of signing the informed consent form (ICF) of PD0055 (including those AEs which are unresolved from PD0053) until the final SFU or EOT/ET visit and will be characterized as pre-treatment and treatment emergent according to intake of study medication. Since participants will start taking study medication in PD0053 and continue taking study medication in PD0055, treatment emergence will be determined according to first intake in PD0053 (regardless of which treatment they are taking in the feeder study). It is therefore not expected that many pre-treatment AEs will be reported during this study. Adverse events with a start date prior to the first dose of study medication will be defined as pre-treatment AEs. A treatment-emergent AE (TEAE) is defined as any AE with a start date on or after the first dose of treatment or any unresolved event already present before administration of treatment that worsens in intensity following exposure to the treatment in PD0055. Any AE with onset date later than the SFU visit will not be considered as treatment-emergent and therefore will not be included in the tabulations of TEAEs. Where dates are missing or partially missing, AEs will be assumed to be treatment-emergent, unless there is clear evidence to suggest otherwise. Missing or partially missing dates for AEs will be handled as described in Section 5.1.1.

An overview of the occurrence and incidence of TEAEs will be provided by treatment group. The overview will present individual occurrences as well as number and percentage of participants experiencing any of the following:

- Any TEAE
- Any Serious TEAE
- Participant discontinuation due to TEAEs
- Any drug related TEAEs
- Any severe TEAEs
- Permanent withdrawal of study medication due to TEAEs
- All deaths (AEs leading to death)
- Deaths (TEAEs leading to death)

Summaries of the occurrence and incidence of SAEs and TEAEs will be provided by MedDRA® SOC, HLT, PT and treatment group (including an "All participants" column which pools all groups together). These summaries will be provided for the following:

- Incidence of TEAEs
- Incidence of SAEs
- Incidence of serious TEAEs and serious TEAEs by relationship
- Incidence of fatal TEAEs and fatal TEAEs by relationship
- Incidence of TEAEs leading to discontinuation
- Incidence of non-serious TEAEs
- Incidence of TEAEs by maximum intensity
- Incidence of TEAEs by relationship and maximum relationship
- Incidence of non-serious TEAEs above reporting threshold of 5% of study participants
- Incidence of non-serious TEAEs above reporting threshold of 5% of study participants by relationship

Summary tables will contain counts of study participant, percentage of study participants in parentheses and the number of events where applicable. A participant who has multiple events in the same SOC, HLT and PT during a given treatment will be counted only once in the participant counts for that treatment, but all events will be included.

In summaries including relationship, the following relationships will be summarized: 'Not related' and 'Related'. Participants who experience the same event multiple times will be included in the most related category for tabulations by maximum relationship. Events with missing relationship will be considered as 'Related' for summary purposes but recorded as missing in the listings.

In summaries including intensity, the following intensity categories will be summarized: 'Mild', 'Moderate', 'Severe'. Participants who experience the same event multiple times will be included in the most severe category for tabulations by maximum intensity. Events with missing intensity will be considered as 'Severe' events for summary purposes but recorded as missing in the listings.

Adverse event summaries will be ordered by alphabetical SOC, alphabetical HLT and decreasing frequency of PT within SOC in the "All participants" group.

The following listings of AEs will be presented based on the ASPS:

- All AEs
- All Serious AEs
- Discontinuation due to AEs
- AEs leading to death
- COVID-19 Infections

All listings will be presented by treatment group and study participant and will include the onset date and outcome date of the event, the event duration (derived), time to onset (derived), pattern of event, intensity, relationship to study medication, action taken and outcome. AEs that led to discontinuation, TEAEs, AESIs and SAEs will be flagged where applicable.

5.4.2.1 Adverse events of special interest (AESI)

An AESI is any AE that a regulatory authority has mandated be reported on an expedited basis, regardless of the seriousness, expectedness, or relatedness of the AE to the administration of a UCB product/compound.

For minzasolmin (UCB0599), the following events require immediate reporting (within 24 hours regardless of seriousness) to UCB:

- Potential Hy's Law, defined as ≥3x upper limit of normal (ULN) alanine aminotransferase (ALT) or aspartate aminotransferase (AST) with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN alkaline phosphatase (ALP), with no alternative explanation for the biochemical abnormality (ie, without waiting for any additional etiologic investigations to have been concluded). Follow up information should then be reported if an alternative etiology is identified during investigation and monitoring of the participant.
- Hypersensitivity reactions (such as rash, angioedema, or anaphylaxis).

These AESIs will be identified based on MedDRA algorithms, standardized MedDRA queries (SMQs), HLTs and PTs as provided in Section 6.1.6 of this SAP.

AESIs will be flagged in the AE listings. Summaries of the occurrence and incidence of AESIs will be provided by MedDRA® SOC, HLT, PT and treatment group.

5.4.3 Additional safety assessments

5.4.3.1 Clinical safety laboratory assessments

Hematology, clinical chemistry, coagulation and urinalysis parameters will be assessed, see Table 5–4 below for a full list of which parameters will be analyzed. Other screening and laboratory tests to be carried out are also covered in this table. The schedule of activities (protocol Section 1.3) gives details on when these assessments are performed.

Hematology, clinical chemistry and coagulation laboratory results that were performed locally should be included in laboratory listings but not in summary tables and figures. Laboratory re-test results will be used in summary tables only if the original scheduled test result is not available, if the original result is available re-tests will be treated as unscheduled.

Table 5–4: Clinical laboratory assessments

Laboratory Assessments	Parameters		
Hematology	Platelet Count	RBC Indices: MCV MCH %Reticulocytes	WBC Count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	RBC Count		
	Hemoglobin		
	Hematocrit		

Table 5–4: Clinical laboratory assessments

Laboratory Assessments	Parameters			
Clinical Chemistry[1]	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (fasting at Screening and nonfasting at any visit thereafter)	Calcium	Alkaline phosphatase	Creatinine phosphokinase, Lactate dehydrogenase, serum aldolase, Cystatin C
Coagulation	International normalized ratio	Prothrombin time	aPTT	Fibrinogen
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Immunoglobulin E • HbA1c (as needed in study participants with type 2 diabetes mellitus) • Urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids, methadone, and benzodiazepines) • Urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential); a positive urine test should be confirmed with a blood test [a] • Serology (HIV antibody, hepatitis B surface antigen, and hepatitis C virus antibody) All study-required laboratory assessments will be performed by a central laboratory.			

Note: Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1.2 and Appendix 6 of the protocol. All events of ALT ≥3×upper limit of normal (ULN) and bilirubin ≥2×ULN (>35% direct bilirubin) or ALT ≥3×ULN and international normalized ratio (INR) >1.5, if INR measured, may indicate severe liver injury (possible Hy's Law) and must be reported as a SAE (excluding studies of hepatic impairment or cirrhosis).

[a] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC

5.4.3.1.1 Laboratory values over time

Laboratory variables will be grouped according to the laboratory function panel and categorized as normal, high or low, if applicable, based on the reference range supplied by the analytical laboratory.

For urinalysis, hematology, coagulation and clinical chemistry observed results for numeric variables at each post-PD0055 Baseline visit will be listed by treatment group, study participant and visit. Listings will flag values that fall outside of the normal range, and will include the reference ranges. Additionally, values that fall outside the reference ranges will be listed separately.

Clinical chemistry and hematology variables will be summarized descriptively by treatment group at each visit, for observed values. These descriptive statistics will only be calculated if at most one third of the individual data points at any visit are missing or not quantifiable. If 3 or less participants have data available at any visit, only n, minimum and maximum will be presented. Plots of mean will be presented by treatment group for all hematology and clinical chemistry laboratory variables. These plots will include all treatment groups overlaid on the same plot and will include error bars based on the SEM (ie, mean +/- SEM).

Measurements that are below the limit of quantification (BLQ) or above the limit of quantification (ALQ) will be presented as BLQ and ALQ in the listings. For the purpose of calculating changes from Baselines or for descriptive statistics, BLQ values will be imputed with half of the lower limit of quantification (LLOQ) and ALQ values will be imputed to the upper quantification limit (if applicable).

A separate listing will be produced for study participants with Elevated Liver Function Results. Elevated results are defined as results meeting the following criteria:

The listing will display all scheduled and unscheduled visit data for participants who meet at least one of the above criteria was fulfilled. A summary of study participants who meet the criteria for potential drug-induced liver injury (PDILI) will be presented and a figure presenting liver function results over time for participants who meet the potential Hy's Law Criteria will be produced.

Any additional laboratory variables not included in the outputs described previously will be listed separately.

5.4.3.2 Vital signs

The following vital signs measurements will be assessed throughout the study:

- Systolic and diastolic blood pressure (3 readings, all readings will be recorded in the eCRF and the average will be derived for analyses), blood pressure has to be measured in the supine and erect positions to assess autonomous dysregulation (Trendelenburg test);
- Pulse rate (3 readings, all readings will be recorded in the eCRF and the average will be derived for analyses).

All vital signs results will be listed by treatment group, study participant and visit. All 3 readings as well as the average will be included in the listing. The listing will include observed results, changes from Baseline (both PD0053 and PD0055 Baselines) and a flag for abnormal values. Changes from baselines will only be calculated and listed for the average of the 3 readings.

5.4.3.2.1 Vital sign values over time

Vital signs measurements (observed values and changes from both PD0053 and PD0055 Baseline) will be summarized by treatment group, measurement, position and visit. Only the average of the 3 readings will be used in summary tables.

The number and percentage of study participants with treatment-emergent markedly abnormal (TEMA)/potentially clinically significant (PCS) vital sign values as calculated by the criteria outlined in the table below will be summarized by treatment group and visit.

Table 5–5: TEMA/PCS criteria for vital signs

Variable	Unit	Low [ab]	High [ab]
Systolic blood pressure	mmHg	Value ≤90 and ≥20 decrease from Baseline	Value ≥180 and ≥20 increase from Baseline
Diastolic blood pressure	mmHg	Value ≤50 and ≥15 decrease from Baseline	Value ≥105 and ≥15 increase from Baseline
Pulse rate	Bpm	Value ≤50 and ≥15 decrease from Baseline	Value ≥120 and ≥15 increase from Baseline

bpm=beats per minute; PCS=potentially clinically significant; TEMA=treatment-emergent markedly abnormal.

[a] Both conditions must be satisfied for a measurement to be considered potentially clinically significant.

[b] These criteria will be summarized based on both PD0053 and PD0055 Baselines.

5.4.3.3 Electrocardiograms

All standard 12-lead ECG recordings will be taken as single reads, with the study participant resting in the supine position for at least 10 minutes before recording. Recordings can be repeated in triplicate if clinically indicated. The individual mean at each time point will be calculated if taken in triplicate and this mean will be used when summarising the data. This mean will be calculated based on the number of measurements for which data are provided.

The following ECG parameters will be reported:

- Heart rate (bpm)
- PR interval (ms)
- QRS duration (ms)
- QT interval (ms)
- QTcF interval (QT corrected for heart rate using Fridericia's formula) (ms)
- Investigator's conclusion on ECG profile

5.4.3.3.1 Electrocardiogram values over time

Individual measurements and the mean of any triplicate measurements will be listed. This listing will include changes from Baseline (for all individual measurements and means, for both PD0053 and PD0055 Baselines) and will be presented by treatment group and visit.

Observed values and changes from Baselines will be summarized by treatment group, ECG variable and visit. The mean change from each Baseline and its 95% CI for each ECG parameter

will also be summarized graphically over scheduled time points with all treatment groups overlaid on the same plot.

The following cut-points in QTcF will be summarized categorically (number and percentage of participants) by treatment group and visit.

For observed data:

- <450 msec (milliseconds)
- ≥450 to <480 msec
- ≥480 to <500 msec
- ≥500 msec

For changes from Baselines in QTcF:

- <30 msec
- ≥30 to <60 msec
- ≥60 msec

All ECG findings for the individual measurements will be listed separately.

5.4.3.4 Physical and neurological examination

Study participants with abnormalities in the physical and neurological examination will have this information listed including details of the abnormality.

5.4.3.5 Suicidal risk monitoring

The Columbia-Suicide Severity Rating Scale (C-SSRS; Posner et al, 2011) evaluations include suicidal ideation, intensity of ideation, suicidal behavior, and actual attempts and will be performed at all study visits (with the exception of screening and the day 10 phone call). Module of the questionnaire, time point, question and the associated response will be listed for all visits where this questionnaire is collected by treatment group. Only data where suicidal ideation/behaviour has been reported needs to be included in the listing.

5.5 Other analyses

5.5.1 Pharmacokinetics

Not applicable.

5.5.2 Pharmacodynamics

All pharmacodynamic estimands/analyses are covered in Section 5.3, see Table 1.1 for which objectives are estimating pharmacodynamic effects.

5.5.3 Biomarkers

Blood and CSF samples are collected for potential exploratory biomarker research which can include but are not limited to ribonucleic acid, protein, and metabolites.

The following blood samples will be collected at the time points specified in the schedule of activities (protocol Section 1.3):

- Blood samples for RNA biomarkers

- Blood samples for other biomarkers

A listing will be produced of these sample collection times for the SS. Analyses of this biomarker data are exploratory and will not be reported in the CSR.

CSF samples should be collected only after all other assessments of the visit have been performed.

The only biomarker data that will be summarized as part of the CSR are the CSF total ASYN marker data. These analyses are also considered exploratory, further details are given in Section 5.3.3.1). All collected samples may be used for research purposes focusing on method development and assay development or to better understand the association between biomarkers and disease progression, clinical phenotypes, or the correlation between different biomarkers or biomarkers and clinical scales. Collection of these samples will enable evaluation of biomarkers relative to disease biology and progression, IMP treatment and response, and/or mechanism of action of the IMP treatment.

5.6 Subgroup analyses

A Summary table will be produced by treatment group and visit, displaying the number and percentage of participants who are confirmed to have an atypical Parkinsonian disorder. The visit to be displayed is the visit where the information is collected, diagnosis is only reconfirmed at PD0055 Baseline and PD0055 Month 18. This table will also display the number and percentage of participants with each of the following atypical disorders (where available):

- Corticobasal degeneration (CBD): Tau (alpha-syn)
- Dementia with Lewy bodies (LBD): Alpha-syn deposition in cortical neurons
- Multiple system atrophy (MSA): Alpha-syn deposition in glial cells/oligodendrocytes
- Progressive supranuclear palsy (PSP): Tau
- Other disorder

A listing will be produced for all participants confirmed to have an atypical Parkinsonian disorder, displaying the date of diagnosis, the visit this information was collected at and the new diagnosis.

Additional subgroup analyses will be detailed in a PD0055 Exploratory Analysis Plan.

5.7 Interim Analyses

No interim analysis will be conducted.

5.8 Planned analysis at 18 months

Since the study was terminated early, this section is no longer applicable.

5.9 Data Monitoring Committee (DMC) or other review board

An independent DMC will conduct safety interim reviews of all available safety data. Available data from PD0055 will be reviewed at DMC meetings for **PD0053**.

This same DMC will review the safety data of PD0055 when the last participant from PD0053 transitioned into PD0055, and then every 18 months thereafter. The DMC will provide a

recommendation on the continuation of the study. The activities of the DMC will be described in a separate charter.

Available data from PD0055 will be reviewed at SMC meetings for **PD0053**.

The SMC will review the safety data of PD0055 when the last participant from PD0053 transitioned into PD0055, and then every 6 months thereafter. Meetings may be adjusted as required based on recruitment rates. Ad-hoc SMC meetings may be scheduled in addition. Details will be described in a separate charter.

6 SUPPORTING DOCUMENTATION

6.1 Appendix 1: Non-key analysis specifications

For all baseline characteristic, demographic and disposition summaries, treatment group will be assigned based on actual treatment received.

6.1.1 Baseline characteristics and demographics

6.1.1.1 Demographics

A listing of demographic characteristics will be presented for all study participants by treatment group, based on the ASPS. This will include year of birth, age (in years at PD0055 baseline), sex, country, race, ethnicity, height (in cm, from PD0053), weight (in kg, from PD0055 baseline) and body mass index (BMI). Most demographic data will not be recollected in PD0055, meaning that some information in this summary will be based on data collected at PD0053 baseline.

Body mass index in kg/m^2 is calculated based on the height (in m) and the weight (in kg) using the following formula (If height is in cm, then height will be converted to meters by dividing by 100):

$$BMI\ (kg/m^2) = weight\ (kg) / [height\ (m)]^2$$

The BMI will be reported to 1 decimal place and should be recalculated even if reported in the eCRF.

All demographic characteristics (except for year of birth) will be summarized by treatment group and for all study participants based on the SS. The summary of age will include descriptive statistics and categorical summaries, the latter based on requirements for European Union Drug Regulating Authorities Clinical Trials (EudraCT) and clinicaltrials.gov reporting.

For the EudraCT reporting, the categories will include:

- 18 to <65 years
- 65 to <85 years
- ≥ 85 years

For the clinicaltrials.gov reporting, the categories will include:

- ≤18 years
- 19 to <65 years

- ≥65 years

6.1.1.2 Baseline disease characteristics

The following PD0055 Baseline disease characteristics will be summarized by treatment group and gender for the SS, based on the data collected at the PD0055 Baseline Visit (Day 0, PD0053 Month 18):

- MDS-UPDRS Part I-III sum score, Part I, Part II score and Part III score
- Modified Hoehn and Yahr Stage
- MoCA
- Confirmation of Parkinson's diagnosis (yes or no)
- LEDD (at the time of Day 0, not cumulative)
- Duration of disease, calculated as follows:

$$Duration\ of\ disease\ (months) = \frac{(Date\ of\ PD0055\ Day\ 0 - Date\ of\ First\ Diagnosis + 1)}{30.3}$$

Partially missing date of first diagnosis will be imputed using the same rules as AE and concomitant medication dates defined in Section 5.1.1.

This data will also be listed based on the SS, by treatment group and participant.

6.1.1.3 Other baseline characteristics

Not applicable.

6.1.2 Protocol deviations

Important protocol deviations will be identified and classified by the deviation types in the IPD document, further details on how IPDs are defined and identified are given in Section 5.1.2.2.

A listing of all IPDs will be presented for all participants based on the SS and will include the deviation type and description. The number and percentage of participants in the SS with IPDs will be summarized by treatment group and overall, for each deviation type. Here treatment group assignment will be based on randomized treatment.

6.1.3 Medical history

Medical history and ongoing medical conditions that were not reported in PD0053 will be listed (based on the SS) by treatment group, MedDRA® system organ class (SOC) and preferred term (PT). The reported term, start date and stop date will be included in the listing.

Family medical history will be collected for any participants with potential drug-induced liver injury, this data will be listed for the SS.

6.1.4 Prior/concomitant medications

Prior medications

Prior medications include any medications that started prior to the date of first dose of study medication. This includes medications that started prior to the first dose and continued after.

Concomitant medications

Concomitant medications included medications with a start date between first dose of study medication (inclusive) and 3 days after the last dose of study medication (inclusive). Medications that started prior to the first dose but stopped after the first dose will be classified as both prior and concomitant.

Since participants will have started taking study medication in PD0053 it is not expected that many prior medications will be reported during PD0055. Prior and concomitant medications will be listed for the SS by treatment group and study participant, and will include WHODD Anatomical Main Group (Level 1), Pharmacological Subgroup (Level 3 term text) and PT. The reported term will be included in the listing. As this is an extension study, only concomitant medications will be summarized in a table. Prior medications which continued into the study period will also be classified as concomitant and included in the summary of concomitant medications. Medications with partially missing dates will be handled as described in Section 5.1.1 for prior/concomitant classification.

All tabulations will be sorted alphabetically by Level 1 term, alphabetical Level 3 term within Level 1 and decreasing frequency of PT in the 'All Participants' column.

Since ST intake is an efficacy variable in this study, separate listings and summaries will be made for these medications. These are covered in Section 5.3.2.

Concomitant medical procedures will be listed by treatment group and study participant for the SS. Additionally, a separate listing of concomitant COVID-19 vaccinations will be produced so that participants who are vaccinated during the study can be easily identified.

6.1.5 Data derivation rules

Not applicable. Any derived variables are defined as part of the analyses in Section 5.

6.1.6 AEs of special interest

The events defined as AESI for minzasolmin (UCB0599) in Section 5.4.2.1 will be summarized as follows:

- Hypersensitivity reactions (such as rash, angioedema, or anaphylaxis).
- Hepatic events and drug induced liver injury

Hypersensitivity reactions

These will include events based on the following SMQs:

- 'Hypersensitivity' (Narrow)
- 'Severe cutaneous adverse reaction' (Narrow)

Hepatic events and drug induced liver injury

Hepatic events will include:

- Events based on the SMQ = 'Drug related hepatic disorders – comprehensive search' (excluding sub SMQs = 'Liver neoplasms, benign [incl cysts and polyps]' and 'Liver neoplasms, malignant and unspecified'). All AEs should be included in the tabulation (including those considered both related and not related to the IMP) which code to a PT included in the Scope=Narrow group within each SMQ
- Potential Hy's Law cases will also be summarized separately in a table of liver function abnormalities (with adjudication for PDILI cases)

6.1.7 Potentially clinically significant criteria for safety endpoints

Not applicable. All clinically significant criteria for safety endpoints are described in their respective sections.

6.1.8 Compliance

At each in-clinic visit after study medication is dispensed, participants must return all unused study medication and empty study medication containers. Drug accountability must be done in the participant's presence in order to obtain explanations regarding discrepancies in compliance with the IMP dosing regimen. The drug accountability eCRF form collects the amount of study medication dispensed and returned, this will be used to determine whether or not a participant has taken the correct amount. IMP compliance will be calculated based on the total number of capsules as follows:

$$Compliance\ (\%) = (actual\ number\ of\ doses\ taken\ /\ planned\ number\ of\ doses) \times 100$$

As described in Section 5.4.1, exposure and compliance to IMP will be calculated based on exposure across both the feeder and extension study, only when participants are taking minzasolmin (UCB0599) (ie, ignoring placebo data). IMP compliance data will be summarized for the SS, both continuous and categorical summary statistics (by treatment group) will be presented. For categorical summaries, the number and percentage of participants who fall into the following categories will be presented:

- <80% compliant
- 80% to 120% compliant (inclusive)
- >120% compliant

This table will also present summary statistics for duration of exposure (see Section 5.4.1 for details).

In addition to the above calculations for compliance, the listing and summary of compliance data will also present compliance calculated under the assumption that no overdosing has occurred. In this case, when the actual number of doses taken by a participant is greater than the planned number of doses, compliance will be set to 100%. With this calculation we are assuming that the discrepancy between planned and actual dosing is due to drug accountability errors by the

participant (for example, lost medication) and not due to the participant taking more medication than needed. All cases where the compliance is set to 100% will be flagged in the data listings.

6.2 Appendix 2: Changes to protocol-planned analyses

The following changes to the protocol-planned analyses have been made in this SAP:

- Exploratory objective II will no longer be implemented.
- Objectives/endpoints that make use of the Delayed-start Arm will still be implemented however it will no longer be assumed that the Delayed-start participants will have received half of the cumulative dose of minzasolmin (UCB0599) compared with the Early-start participants.
- Cumulative LEDD will be summarized up to Month 24 post PD0053 baseline instead of at Month 36 post PD0053 baseline.
- A Full Analysis Set has been defined and will be used for the efficacy outputs.
- Disease duration has been removed from the statistical analysis of DaT-SPECT.
- A "PD0055 EOT/ET" timepoint has been defined for the DaT-SPECT data collected between PD0055 Month 6 and PD0055 Month 18 inclusive for use in the statistical analysis.
- Descriptive statistics will not be displayed by age category for DaT-SPECT, LEDD, WOQ-9 or MoCA.
- Annualized change from PD0053 Baseline will be summarized for DaT-SPECT.
- Sensitivity and supporting analysis have been removed for DaT-SPECT.
- Plots for Striatal sub-regions, CSF ASYN, Fatigue PRO, EQ-5D-5L, MDS-NMS and MoCA will not be produced
- Descriptive statistics will not be displayed by gender for CSF, FATIGUE-PRO, MDS-NMS, MDS-UPDRS, EQ-5D-5L or H&Y.
- Heat maps for WOQ-9 and Fatigue-PRO will not be produced.
- An additional subscore (ePD scubscore) has been added for MDS-UPDRS. Descriptive statistics will be produced for this subscore.
- For plots with error bars, SEM will be used in place of SD.
- The planned analysis at PD0055 Month 18 has been removed.

6.3 Appendix 3: Producing summaries by treatment group and overall

Table 6–1: Treatment groups to be presented in summary tables

Summary category	Analysis Set[c]	Treatment group					
		Screen Failures	Delayed-start UCB0599 [redacted]	Early-Start UCB0599 [redacted]	Early-start UCB0599 [redacted]	Pooled Early-start UCB0599	All participants
Participant disposition	SS (Actual)	X[a]	X	X	X		X
Important Protocol deviations	SS (Randomized)		X	X	X		X
Demographics and Baseline characteristics	SS (Actual)		X	X	X		X
Medical history and medications	SS (Actual)		X	X	X		X
Adverse Events	SS (Actual)		X	X	X		X
Other safety analyses	SS (Actual)		X	X	X		
IMP Compliance	SS (Actual)		X	X	X		
Efficacy endpoints	FAS (Randomized)		X	X	X	X[b]	

[a] Only reasons for screen failure and disposition of analysis sets will include screen failed participants.

[b] Sensitivity analyses for the primary and secondary estimands only.

[c] "Actual" refers to treatment predominantly received. "Randomized" refers to treatment group randomized to in PD0053.

Note: This table is a guide, the study TFL shells should be followed for which groups to display for each individual output.

6.4 Appendix 4: UPSIT percentile reference tables

Table 6–2: Male UPSIT percentile categories

	Age category (years)							
UPSIT score	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79
0	1	1	1	1	1	1	1	1
1	1	1	1	1	1	1	1	1
2	1	1	1	1	1	1	1	1
3	1	1	1	1	1	1	1	1
4	1	1	1	1	1	1	1	1
5	1	1	1	1	1	1	1	1
6	1	1	1	1	1	1	1	1
7	1	1	1	1	1	1	1	1
8	1	1	1	1	1	1	1	1
9	1	1	1	1	1	1	1	1
10	1	1	1	1	1	2	1	1
11	1	1	1	1	1	2	2	2
12	1	1	1	2	2	3	3	3.5
13	1	1	1	2	3	4	4	5
14	1	1	1	3	3	5	5	6
15	1	1	1	3	4	5	6	6
16	1	1	1	3	4	6	6	7.5
17	1	1	1	4	5	7	7	9.5
18	1	1	1	4	6	8	8	11
19	1	1	1	5	7	8	9	12.5

Table 6–2: Male UPSIT percentile categories

	Age category (years)							
UPSIT score	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79
20	1	1	1	5	8	9	10	14
21	1	1	2	6	9	10	11	15
22	1	1	3	6	10	11	12.5	16.5
23	1	1	3	7	11	12	14.5	19
24	1	1	4	7	12	13.5	16	21.5
25	1	1	5	8	13	15.5	18.5	24
26	5	1	5	9	14.5	17.5	21.5	27.5
27	6	5	6	11.5	16.5	20	24.5	31.5
28	6	6	7	13.5	19	23.5	29	36
29	6	7	9	16.5	22.5	28	34.5	41
30	8	10	10.5	20.5	27	33	41	46.5
31	11	10	15.5	25	32.5	39	47.5	52.5
32	13	11	22.5	31	39.5	47	55	60.5
33	17	15	30	40	49	55.5	64	70.5
34	21	22	38	51	59.5	65	72.5	78.5
35	26	31	50.5	62	69.5	75.5	81	85
36	43	49	66.5	74	80.5	85	88.5	91.5
37	53	58	81	84	90.5	93	94	96.5
38	75	70	91.5	91.5	96.5	97.5	97.5	99
39	91	90	97.5	97	99	99	99	100

Table 6–2: Male UPSIT percentile categories

	Age category (years)							
UPSIT score	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79
40	100	100	100	99.5	100	100	100	100

Table 6–3: Female UPSIT percentile categories

	Age category (years)							
UPSIT score	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79
0	1	1	1	1	1	1	1	1
1	1	1	1	1	1	1	1	1
2	1	1	1	1	1	1	1	1
3	1	1	1	1	1	1	1	1
4	1	1	1	1	1	1	1	1
5	1	1	1	1	1	1	1	1
6	1	1	1	1	1	1	1	1
7	1	1	1	1	1	1	1	1
8	1	1	1	1	1	1	1	1
9	1	1	1	1	1	1	1	1
10	1	1	1	1	1	1	1	1
11	1	1	1	1	1	1	2	1
12	1	1	1	1	2	2	2	2
13	1	1	1	1	2	3	3	3

Table 6–3: Female UPSIT percentile categories

	Age category (years)							
UPSIT score	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79
14	1	1	1	1	2	3	3	3
15	1	1	1	1	2	3	4	4
16	1	1	1	1	3	4	5	4.5
17	1	1	1	1	3	4	5	6
18	1	1	1	1	3	5	6	6
19	1	1	1	2	3	5	7	6.5
20	1	1	1	2	4	5	7	8
21	1	1	1	2	4	6	8	9
22	1	1	1	2	5	7	9	11
23	1	1	1	2	5	8	10	13.5
24	1	1	1	2	6	9	11	15
25	1	1	2	2	7	10	12.5	16.5
26	1	1	2	3	8	11	14	18.5
27	1	1	2	3	9	12.5	15.5	21.5
28	1	1	3	4	10	15	18.5	25
29	1	1	4	5.5	12	18.5	22	28.5
30	5	1	6	7.5	15	22.5	26.5	34
31	7	1	10.5	10	18.5	27	31.5	42
32	10	5	15	14	24	32.5	37.5	50
33	11	6	21	20.5	32	40	47	59.5

Table 6–3: Female UPSIT percentile categories

	Age category (years)							
UPSIT score	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79
34	15	6	31	30.5	42	50	59.5	70
35	17	16	44	45	55	63	73	80.5
36	26	22	60.5	62.5	70	77	84.5	90
37	39	49	78.5	78.5	84	88.5	93	96
38	60	70	91.5	89.5	94	95.5	98	98.5
39	84	87	97.5	96	98.5	98.5	100	100
40	100	100	100	99.5	100	100	100	100

6.5 Appendix 5: Key inclusion/exclusion criteria for the FAS definition

Participants who did not meet the key inclusion criteria (from PD0053) stated below will be excluded from the FAS:

Protocol Criterion 1a: Study participant's age at baseline must be >39 and <76 years, i.e. Study participant must be 40 to 75 years of age inclusive, at the time of signing the informed consent.

Protocol Criterion 2a: Study participant has PD, with a diagnosis made by a neurologist according to the 2015 Movement Disorder Society criteria within 2 years of Baseline Visit (including diagnosis during Screening), at the time of signing the informed consent.

In practice, this be implemented by excluding participants with a disease duration greater than 27 months (3 months over the protocol-defined threshold).

Protocol Criterion 4b: A Screening DaT-SPECT, or a historical DaT-SPECT within 3 months of the Screening Visit (V1) that has been qualified by the central reader, shows evidence of dopamine transporter deficit per study requirements (refer to Section 4.2 of the protocol) and as determined by a central reader.

Protocol Criterion 6a: Study participant is in the ≤2.5 modified Hoehn and Yahr stage at Screening.

Criterion 7a. Study participant has never taken medications for the treatment of motor symptoms of PD and is not expected to require starting ST with a high likelihood in the next 6 months as far as clinical judgement allows.

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