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

PROTOCOL PD0055 AMENDMENT 4

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

Sponsor:
UCB Biopharma SRL
Allée de la Recherche 60
1070 Brussels
BELGIUM

Regulatory agency identifying numbers:

EU CT Number:	2022-500424-30-00
EUDAMED Number:	Not applicable
IND Number:	141003
IDE Number:	Not applicable
NCT Number:	NCT05543252

Confidential Material

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document History		
Document	**Date**	**Type of amendment**
Amendment 4	09 Oct 2024	Substantial
Amendment 3	18 Sep 2023	Substantial
Amendment 2	30 Jun 2023	Substantial
Amendment 1	07 Nov 2022	Not applicable
Original Protocol	29 Apr 2022	Not applicable

Amendment 4 (09 Oct 2024)

Overall Rationale for the Amendment

PD0055 Protocol Amendment 4 was completed to extend the study duration by an additional 30 months to Month 60 to collect longer term efficacy, safety, and tolerability data.

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Section # and name	Description of change	Brief rationale
Title page	NCT number was added.	To complete the table with regulatory agency identifying numbers.
Global	Timepoints of analysis and references to the EOT were updated throughout: • Section 1.1 'Overall design' and 'Treatment groups and duration' • Objectives and endpoints tables (refer to changes described for Section 1.1 and Section 3 below) • Section 4.1 Overall design (13th paragraph) • Section 9.3 Planned efficacy/outcome analyses (refer to changes described below)	To reflect the extended study duration to Month 60.
Global	Where the external control arm is described, 'external benchmark/reference data' was changed to 'external real-world data.'	To provide clarification for the external control arm in the study.

Section # and name	Description of change	Brief rationale
Section 1.1 Synopsis - Objectives and endpoints and Section 3 OBJECTIVES AND ENDPOINTS	PD0055 Month 60 was added as timepoint of analysis for the Primary Efficacy Endpoint (DaT-SPECT whole striatum SBR) and the Secondary Efficacy Endpoint (cumulative LEDD).	To reflect the extended study duration to Month 60.
	Under Exploratory objectives I, II, and III, the text in **bold** was added to the following endpoints: • MDS-UPDRS Part II subscale (or selected items **and emerging symptoms**) • MDS-UPDRS Part III subscale (or selected items/**subscore**)	To clarify the exploratory efficacy endpoints following PD0053 Protocol Amendment 6.
	The wording of the Exploratory objective II. Effectiveness was revised for clarity: 'Pharmacodynamic effect' was reworded to 'effectiveness.' In addition, '3-years post diagnosis and beyond' was revised to 'beyond 18-months duration of PD0053' to account for participants who may have less than 3 years PD duration when enrolled in PD0055.	To clarify the exploratory objective using more appropriate wording and to provide a more objective and clearer description of the population and period evaluated.
	In the list of 'Exploratory Endpoints (Clinical Outcomes)' for Exploratory objectives I, II, and III, the MDS-UPDRS Part III-related endpoint was revised to remove the reference to ON and OFF states.	To align with what is actually being done in practice during the study.
	In the list of 'Exploratory Endpoints (Clinical Outcomes)' for Exploratory objective II. Effectiveness, the MoCA was added below LEDD.	The MoCA is already included as an endpoint in PD0055 Exploratory objective I. It is added in Exploratory objective II to complete the list of endpoints that support this exploratory study objective.

Section # and name	Description of change	Brief rationale
Section 1.1 Synopsis - Objectives and endpoints and Section 3 OBJECTIVES AND ENDPOINTS	The wording of the Exploratory objective III. Efficacy was revised for clarity (**bold** text added): To estimate the pharmacodynamic effects of **Early-start** minzasolmin (UCB0599) 360mg versus **Early-start** minzasolmin (UCB0599) 180mg on the clinical course of PD, need for ST and brain pathophysiology in participants originally diagnosed with new onset PD	To clarify the exploratory objective.
	PD0055 Month 60 was added as timepoint of analysis for the Exploratory objective IV. Atypical Parkinsonism.	To reflect the extended study duration to Month 60.
Section 1.1 Synopsis - Overall design	In the second paragraph, in the fourth sentence summarizing the exploratory study objectives and related to objectives assessing methodology, 'identification of endpoints not affected by ST' was changed to 'identification of novel endpoints.' The same change was made in Section 4.1 Overall design.	To implement more appropriate wording.
	In the fourth paragraph, the description of the effectiveness estimation using external real-world data was revised.	To clarify how effectiveness will be evaluated and to align with the updated wording of Exploratory objective II. Effectiveness.
Section 1.1 Synopsis - Number of participants	Enrollment and expected study completion numbers at PD0055 Month 18 and Month 60 were updated. The same changes were implemented in Section 4.1 Overall design and Section 9.8 Determination of sample size.	To update participant numbers after PD0053 study completion.
Section 1.2 Schema	Figures were updated.	To reflect the extended study duration to Month 60.
	The following note was added below Figure 1-3 Low dose-arm design: Note: Data of study participants transitioning from the placebo arm to the 360mg arm will not be part of the comparison of the 360mg and 180mg treatment arms.	To clarify the planned comparisons.
	The note with an asterisk (*) below Figure 1-4 External real-world data was revised.	To align with updated wording of Exploratory objective II. Effectiveness.

Section # and name	Description of change	Brief rationale
Section 1.2 Schema	An additional note was added below Figure 1-4 External real-world data: Note: Data of study participants transitioning from the placebo or 180mg arm to the 360mg arm will not be part of the comparison of the 360mg treatment arm to the external reference arm.	To clarify the planned comparisons.
Section 1.3 Schedule of Activities	V11 (M36), V12 (M42), V13 (M48), V14 (M54), and V15/EOT/ET (M60) were added.	To reflect the extended study duration to Month 60.
	'EOT/ET' was moved from V10 to V15.	To reflect that V15 (Month 60 in PD0055) is now the end-of-treatment visit.
	A new informed consent procedure was added for study participants to provide written consent to participate in the optional in-study patient interviews (applicable to US and UK sites only).	To implement a change from local protocol amendments 3.2 (UK) and 3.3 (US) dated Jun 2024 in the global protocol amendment 4.
	A new assessment was added: 'Optional in-study patient interviews (US and UK only)'	To implement a change from local protocol amendments 3.2 (UK) and 3.3 (US) dated Jun 2024 in the global protocol amendment 4.
	A sentence was added to footnote 'i' to clarify that the DaT-SPECT at V8 (M18) and V15/EOT/ET (M60) can be done within a time window of ±28 days.	To clarify protocol procedures.
	The letter 'k' was added to the new MoCA assessments at V11 (M36) and V15/EOT/ET (M60). Footnote 'k' was revised to specify the MoCA versions to be used at the different visits.	To clarify the MoCA version to be used at the new timepoints of assessment.
	New footnote 's' was added to further clarify the timepoint of assessment for the in-study patient interviews (applicable to US and UK sites only).	To implement a change from local protocol amendments 3.2 (UK) and 3.3 (US) dated Jun 2024 in the global protocol amendment 4.

Section # and name	Description of change	Brief rationale
Section 4.1 Overall design	In the seventh paragraph, the description of the effectiveness estimation using external real-world data was revised. The following sentence was removed: ~~This is subject to detailed feasibility assessment of external data sources to evaluate their suitability to address the Exploratory Objective II (refer to Section 3).~~	To clarify how effectiveness will be evaluated and to align with the updated wording of Exploratory objective II. Effectiveness.
	The last sentence in the section was removed: ~~The Sponsor may decide to extend the treatment duration beyond the 30-month period via a protocol amendment depending on the drug development strategy.~~	To remove text that no longer applies.
Section 4.2 Scientific rationale for study design	The fifth paragraph describing the exploratory objective III (of efficacy) was revised.	To clarify the study objective.
Section 6.5.2 Prohibited concomitant treatments (medications and therapies)	The last sentence below the list of treatments not allowed during the 50 days before DaT-SPECT imaging was removed: ~~If a protocol deviation is to occur, a Washout Period of 50 hours (or 5 half-lives) must be completed prior to performing the DaT-SPECT measurement.~~	To remove redundancy.
Section 6.9 Digital Health Technology	The title of the last subsection 'End of study' was changed to 'End of Digital Health Technology use.'	To reflect that end of Digital Health Technology use at M18 is no longer at the end of the study.
Section 8.1.1.1 DaT-SPECT	In the second paragraph, the number of injections, maximum total effective dose, and risk level (ICR62) were updated.	To reflect the additional DaT-SPECT at Month 60.
Section 8.1.3 In-study patient interviews (US and UK only)	New section was added to describe the optional in-study patient interviews (applicable to US and UK sites only). The subsequent section was renumbered to 8.1.4 Koneksa Neuroscience Toolkit.	To implement a change from local protocol amendments 3.2 (UK) and 3.3 (US) dated Jun 2024 in the global protocol amendment 4.
Section 8.3.8 Safety reporting for in-study patient interviews (US and UK only)	New section was added to clarify the safety reporting for events reported during in-study patient interviews (applicable to US and UK sites only).	To implement a change from local protocol amendments 3.2 (UK) and 3.3 (US) dated Jun 2024 in the global protocol amendment 4.

Section # and name	Description of change	Brief rationale
Section 9.2.1 Descriptive statistics and modeling	The bullets in the third paragraph were revised to add the analysis at PD0055 Month 60. The last sentence in the section was revised to note that analyses will be adjusted for gender and age but no longer for disease duration, in line with the updated PD0053 analysis.	To reflect the extension of the study to Month 60, clarify the planned comparisons, and align with updates to the PD0053 analysis.
Section 9.3 Planned efficacy/outcome analyses	Throughout the section, lists of analysis timepoints were replaced by "all available timepoints" for the following assessments: • DaT-SPECT • WOQ-9 • MoCA • FATIGUE-PRO • MDS-NMS • MDS-UPDRS Parts I, II, III subscales or selected items • MDS-UPDRS Parts I-III sum score • Early PD Function Slowness and Early PD Mobility PROs • CSF ASYN • EQ-5D-5L	To simplify the description in the protocol.
	References to the 'PD0055 Exploratory Analysis Plan' were updated to 'PD0055 Exploratory **Efficacy** Analysis Plan' throughout.	Minor clarification.
Section 9.3.1.1 DaT-SPECT	Text under 'Main analytical approach' was updated.	To add the analysis at PD0055 Month 60 and to align with updates to the PD0053 analysis.
	The last sentence in the section was revised (strikethrough text removed; **bold** text added): Any ~~noise-to-signal improvement~~ exploratory investigations **based on advanced image analysis methods** will be detailed in a separate PD0055 Analysis Plan.	To clarify the planned exploratory analyses.
Section 9.3.2.1 LEDD	Timepoints of analysis were updated throughout.	To add the analysis at PD0055 Month 60.

Section # and name	Description of change	Brief rationale
Section 9.3.3.2 MoCA	References to MoCA versions were removed; these are provided in footnote 'k' below the Schedule of Activities.	To reduce redundancy with other protocol sections.
Section 9.3.4.2 Use of external real-world data	Section was revised to update the description of the external, real-world comparator arm.	To clarify the use of external real-world data to evaluate the effectiveness of minzasolmin versus SoC on clinical and QoL outcomes.
Section 9.4.2 Other analyses	A sentence was added to describe the analyses related to the in-study patient interviews (US and UK only).	To implement a change from local protocol amendments 3.2 (UK) and 3.3 (US) dated Jun 2024 in the global protocol amendment 4. Text from the local amendments was revised for clarity.
Section 9.7 Planned analysis and data monitoring	Section was revised to add the PD0055 Month 60 analysis and clarify that additional analyses may be conducted.	To reflect the extension of the study to Month 60 and to clarify that additional analyses may be done for publication purposes and to support regulatory interactions.
Section 10.1.6 Dissemination of clinical study data	Section was revised to update the description of results posting on public registries.	To reflect current UCB standard for results reporting.
Section 10.6 Appendix 6: Liver safety – suggested actions and follow-up assessments	Abbreviations and footnotes below Table 10-1: Phase 2 liver chemistry stopping criteria and follow-up assessments were added back.	Correction (text was unintentionally removed in protocol amendment 3)
Section 10.9 Appendix 9: Country-specific requirements	Section 10.9.1 was added to provide an overview of the changes from local protocol amendments 3.2 (UK) and 3.3 (US).	To summarize country-specific protocol changes applicable in the UK and US.
Section 11 REFERENCES	New reference cited in Section 8.1.3 was added.	Minor administrative change.
Throughout	Minor editorial and document formatting revisions.	Minor, therefore have not been summarized.

SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
Fax	**Europe and Rest of the World:** +32 2 386 24 21 **US and Canada:** +1 800 880 6949 or +1 866 890 3175
Email	**Global:** DS_ICT@ucb.com (for interventional clinical studies)

REPORTING OF ADVERSE DEVICE EFFECTS (SERIOUS AND NONSERIOUS) AND DEVICE DEFICIENCIES

Reporting of adverse device effects (serious and nonserious) and device deficiencies for non-UCB devices used in the study (24h)	
Email	Complete paper Adverse Event and Device Deficiency Form and email to help@koneksahealth.com. Note: Device deficiencies for non-UCB devices should not be captured in the electronic data collection tool.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol title:

A dose-blinded extension study to evaluate the long-term efficacy, safety, and tolerability of minzasolmin (UCB0599) in study participants with Parkinson's disease

Short title:

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

Rationale:

Minzasolmin (UCB0599) is an orally available inhibitor of alpha-synuclein (ASYN) misfolding and downstream aggregation. Aggregated forms of ASYN are the hallmark fibrillar protein deposits in Parkinson's disease (PD) and other synucleinopathies, and evidence suggests that it is the misfolded forms of ASYN that propagate through the central nervous system (CNS) during disease progression. These accumulations of ASYN containing neuronal inclusions form Lewy bodies and Lewy neurites.

A first-in-human study, UP0030, using minzasolmin (UCB0599), conducted in healthy elderly participants (defined as ≥55 to ≤75 years of age), provided the safety, tolerability, and pharmacokinetics (PK) information for single dose exposures up to 450mg and multiple dose exposures of 180mg/day for up to 21 days. The first study in the target population, UP0077, provided safety, tolerability, and PK information for multiple dose exposures of 180mg/day and 360mg/day for 28 days in study participants with PD. An ongoing double-blind, placebo-controlled, randomized, Phase 2a study, PD0053, in participants with early-stage PD, is designed to provide proof-of-concept for the efficacy of the ASYN misfolding inhibitor minzasolmin (UCB0599) at doses of 180mg/day or 360mg/day in slowing disease progression and to instruct later stage development.

PD0055, a dose-blinded extension study of PD0053, is designed to provide further evidence and understanding of the efficacy, safety, and tolerability of minzasolmin (UCB0599) in slowing the progression of PD study participants who have completed 18 months of treatment in PD0053.

Objectives and endpoints

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 and Month 60 **Exploratory Efficacy Endpoints** • DaT-SPECT striatal sub-regions SBR • CSF total ASYN

Objectives	Endpoints
	• 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 and Month 60 **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 PD 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 and emerging symptoms) • MDS-UPDRS Part III subscale (or selected items/subscore) • Modified H&Y • FATIGUE-PRO • Early PD Function Slowness PRO • Early PD Mobility PRO **Exploratory Endpoints (Other)** • Koneksa Neuroscience Toolkit

Objectives	Endpoints
II. Effectiveness: To estimate the effectiveness of minzasolmin (UCB0599) versus SoC on clinical outcomes and QoL beyond 18 months duration of PD0053, using external real-world 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 and emerging symptoms) • MDS-UPDRS Part III subscale (or selected items/subscore) • Modified H&Y
III. Efficacy: To estimate the pharmacodynamic effects of Early-start minzasolmin (UCB0599) 360mg versus Early-start minzasolmin (UCB0599) 180mg 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 and emerging symptoms) • MDS-UPDRS Part III subscale (or selected items/subscore) • Modified H&Y • FATIGUE-PRO • Early PD Function Slowness PRO • Early PD Mobility PRO **Exploratory Endpoints (Biomarkers)** • DaT-SPECT whole striatum SBR (and striatal sub-regions SBR) • CSF total ASYN • CSF ASYN oligomers/seeding capacity

Objectives	Endpoints
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 and Month 60	**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:

- 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

Overall 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.

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 secondary efficacy objective of the extension study is to estimate the pharmacodynamic effects of minzasolmin (UCB0599) on the need for symptomatic treatment (ST) in participants originally diagnosed with new onset PD, taking advantage of the Early-start versus Delayed-start arms design. The secondary safety objective of the study is to assess the safety and tolerability of minzasolmin (UCB0599) in participants originally diagnosed with new onset PD and will include recording of incidences of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and TEAEs leading to withdrawal from study. The exploratory objectives of the study include assessments of methodology (ie, identification of novel endpoints), effectiveness (strengthening of the patient value stemming from impact on key motor outcomes), efficacy (estimation of pharmacodynamic effects of minzasolmin (UCB0599) that may inform any dose-response modeling), and identification of participants with Atypical Parkinsonism to perform sensitivity analyses.

A study overview of PD0055 is provided in Figure 1-1. The study will comprise 3 embedded designs. The active arm will be considered to be minzasolmin (UCB0599) 360mg. Two comparator arms will be used to provide further insight into the efficacy of minzasolmin (UCB0599):

- Delayed-start arm (360mg) (Figure 1-2)
- Low-dose arm (180mg) (Figure 1-3)

In addition, external real-world data (where available) will be used to estimate the effectiveness of minzasolmin (UCB0599) (selected endpoints only) versus the SoC beyond the 18 months duration of the feeder study PD0053 (Figure 1-4).

The primary and secondary efficacy objectives of the study will make use of the Delayed-start arm.

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 investigational medicinal product (IMP) for up to 60 months. Participants who have been treated with minzasolmin (UCB0599) 180mg/day during PD0053 will continue to receive minzasolmin (UCB0599) 180mg/day in extension study PD0055. Participants who have been treated with minzasolmin (UCB0599) 360mg/day during PD0053 will continue to receive minzasolmin (UCB0599) 360mg/day in PD0055. Participants who received placebo during PD0053 will receive minzasolmin (UCB0599) 360mg/day in PD0055.

After completing, at the minimum, the Month 18 Visit in PD0055, participants will be switched to the best dose, as determined from the results of PD0053. All study participants and Investigators will remain blinded to treatment/dose received in PD0053 and PD0055 at least until all participants have completed the Month 18 assessments in PD0055. Thereafter, PD0055 will be open label.

Throughout the study, data will be reviewed on an ongoing basis by a Data Monitoring Committee (DMC) and a Safety Monitoring Committee (SMC).

PD0055 aims to provide further evidence and understanding of the efficacy, safety, and tolerability of minzasolmin (UCB0599) in study participants who completed 18 months of treatment in PD0053.

Number of participants

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 adverse events (AEs) upon initiating minzasolmin (UCB0599) 360mg/day (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 and 314 participants would be expected to reach PD0055 Month 18 and Month 60, respectively.

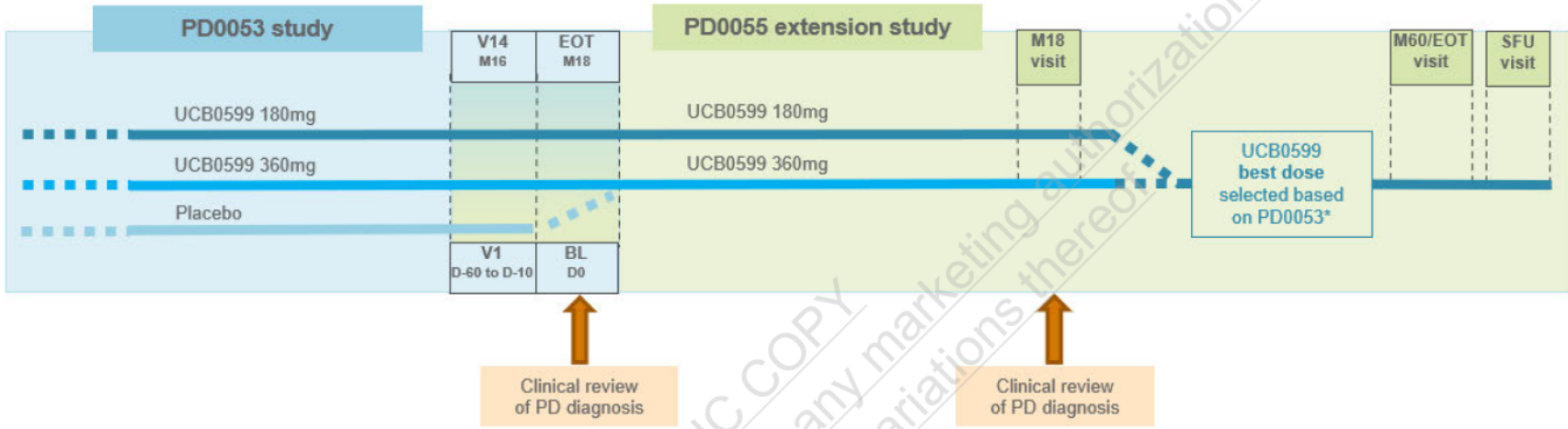
Treatment groups and duration

PD0055 includes a Screening Period of up to 60 days (overlapping with the Treatment Period of PD0053), followed by a Treatment Period of 60 months and a Safety Follow-up (SFU) Visit 30 days after the last dose.

Participants will receive either minzasolmin (UCB0599) 180mg/day (90mg twice daily [BID]) or minzasolmin (UCB0599) 360mg/day (180mg BID) until they reach Month 18. Once the best dose is defined based on results from PD0053, all participants in PD0055 will be transitioned to that dose as long as they have completed their Month 18 Visit.

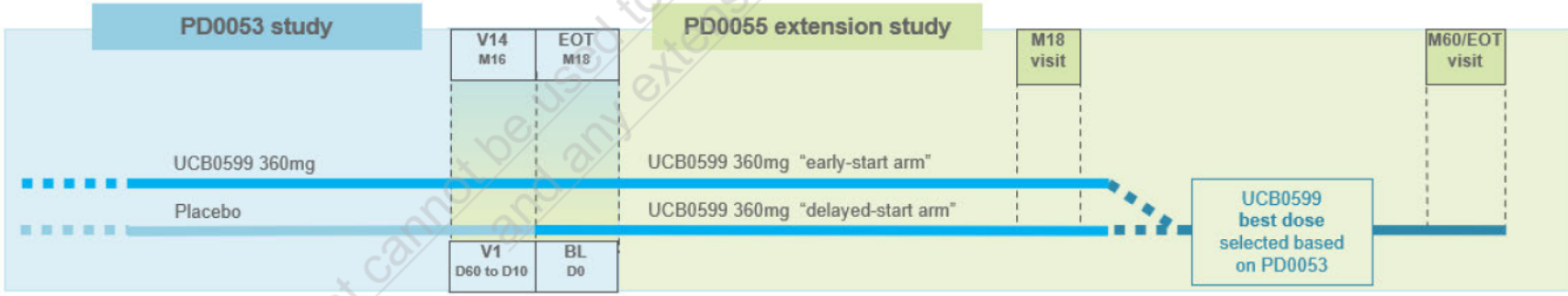
1.2 Schema

Figure 1-1: Study overview



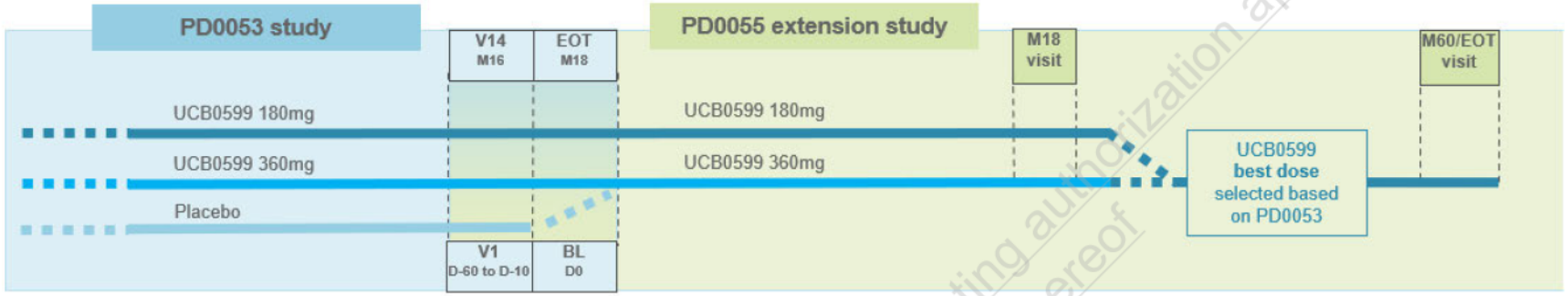
BL=PD0055 Baseline Visit; D=day; EOT=End of Treatment; M=month; PD=Parkinson's disease; SFU=Safety Follow-up Visit; V=visit
* Study participants will be switched to the best dose once the dose has been selected, but not before they completed the M18 Visit.

Figure 1-2: Delayed-start arm design



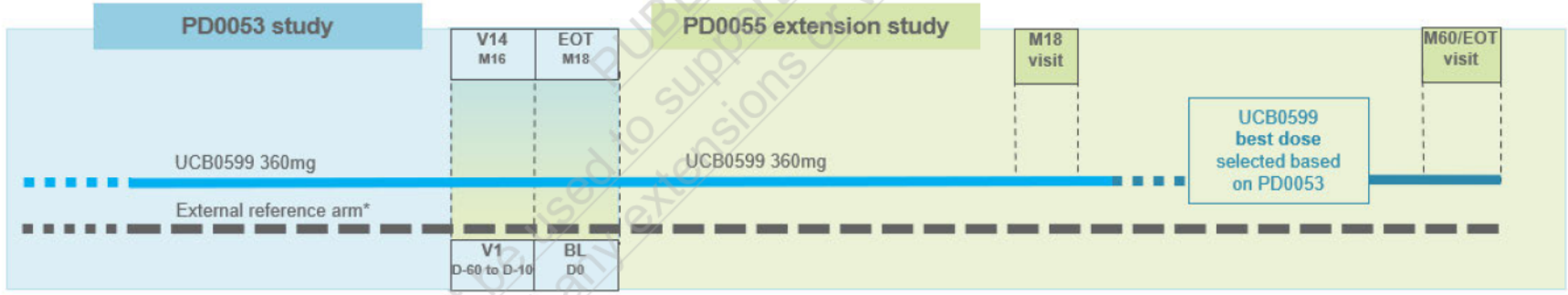
BL=PD0055 Baseline Visit; D=day; EOT=End of Treatment; M=month; V=visit

Figure 1-3: Low-dose arm design



BL=PD0055 Baseline Visit; D=day; EOT=End of Treatment; M=month; V=visit
Note: Data of study participants transitioning from the placebo arm to the 360mg arm will not be part of the comparison of the 360mg and 180mg treatment arms.

Figure 1-4: External real-world data



BL=PD0055 Baseline Visit; D=day; EOT=End of Treatment; M=month; PD=Parkinson's disease; V=visit
* External real-world data (where available) will include observational data for the same PD population.
Note: Data of study participants transitioning from the placebo or 180mg arm to the 360mg arm will not be part of the comparison of the 360mg treatment arm to the external reference arm.

1.3 Schedule of Activities

	Scr	Treatment Period																
	V1[a]	V2[b]	V3	V4	V4a[m]	V5	V5a[m]	V5b[m]	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15/ EOT/ ET	SFU
		BL	PC	M1	M2	M3	M4	M5	M6	M12	M18	M24	M30	M36	M42	M48	M54	M60	
Procedure	Day -60 to Day -10	Day 0	Day 10 ±2d	Day 30 ±5d	Day 60 ±5d	Day 90 ±5d	Day 120 ±5d	Day 150 ±5d	Day 180 ±7d	Day 360 ±14d	Day 540 ±14d	Day 720 ±14d	Day 900 ±14d	Day 1080 ±14d	Day 1260 ±14d	Day 1440 ±14d	Day 1620 ±14d	Day 1800 ±14d	30d after last dose
Informed consent	X																		
Informed consent for optional in-study patient interviews (US and UK only)[s]			X																
Verification of inclusion/ exclusion criteria	X	X																	
Withdrawal criteria[c]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs[d]		X		X		X			X	X	X	X	X	X	X	X	X	X	X
Weight		X																	
Physical examination		X		X		X			X	X	X	X	X	X	X	X	X	X	X
Neurological examination		X		X		X			X	X	X	X	X	X	X	X	X	X	X
Adverse events[e]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Procedure	Scr	Treatment Period																
	V1[a]	V2[b]	V3	V4	V4a[m]	V5	V5a[m]	V5b[m]	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15/ EOT/ ET	SFU
		BL	PC	M1	M2	M3	M4	M5	M6	M12	M18	M24	M30	M36	M42	M48	M54	M60	
	Day -60 to Day -10	Day 0	Day 10 ±2d	Day 30 ±5d	Day 60 ±5d	Day 90 ±5d	Day 120 ±5d	Day 150 ±5d	Day 180 ±7d	Day 360 ±14d	Day 540 ±14d	Day 720 ±14d	Day 900 ±14d	Day 1080 ±14d	Day 1260 ±14d	Day 1440 ±14d	Day 1620 ±14d	Day 1800 ±14d	30d after last dose
Koneksa Neuroscience Toolkit safety		X	X	X	X	X	X	X	X	X	X								
C-SSRS		X		X		X			X	X	X	X	X	X	X	X	X	X	X
Concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sampling for chemistry, hematology, coagulation		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis		X		X		X			X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[f]		X		X					X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test[g]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contact IRT	X	X				X			X	X	X	X	X	X	X	X	X	X	
IMP dispensing/ return[h]		X				X			X	X	X	X	X	X	X	X	X	X	
DaT-SPECT[i]		X									X							X	

Procedure	Scr	Treatment Period																
	V1[a]	V2[b]	V3	V4	V4a[m]	V5	V5a[m]	V5b[m]	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15/ EOT/ ET	SFU
		BL	PC	M1	M2	M3	M4	M5	M6	M12	M18	M24	M30	M36	M42	M48	M54	M60	
	Day -60 to Day -10	Day 0	Day 10 ±2d	Day 30 ±5d	Day 60 ±5d	Day 90 ±5d	Day 120 ±5d	Day 150 ±5d	Day 180 ±7d	Day 360 ±14d	Day 540 ±14d	Day 720 ±14d	Day 900 ±14d	Day 1080 ±14d	Day 1260 ±14d	Day 1440 ±14d	Day 1620 ±14d	Day 1800 ±14d	30d after last dose
Koneksa Neuroscience Toolkit consent and training[n]	X																		
Deployment of Koneksa Neuroscience Toolkit		X																	
Detailed check on Koneksa Neuroscience Toolkit usage and re-training			X	X															
Active Koneksa Neuroscience Toolkit tests on cell phone at home		X (weekly - once in "OFF" state and once in "ON" state for participants on ST medication and once weekly for participants not on ST medication)																	
Passive Koneksa Neuroscience Toolkit data collection via smartwatch		X (once weekly for approximately 24 hours)																	

Procedure	Scr	Treatment Period																
	V1[a]	V2[b]	V3	V4	V4a[m]	V5	V5a[m]	V5b[m]	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15/ EOT/ ET	SFU
		BL	PC	M1	M2	M3	M4	M5	M6	M12	M18	M24	M30	M36	M42	M48	M54	M60	
	Day -60 to Day -10	Day 0	Day 10 ±2d	Day 30 ±5d	Day 60 ±5d	Day 90 ±5d	Day 120 ±5d	Day 150 ±5d	Day 180 ±7d	Day 360 ±14d	Day 540 ±14d	Day 720 ±14d	Day 900 ±14d	Day 1080 ±14d	Day 1260 ±14d	Day 1440 ±14d	Day 1620 ±14d	Day 1800 ±14d	30d after last dose
Return of Koneksa Neuroscience Toolkit											X[o]		X[p]						
LEDD (cumulative)		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
WOQ-9[q]		X							X	X	X			X				X	
MDS-UPDRS Part I		X							X	X	X	X	X	X	X	X	X	X	
MDS-UPDRS Part II		X							X	X	X	X	X	X	X	X	X	X	
MDS-UPDRS Part III		X							X	X	X	X	X	X	X	X	X	X	
MDS-UPDRS Part IV		X									X	X	X	X	X	X	X	X	
Modified H&Y		X							X	X	X	X	X	X	X	X	X	X	
MDS-NMS		X							X	X	X			X				X	
MoCA		X[j]									X[k]			X[k]				X[k]	
Early PD function slowness PRO		X							X	X	X	X	X	X	X	X	X	X	
Early PD mobility PRO		X							X	X	X	X	X	X	X	X	X	X	

Procedure	Scr	Treatment Period																
	V1[a]	V2[b]	V3	V4	V4a[m]	V5	V5a[m]	V5b[m]	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15/ EOT/ ET	SFU
		BL	PC	M1	M2	M3	M4	M5	M6	M12	M18	M24	M30	M36	M42	M48	M54	M60	
	Day -60 to Day -10	Day 0	Day 10 ±2d	Day 30 ±5d	Day 60 ±5d	Day 90 ±5d	Day 120 ±5d	Day 150 ±5d	Day 180 ±7d	Day 360 ±14d	Day 540 ±14d	Day 720 ±14d	Day 900 ±14d	Day 1080 ±14d	Day 1260 ±14d	Day 1440 ±14d	Day 1620 ±14d	Day 1800 ±14d	30d after last dose
FATIGUE-PRO		X							X	X	X	X	X	X	X	X	X	X	
EQ-5D-5L		X							X	X	X	X	X	X	X	X	X	X	
Optional in-study patient interviews (US and UK only)[s]			X																
UPSIT[r]				X															
CSF sampling (optional)[l]		X									X		X					X	
Blood sampling for RNA biomarkers		X									X		X					X	
Blood sampling for other biomarkers		X									X		X					X	

BL=Baseline Visit; BP=blood pressure; C-SSRS=Columbia-Suicide Severity Rating Scale; COVID-19=Coronavirus Disease-2019; CSF=cerebrospinal fluid; d=days; DaT-SPECT=Dopamine Transporter Imaging With Single Photon Emission Computed Tomography; ECG=electrocardiogram; eCRF=electronic Case Report form; EOT=End of Treatment; EQ-5D-5L=Euro Quality of life 5-Dimensions 5-Level; ET=Early Termination; H&Y=Hoehn and Yahr; IMP=investigational medicinal product; IRT=interactive response technology; LEDD=Levodopa Equivalent Daily Dose; M=month; MDS-NMS=Movement Disorder Society Non-Motor Rating Scale; MDS-UPDRS=Movement Disorder Society Unified Parkinson's Disease Rating Scale; MoCA=Montreal Cognitive Assessment; PC=Phone call; PD=Parkinson's disease; PRO=patient-reported outcome; RNA=ribonucleic acid; Scr=Screening; SFU=Safety Follow-up; ST=symptomatic treatment; UPSIT=University of Pennsylvania Smell Identification Test; V=Visit; WOQ-9=Wearing-off Questionnaire–9

[a] Visit 1 may coincide with V14 of PD0053.

Procedure	Scr	Treatment Period																	
	V1[a]	V2[b]	V3	V4	V4a[m]	V5	V5a[m]	V5b[m]	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15/ EOT/ ET	SFU
		BL	PC	M1	M2	M3	M4	M5	M6	M12	M18	M24	M30	M36	M42	M48	M54	M60	
	Day -60 to Day -10	Day 0	Day 10 ±2d	Day 30 ±5d	Day 60 ±5d	Day 90 ±5d	Day 120 ±5d	Day 150 ±5d	Day 180 ±7d	Day 360 ±14d	Day 540 ±14d	Day 720 ±14d	Day 900 ±14d	Day 1080 ±14d	Day 1260 ±14d	Day 1440 ±14d	Day 1620 ±14d	Day 1800 ±14d	30d after last dose

[b] Visit 2 (PD0055 Baseline Visit) typically coincides with V15 (M18) of PD0053. Only assessments not done at V15 in PD0053 will need to be completed for PD0055 V2. If PD0055 V2 is conducted more than 2 weeks after V15 of PD0053, all assessments (except DaT-SPECT, CSF sampling, and sampling for biomarkers) will need to be repeated. Participants who newly consented to provide CSF samples in PD0055 need to undergo CSF sampling at V2.

[c] All study participants prematurely terminating from the study should be encouraged to undergo final evaluation procedures in accordance with the EOT/ET Visit and SFU Visit schedule (30 days after the last dose), as soon as possible after the last dose of study medication.

[d] Blood pressure has to be measured in the supine and erect positions to assess autonomous dysregulation (Trendelenburg test). Vital signs (to be taken before blood collection for laboratory tests) will consist of 3 pulse and 3 BP measurements (3 consecutive BP readings will be recorded at intervals of at least 1 minute).

[e] Questioning at the time of participant visits should be explicit regarding symptoms of hypersensitivity, hepatic and/or renal dysfunction, and signs and symptoms of COVID-19.

[f] Electrocardiogram recordings will be single reads but can be repeated in triplicate if clinically indicated. The study participant should be resting in the supine position for at least 10 minutes before recording.

[g] Pregnancy test only for women of child-bearing potential. A positive urine test should be confirmed with a blood test.

[h] First day of minzasolmin (UCB0599) administration will be Day 1; last administration will be in the morning of the EOT Visit.

[i] In case of early termination of IMP before the M60 Visit, the DaT-SPECT will occur at the EOT/ET Visit, provided that the last DaT-SPECT occurred more than 6 months prior to the EOT/ET Visit. The DaT-SPECT at M18 (V8) and M60 (V15/EOT/ET) can be done within a time window of ±28 days.

[j] The V2 (PD0055 Baseline Visit) assessment (typically coinciding with PD0053 M18) will be done based on MoCA version 7.2.

[k] The V8 (M18), V11 (M36), and V15/EOT/ET (M60) assessments will be done based on MoCA versions 8.2, 8.1, and 8.3, respectively.

[l] Optional CSF sampling for all participants regardless of their consenting to CSF sampling in PD0053. Participants have the opportunity to opt out of CSF sampling. The CSF sampling should occur at the same time of day as in PD0053 and should be timed with blood sampling. These samples should be collected only after all other assessments of the visit have been performed.

[m] Data resulting from Visits 4a, 5a, and 5b will be documented as an unscheduled visit in the eCRF until the relevant eCRF pages for these visits are available.

[n] Koneksa Neuroscience Toolkit consenting and training can be done at any time from Visit 1 to Visit 2, if needed as an unscheduled visit.

[o] If a study participant decides to stop using the Digital Health Technology prior to V8 (M18) the reason needs to be documented in the CRF.

[p] Applies only in the case of ET.

[q] The WOQ-9 will only be completed by study participants who have initiated ST.

[r] Study participants who have already completed V4 (M1) will complete the UPSIT at the next visit.

[s] **US and UK only**: In-study patient interviews will be optional, subject to the participant having signed the specific informed consent, and will be conducted within 10 days after Baseline (V2). If the participant has already completed the Baseline visit, the interview should be performed within 10 days after the Month 1 visit (V4).

2 INTRODUCTION

2.1 Study rationale

Minzasolmin (UCB0599) is an orally available inhibitor of ASYN misfolding and downstream aggregation. Aggregated forms of ASYN are the hallmark fibrillar protein deposits in PD and other synucleinopathies, and evidence suggests that it is the misfolded forms of ASYN that propagate through the CNS during disease progression. These accumulations of ASYN-containing neuronal inclusions form Lewy bodies and Lewy neurites.

Nonclinical and in vivo pharmacology studies have provided scientific evidence suggesting that minzasolmin (UCB0599) may slow down disease progression in PD, which remains the main unmet medical need in this condition. A first-in-human study, UP0030, using minzasolmin (UCB0599), conducted in healthy elderly participants (defined as ≥55 to ≤75 years of age), provided the safety, tolerability, and PK information for single dose exposures up to 450mg and multiple dose exposures of 180mg/day for up to 21 days. The first study in the target population, UP0077, provided safety, tolerability, and PK information for multiple dose exposures of 180mg/day and 360mg/day for 28 days in study participants with PD. An ongoing double-blind, placebo-controlled, randomized, Phase 2a study, PD0053, in participants with early-stage PD, is designed to provide proof-of-concept for the efficacy of the ASYN misfolding inhibitor minzasolmin (UCB0599) in slowing disease progression at doses of 180mg/day or 360mg/day and to instruct later stages of development.

The current extension study, PD0055, is designed to provide further longer-term evidence and understanding of the efficacy, safety, and tolerability of minzasolmin (UCB0599) in slowing the progression of PD in study participants who have completed 18 months of treatment in PD0053.

2.2 Background

Parkinson's disease is a progressive neurodegenerative disorder that presents with a spectrum of motor and nonmotor signs and symptoms. The mean age at onset is 60 years. The clinical diagnosis of PD relies on the presence of the cardinal motor signs: bradykinesia, rigidity, tremor, and postural instability. However, nonmotor symptoms such as loss of smell, depression, constipation, and rapid eye movement sleep behavior disorder can occur several years before the onset of motor symptoms.

Early PD is characterized by mild, manageable motor symptoms that may not require ST, or that show a good response to low-dose levodopa, which represents standard of care (SoC)first-line treatment. Other commonly used SoC medications include dopamine agonists, monoamine oxidase-B inhibitors, and catechol-O-methyltransferase (COMT) inhibitors. As PD progresses, the motor and nonmotor symptoms become more bothersome, and patients may start experiencing motor complications. After 2 to 5 years of treatment with levodopa, 30% to 50% of patients develop motor fluctuations. Advanced PD is characterized by marked motor disability with loss of independent ambulation. After ≥10 years since onset, most patients suffer from difficult-to-treat motor symptoms (eg, falls, freezing of gait, dysarthria, and dysphagia) and from nonmotor symptoms for which treatment options are limited (eg, dementia, psychosis, depression, autonomic dysfunction, and pain). Patients are often bedridden after 10 to 14 years (Poewe, 2006). To this day, slowing disease progression remains the main unmet medical need in PD.

Parkinson's disease is pathologically characterized by the loss of dopaminergic neurons in the substantia nigra, associated with ASYN pathology (neuronal cytosolic inclusions called Lewy bodies which consist of misfolded, pathological aggregates of ASYN). Treatments that prevent misfolding and aggregation of ASYN may slow the neurodegeneration in PD, resulting in slower progression of motor symptoms, thus providing a therapeutic benefit to patients with PD.

Minzasolmin (UCB0599) is an orally available inhibitor of ASYN misfolding and downstream ASYN aggregation. In vivo and nonclinical pharmacology data suggest minzasolmin (UCB0599) may slow neurodegeneration in PD, resulting in slower disease progression, thus providing a therapeutic benefit to patients with PD.

Minzasolmin (UCB0599) has not been approved by any health authorities worldwide as of the date of this document. UCB has conducted 5 Phase 1 clinical studies to support the development of minzasolmin (UCB0599) that have demonstrated good PK properties and an acceptable safety and tolerability profile (UP0023, UP0030, TM0017, and UP0077) as well as a minimal food effect on the PK profile for minzasolmin (UCB0599) (UP0078). Further information regarding UP0023, UP0030, TM0017, UP0077, and UP0078 is provided in the Investigator's Brochure (IB).

2.3 Benefit/risk assessment

Parkinson's disease was chosen as the target indication on the basis of a strong scientific rationale and a significant unmet medical need.

The currently available treatments for PD are most effective in treating the motor symptoms in the early stages; however, they do not slow/stop the disease progression and provide limited benefit in later stages of the disease due to the continuing neuronal loss. To date, there are no approved treatments to stop or slow down the clinical progression of the disease in patients with early PD, which remains a large unmet medical need.

Findings from genetic, clinical pathology, and animal model studies indicate that the neuronal accumulation of toxic aggregates of a synaptic protein called ASYN contributes to the underlying pathophysiology of PD. Thus, a therapeutic agent that prevents the formation, or enhances the clearance, of these toxic forms of ASYN may prevent or slow neurodegenerative processes in PD and related disorders.

Nonclinical pharmacologic studies demonstrate that minzasolmin (UCB0599) interacts directly with ASYN to reduce the misfolding and the formation of ASYN aggregates and, more specifically, to reduce the formation of oligomeric ASYN structures associated with ASYN-mediated cellular toxicity.

The important identified risk is drug hypersensitivity, and the potential risks are hepatotoxicity (based on clinical data) and cardiac effects. Renal laboratory abnormalities are also kept under close safety monitoring.

In Phase 1 development of minzasolmin (UCB0599), 5 studies (UP0030, TM0017, UP0023, UP0077, and UP0078) demonstrated that minzasolmin (UCB0599) has acceptable safety, PK, and tolerability profiles for further clinical development. Overall, the majority of TEAEs were mild or moderate in intensity and resolved. In UP0030, 2 events of hypersensitivity were reported. An additional 2 events of hypersensitivity occurred in study participants who received minzasolmin (UCB0599) in UP0077. A causal relationship between the reported events of drug

hypersensitivity and minzasolmin (UCB0599) is considered plausible. The hypersensitivity reactions are further described in the IB. As a result of these clinical data, drug hypersensitivity is now considered an important identified risk by the Sponsor and, therefore, further measures of risk monitoring and minimization are included.

Sites will be informed and trained appropriately about the risk of a hypersensitivity reaction (such as rash, angioedema, or anaphylaxis) and the actions that need to be taken in case of a hypersensitivity reaction. The participant will be informed by the Investigator during the consent procedure about the risk of a hypersensitivity reaction (such as rash, angioedema, or anaphylaxis) and other important potential risks for minzasolmin (UCB0599). Risk mitigation measures include using a standard approach of: (1) obtaining a detailed history of the hypersensitivity reaction and its evolution; (2) response with appropriate treatment, if needed; (3) a detailed physical examination and regular monitoring of vital signs; and (4) the addition of a guidance for the evaluation of suspected hypersensitivity reactions (please refer to Section 8.3.6.1) and reporting of the suspected hypersensitivity reaction as an adverse event of special interest (AESI).

To monitor the potential risk of hepatotoxicity, monthly routine liver function tests are mandated during the first 6 months of treatment for study participants who receive multiple doses of study medication (see Schedule of Activities, Section 1.3). In addition, any cases meeting Hy´s law criteria must be reported as an AESI. Sites will be informed and trained appropriately.

With the current risk management measures for minzasolmin (UCB0599), the benefit-risk profile appears to be favorable for further development. The limited clinical data collected thus far have not identified any safety concerns that would preclude further development of minzasolmin (UCB0599) in PD.

More detailed information about the known and expected benefits and risks and reasonably expected adverse reactions of minzasolmin (UCB0599) is provided in the IB.

2.3.1 Coronavirus Disease-2019 benefit/risk assessment

Minzasolmin (UCB0599) is not known to exert an effect on the immune or respiratory systems, and its mechanism of action is not linked to immune or respiratory system agonism or inhibition.

To date, no increased risk of infection or respiratory problems has been identified in association with clinical minzasolmin (UCB0599) administration. No such risks have been identified through regular review of published literature. PD0055 will include study participants with early-stage PD who completed the Treatment Period of PD0053.

Although there is some evidence that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) might affect the CNS, there is no reason to assume on the basis of the mechanism of action that minzasolmin (UCB0599) will have any substantial effect to worsen a Coronavirus Disease-2019 (COVID-19) infection or increase the risk of CNS and other complications in case a study participant with PD acquires SARS-CoV-2. There is no evidence that ASYN plays a role in immunological pathways of the CNS. Furthermore, there is no reason to assume that minzasolmin (UCB0599) may enhance the infection risk or the disease manifestation.

Therefore, minzasolmin (UCB0599) is not expected to pose an additional risk of complications or poor prognosis of COVID-19.

Considering the mechanism of action, the inclusion and exclusion criteria, and the measures to mitigate risks described in this protocol, the risk to study participants in PD0055, both in terms of exposure to SARS-CoV-2 and morbidity from COVID-19, is not expected to be significantly different from the general population of individuals with PD. The benefit-risk profile of minzasolmin (UCB0599) in PD0055 in the context of COVID-19 vaccination remains positive.

Consequently, there are no restrictions on COVID-19 vaccination during PD0055 (ie, study participants should be free to receive COVID-19 vaccination as per local or national guidance/regulations).

2.3.1.1 COVID-19 risk mitigation measures

- Current national laws and local recommendations for the prevention and control of the pandemic will be strictly adhered to.
- Participants are asked to follow the visit schedule to the extent possible. If they are unable to come to the study site, the Investigator may contact the participant directly via telephone and/or video conference calls. If participants visit another facility for a medical issue (or have to switch study sites for a COVID-19-related reason), they are asked to inform the Investigator to obtain the details of their condition and their participation.
- Participants will be closely monitored for and encouraged to report any signs and symptoms of COVID-19. The Investigator will consider the individual benefit/risk of the study participant upon identification of any signs and symptoms of COVID-19 infection (eg, continuation of dosing, site visits).
- COVID-19 testing by optional laboratory assessment will be conducted based on availability and other practical considerations (eg, test capacity and turnaround time) of approved tests and at the Investigator's discretion. The Investigator will consider the individual benefit/risk of the study participant in case of a positive COVID-19 test.
- The possibility of virus transmission will be controlled as much as possible by:
  - Advising participants to adhere to local requirements for reduction of exposure to the public while ambulatory.
  - Advising participants to adhere to clinical site requirements for reduction of exposure while at the site or interacting with site staff. This advice will be included in the Informed Consent form (ICF).
- COVID-19 testing for clinical staff will be conducted if required by local guidelines.

2.3.1.2 COVID-19 benefit/risk conclusion

Considering the mechanism of action of minzasolmin (UCB0599), the inclusion and exclusion criteria, and the measures to mitigate risks described in this protocol, the risk to study participants in PD0055, both in terms of exposure to SARS-CoV-2 and morbidity from COVID-19, is not expected to be significantly different from the general population of individuals with PD.

2.3.2 Digital Health Technology benefit/risk assessment

In this study, the Koneksa Neuroscience Toolkit is used as noninvasive Digital Health Technology to collect data on signs and symptoms of PD. Briefly, the Koneksa Neuroscience Toolkit consists of a mobile software application which is executed on an Apple iPhone; the Koneksa Neuroscience Toolkit also utilizes the ActiGraph CentrePoint® Insight Watch (CPIW), a wrist-worn smartwatch, and the ActiGraph CPIW Data Hub for data transfer. Refer to Section 6.9 and Section 8.1.4 for detailed descriptions of the Koneksa Neuroscience Toolkit.

There are long-term benefits for the PD patient community associated with increasing the evidence base regarding the utility of the Digital Health Technology (eg, Koneksa Neuroscience Toolkit) to capture changes in the signs and symptoms of PD over time.

The Koneksa Neuroscience Toolkit is designed for use at home and allows for an objective assessment of signs and symptoms of PD without requiring study participants to visit the clinical site, potentially minimizing patient burden by reducing site visits in future clinical studies.

The risks associated with the Koneksa Neuroscience Toolkit are minimal. The active assessments are software application based and have been selected considering the safety of study participants while performing the assessment in an unsupervised environment. The potential risks and the associated mitigation strategies are listed in Table 2–1.

Table 2–1: Potential risks and mitigation strategies for Koneksa Neuroscience Toolkit

Risk	Description
Falling while performing an assessment and confusion and/or embarrassment and fatigue and/or pain	The risk associated with falling may be present during the active gait and balance assessment. The application has been designed to prompt the user to only complete the assessment if they can safely perform this task without falling. Study participants will explicitly respond if they feel they can or cannot complete the gait and balance assessment safely. If study participants respond they cannot complete the task safely, they will not be asked to complete the assessment, and this will not be considered a compliance failure. Harm associated with use of the Koneksa Neuroscience Toolkit in accordance with the protocol may also include confusion and/or embarrassment, and fatigue and/or pain. These risks are mitigated by proper study participant screening and training, application design facilitates use for assessments, patient support through quick start guide, patient guide, video and phone support, the option to mark the task as not safe prior to the start of the task, and stopping any time during the tasks.
Allergic reaction to the ActiGraph CPIW smartwatch and wrist band	There is a risk that skin reactions (eg, irritation, itchiness, rash) may occur during prolonged use and skin contact with the ActiGraph CPIW. However, the ActiGraph CPIW is composed of materials with a low potential of allergic reactions and has been widely used. If a participant has a known allergy to copolymer materials, they should seek medical advice before using the ActiGraph CPIW. Additionally, the ActiGraph CPIW and the Koneksa Neuroscience Toolkit patient guides provide instructions for handling cases of skin reactions.

Table 2–1: Potential risks and mitigation strategies for Koneksa Neuroscience Toolkit

Risk	Description
Shock due to electromagnetic radiation from ActiGraph CPIW	It is unlikely that study participants will experience discomfort or shock due to electromagnetic radiation from the ActiGraph CPIW given the conformity of this smartwatch with CE Mark (EU and UK) (EN60601-1) and registrations Part 15.109, Part 15.249 (US), and ICES-003 (Canada).
Electromagnetic interference with any kind of implantable active devices	The Apple iPhone contains magnets, as well as components and/or wireless elements that generate electromagnetic fields. These magnets and electromagnetic fields can cause interference with medical devices, such as implanted pacemakers and defibrillators, which may contain sensors that respond to magnets or radio elements when in close contact. Potential interaction with these implanted devices could occur if the Apple iPhone comes closer than 30cm to the implanted device. Therefore, study participants with any implanted active medical device are excluded from using the Koneksa Neuroscience Toolkit.
Physical discomfort such as cramps, fainting, eye aches, or headaches	Study participants may experience physical discomfort such as cramps, fainting, eye aches, or headaches, which may be due to the use of the Apple iPhone. Study participants will be cautioned to stop using the Koneksa Neuroscience Toolkit in case of physical discomfort and to contact and seek guidance from the Investigator.
Data security	There are risks associated with security breaches affecting data privacy and/or integrity. These are minimized by several measures. No personal identifiable information is captured on the platform; all personal data are pseudonymized. Data are encrypted at rest and in transit using a 2048-bit encryption. Backend access to the platform is limited following a least privileged/role-based approach. Finally, the result of patient assessment can only be assessed within the Koneksa application.

CE=Conformité Européenne; CPIW=CentrePoint Insight Watch

Besides the risk and mitigations described above, no further risks associated to the mobile software application, the Apple iPhone, and the ActiGraph CPIW and its Data Hub were identified based on information available to UCB. Please refer to the Apple iPhone User Guide (available at: https://support.apple.com/guide/iphone/welcome/ios), ActiGraph CPIW User Guide (CentrePoint Insight Watch User Guide. Pensacola, FL: ActiGraph, LLC; 2023), and ActiGraph CPIW Data Hub User Guide (CentrePoint Data Hub User Guide. Pensacola, FL: ActiGraph, LLC; 2023).

Considering the risk mitigation measures in place, the Koneksa Neuroscience Toolkit does not pose significant risks to study participants. The overall residual risk is acceptable for the Koneksa Neuroscience Toolkit's intended use in this investigational clinical study. Based on the information available to UCB and given the unmet medical need, potential for benefit, risks, and risk mitigation measures, the benefit-risk for inclusion of the Koneksa Neuroscience Toolkit is considered positive.

3 OBJECTIVES AND ENDPOINTS

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 and Month 60 **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 and Month 60 **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 and emerging symptoms) • MDS-UPDRS Part III subscale (or selected items/subscore) • Modified H&Y

Objectives	Endpoints
	• FATIGUE-PRO • Early PD Function Slowness PRO • Early PD Mobility PRO **Exploratory Endpoints (Other)** • Koneksa Neuroscience Toolkit
II. Effectiveness: To estimate the effectiveness of minzasolmin (UCB0599) versus SoC on clinical outcomes and QoL beyond 18 months duration of PD0053, using external real-world 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 and emerging symptoms) • MDS-UPDRS Part III subscale (or selected items/subscore) • Modified H&Y
III. Efficacy: To estimate the pharmacodynamic effects of Early-start minzasolmin (UCB0599) 360mg versus Early-start minzasolmin (UCB0599) 180mg 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 and emerging symptoms) • MDS-UPDRS Part III subscale (or selected items/subscore) • Modified H&Y • FATIGUE-PRO • Early PD Function Slowness PRO • Early PD Mobility PRO

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 and Month 60	**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

4 STUDY DESIGN

4.1 Overall 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 up to 60 months. Parkinson’s disease clinical diagnosis will be reviewed at the PD0055 Baseline Visit and at PD0055 Month 18 (ie, 36 months post PD0053 Screening).

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) 360mg/day (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 and 314 participants would be expected to reach PD0055 Month 18 and Month 60, respectively.

Participants who have been treated with minzasolmin (UCB0599) 180mg/day during PD0053 will continue to receive minzasolmin (UCB0599) 180mg/day in extension study PD0055. Participants who have been treated with minzasolmin (UCB0599) 360mg/day during PD0053

will continue to receive minzasolmin (UCB0599) 360mg/day in PD0055. Participants who received placebo during PD0053 will receive minzasolmin (UCB0599) 360mg/day in PD0055.

After completing, at the minimum, the Month 18 Visit in PD0055, participants will be switched to the best dose, as determined from the results of PD0053. All study participants and Investigators will remain blinded to treatment/dose received in PD0053 and PD0055 at least until all participants have completed the Month 18 assessments in PD0055. Thereafter, PD0055 will be open label.

Throughout the study, data will be reviewed on an ongoing basis by a DMC and a SMC. Refer to Section 9.7 for details on specific data review and timings.

A study overview of PD0055 is provided in Figure 1-1. The study will comprise 3 embedded designs. The active arm will be considered to be minzasolmin (UCB0599) 360mg. Two comparator arms will be used to provide further insight into the efficacy/effectiveness of minzasolmin (UCB0599):

- Delayed-start arm (360mg) (Figure 1-2)
- Low-dose arm (180mg) (Figure 1-3)

In addition, external real-world data (where available) will be used to estimate the effectiveness of minzasolmin (UCB0599) (selected endpoints only) versus the SoC beyond the 18 months duration of the feeder study PD0053 (Figure 1-4).

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 secondary efficacy objective of the extension study 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 secondary safety objective of the study is to assess the safety and tolerability of minzasolmin (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.

The exploratory objectives of the study include assessments of methodology (ie, identification of novel endpoints), effectiveness (strengthening of the patient value stemming from impact on key motor outcomes), efficacy (estimation of pharmacodynamic effects of minzasolmin (UCB0599) that may inform any dose-response modeling), and identification of participants with Atypical Parkinsonism.

The primary and secondary efficacy objectives of the study, as well as the exploratory methodology objective, will make use of the Delayed-start arm (Figure 1-2). The exploratory efficacy objective will make use of the Low-dose arm (Figure 1-3). Finally, the exploratory effectiveness objective will make use of the external real-world data (Figure 1-4).

The analyses to be performed for the primary and secondary efficacy objectives, for the exploratory objectives I (methodology) and II (effectiveness), as well as for safety analyses will use all study data (up to 60 months post PD0055 Baseline Visit). The analyses to be performed

for the exploratory objective III (efficacy [dose comparison]) will use data from the first 18 months of PD0055 only.

PD0055 includes a Screening Period of up to 60 days (overlapping with the Treatment Period of PD0053) followed by a Treatment Period of 60 months 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.

4.2 Scientific rationale for study design

The primary objective of the PD0055 extension study is to address a question complementary to the one answered by the primary objective of the proof-of-concept study, PD0053. 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). 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 objective of PD0055 is to estimate the pharmacodynamic effects of minzasolmin (UCB0599) on the need for ST in Early-start versus Delayed-start participants. 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.

To address the exploratory objective I (of methodology), 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.

The results from the exploratory objective II (of effectiveness) will allow the strengthening of the patient value stemming from impact on key motor outcomes through (potentially) showing an impact also on Quality of Life (QoL) outcomes. Research with national payers indicates that this combination would be particularly impactful in demonstrating patient value.

The results obtained from the exploratory objective III (of efficacy) may inform any dose-response modeling, confirm any difference seen in efficacy in PD0053, or inform on any longer term impact of the cumulative dose of minzasolmin (UCB0599).

Finally, the exploratory objective IV, where the initial PD clinical diagnosis will be re-assessed, 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).

4.2.1 Patient input into design

There was no patient input in the study design of PD0055 (PD0053 extension).

4.3 Justification for dose

The rationale for testing the proposed clinical dose levels of minzasolmin (UCB0599) 180mg/day (90mg BID) and 360mg/day (180mg BID) in extension study PD0055 is to allow participants to continue into PD0055 on the same dose level as they were randomly assigned to in PD0053.

The doses in PD0053 were based on (1) the safety margin estimates comparing systemic exposures at the no observed adverse effect level in monkey with human observed exposures in study participants with PD treated in UP0077, and (2) exposures that have shown pharmacological activity in transgenic mice that overexpress the human wildtype ASYN gene (synuclein alpha) in the CNS. Upward or down titration of minzasolmin (UCB0599) dose is not necessary. The maximum daily dose tested in the program is minzasolmin (UCB0599) 360mg/day (180mg BID).

All participants from the placebo arm of PD0053 will be assigned to a single dose level of minzasolmin (UCB0599) in PD0055, which will be the dose currently believed to provide most efficacy, ie, 360mg/day. This design will allow the number of participants included in the Delayed-start analysis to be maximized.

After completing, at the minimum, the Month 18 Visit in PD0055, participants will be switched to the best dose. The best dose will be decided by UCB based upon efficacy and safety data from completed PD0053 and safety input from the DMC.

Potential food effect, as well as potential drug-drug interaction with itraconazole, a strong cytochrome P450 3A4 (CYP3A4) inhibitor, were evaluated in Phase 1 study UP0078 after a single dose of minzasolmin (UCB0599) 180mg. Data from UP0078 confirmed that no food effect-requiring dose adjustment is needed in PD0055. However, strong CYP3A4 inhibitors (and inducers) should not be co-administered with minzasolmin (UCB0599).

4.4 End of study definition

A participant is considered to have completed the study if he/she has completed all periods of the study including the SFU Visit (30 days after last dose).

The global end of the study is defined as the date of the last visit of the last participant in the study.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Type of participant and disease characteristics

1. Participant completed the Treatment Period of PD0053. The Baseline Visit for PD0055 (Visit 2) should be no later than 4 weeks following the EOT Visit in PD0053. Any delay needs to be justified by the Investigator and approved by the Sponsor.

Sex

2. Contraception
   - A male study participant must agree to use contraception as detailed in Appendix 4 (Section 10.4) during the Treatment Period and for at least 90 days after the last dose of the IMP and refrain from donating sperm during this period.
   - A female study participant is eligible to participate if she is not pregnant, not breastfeeding, and at least 1 of the following conditions applies:
     - Not a woman of childbearing potential (WOCBP) as defined in Appendix 4 (Section 10.4)
       OR
       A WOCBP who agrees to follow the contraceptive guidance during the Treatment Period and for at least 1 month after the last dose of IMP. The study participant must have a negative urine pregnancy test at Screening (Visit 1), which is to be confirmed negative by urine testing prior to the first dose of IMP at PD0055 Baseline Visit. If oral contraception is used, an additional barrier method will be required during the study as an IMP-related gastrointestinal upset or a drug interaction by CYP3A4 induction could interfere with efficacy.

Informed consent

3. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1.3) which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2 Exclusion criteria

Participants are excluded from the study if any of the following criteria apply:

Medical conditions

1. Study participant has any medical or psychiatric condition that, in the opinion of the Investigator, could jeopardize or would compromise the study participant's ability to participate in this study.
2. A female study participant who tests positive for pregnancy, plans to get pregnant during the participation in the study, or who is breastfeeding.

Other exclusions

3. Study participant had previously participated in PD0055.
4. Study participant meets any withdrawal criteria in PD0053.
5. Study participants wearing any kind of implantable active device, including cardiac pacemakers, pumps, and implantable cardioverters, will be excluded from using the Koneksa Neuroscience Toolkit, but may participate in the main study.
6. Study participant does not agree to refrain from donating blood or blood products or other body fluids.

5.3 Lifestyle restrictions

5.3.1 Meals and dietary restrictions

The study participant must not ingest grapefruit, starfruit, or pawpaw (as beverage, fruit, or supplements) throughout the study.

5.3.2 Caffeine, alcohol, and tobacco

There are no restrictions for caffeine or tobacco during the study. Prior documentation of alcohol abuse was an exclusion criterion for PD0053. Study participants are requested to limit alcohol consumption (no more than moderate alcohol consumption).

5.3.3 Activity

There are no restrictions on any activities.

5.4 Screen failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to IMP in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

There will be no rescreening in PD0055.

6 STUDY TREATMENTS/INVESTIGATIONAL DEVICE

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 Treatments administered

Arm Name	Minzasolmin (UCB0599) 180mg/day	Minzasolmin (UCB0599) 360mg/day
Intervention name	Minzasolmin (UCB0599)	Minzasolmin (UCB0599)
Type	Drug	Drug
Dose formulation	Granules in capsules and matching placebo capsules	Granules in capsules
Unit dose strength(s)	90mg and 0mg	90mg
Dosage level(s)	180mg/day (90mg BID)	360mg/day (180mg BID)
Route of administration	Oral – 2 capsules 90mg and 2 matching placebo capsules per day BID approximately 12 hours apart	Oral – 4 capsules 90mg per day BID approximately 12 hours apart
Use	Experimental	Experimental
IMP and NIMP/AxMP	IMP	IMP
Sourcing	IMP will be supplied by UCB Clinical Trial Supply or designee.	IMP will be supplied by UCB Clinical Trial Supply or designee.
Packaging and labeling	The IMP is manufactured, packaged, and labeled according to GMP guidelines and in accordance with all applicable laws or regulations. Each IMP carton will be labeled according to individual country requirements. Details of the packaging and labeling will be provided in the IMP Handling Manual.	The IMP is manufactured, packaged, and labeled according to GMP guidelines and in accordance with all applicable laws or regulations. Each IMP carton will be labeled according to individual country requirements. Details of the packaging and labeling will be provided in the IMP Handling Manual.
Current/Former name(s) or alias(es)	NA	NA

AxMP=auxiliary medicinal product; BID=twice daily; GMP=Good Manufacturing Practices; IMP=investigational medicinal product; NA=not applicable; NIMP=noninvestigational medicinal product

6.2 Preparation, handling, storage, and accountability requirements

The Investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all IMP received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive the IMP and only authorized site staff may supply or administer the IMP. All IMP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the Investigator and authorized site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for IMP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

In case an out-of-range temperature is noted, it must be immediately reported as per instructions contained in the IMP Handling Manual.

The Investigator (or designee) will instruct the participant to store the IMP following the instructions on the label.

Further guidance and information for the final disposition of unused IMP are provided in the IMP Handling Manual.

6.2.1 Drug accountability

A Drug Accountability form will be used to record IMP dispensing and return information on a by-participant basis and will serve as source documentation during the course of the study. Details of any IMP lost, damaged (due to breakage or wastage), not used, partially used, disposed of at the study site, or returned to the Sponsor or designee must also be recorded on the appropriate forms. All supplies and pharmacy documentation must be made available throughout the study for UCB (or designee) to review.

The Investigator (or designee) is responsible for retaining all used, unused, and partially used containers of IMP until returned or destroyed.

The Investigator may assign some of the Investigator's duties for drug accountability at the study site to an appropriate pharmacist/designee.

The Investigator must ensure that the IMP is used only in accordance with the protocol.

Periodically, and/or after completion of the clinical phase of the study, all used (including empty containers/partially used), unused, damaged, and/or expired IMP must be reconciled and either destroyed at the site according to local laws, regulations, and UCB standard operating procedures (SOPs) or returned to UCB (or designee). Investigational medicinal product intended for the study cannot be used for any other purpose than that described in this protocol.

6.3 Measures to minimize bias: randomization and blinding

The randomized study participants in PD0053 who choose to enter PD0055 will retain their PD0053 randomization number and study participant number.

Participants will have already been randomized to a treatment regimen in PD0053, and their PD0055 treatment assignment is determined based on the treatment received in the feeder study. There is no rerandomization in PD0055. An interactive response technology (IRT) will be used for assigning eligible participants to a treatment regimen (as applicable) based on a predetermined production packaging schedule provided by UCB (or designee). The IRT will generate individual assignments for kits of IMP, as appropriate, according to the visit schedule. The participant number will be required in all communication between the Investigator or designee and the IRT regarding a particular participant. Participant numbers and kit numbers will be tracked via the IRT. The IRT will allocate kit numbers to the participant based on the participant number during the course of the study. The randomization number must be incorporated into the electronic Case Report form (eCRF).

All participant treatment details will be allocated and maintained by the IRT. The following individuals will have received the randomization code at the start of the PD0053 study:

- Designated contract research organization (CRO) bioanalytical staff analyzing samples
- Sponsor clinical study supply staff
- IRT provider

The following individuals may have access to the randomization code as indicated:

- Sponsor patient safety staff as needed for reporting SAEs to regulatory authorities
- On request, members of the DMC who participate in unblinded (closed) sessions will be given information about the IMP allocation for those participants for whom data are provided at these sessions
- Unblinded CRO staff supporting preparation of the data outputs for the DMC review

6.3.1 Procedures for maintaining and breaking the treatment blind

6.3.1.1 Maintenance of study treatment blind

All participant treatment details will be allocated and maintained by the IRT system.

All study participants and Investigators will remain blinded to treatment/dose received in PD0053 and PD0055 at least until all participants have completed the Month 18 assessments in PD0055. Thereafter, PD0055 will be open label.

When PD0053 is unblinded, the Sponsor will become unblinded to the PD0055 treatment assignment.

6.3.1.2 Breaking the dose blind in an emergency situation

All participants are on active treatment; as such, unblinding will not be necessary in an emergency situation.

6.4 Treatment compliance

At each visit after the IMP is dispensed, participants must return all unused IMP and empty IMP containers. Drug accountability must be done in the participant's presence in order to obtain explanations regarding discrepancies in compliance with the dosing regimen. Drug accountability must be recorded on the Drug Accountability form.

If a participant is found to be persistently noncompliant (<80% or >120% compliant), the Sponsor, in conjunction with the Investigator, will make a decision as to whether the participant should be withdrawn from the study.

6.5 Concomitant medication(s)/treatment(s)

6.5.1 Permitted concomitant treatments (medications and therapies)

6.5.1.1 Permitted (auxiliary) treatments for performing measurements

6.5.1.1.1 DaT-SPECT

The DaTscan® tracer for DaT-SPECT (Anatomical Therapeutic Chemical [ATC] code: [redacted]) imaging will be sourced from GE-Healthcare via Invicro on behalf of UCB. The tracer is approved for commercial use in Europe, US, and Canada and will be used according to the product label. Approximate radioactivity per dose is 185 MBq.

Iodine-based thyroid protecting solutions (eg, Lugol's solution) must be administered before DaT-SPECT. These solutions will be sourced by the sites.

6.5.1.2 Permitted Coronavirus Disease-2019 vaccination

Should a COVID-19 vaccine be administered during study participation, full details will be recorded in the concomitant medication eCRF page. The specific name of the vaccine and the exact date of administration should be recorded, as instructed in the completion guideline.

6.5.2 Prohibited concomitant treatments (medications and therapies)

For rescue treatment of PD symptoms, refer to Section 6.5.3.

Strong CYP3A4 inhibitors and inducers, as well as sensitive CYP3A4 substrates with narrow therapeutic index are not allowed during the study.

The following medications are not allowed during the 50 days before DaT-SPECT imaging due to known interactions:

- Metoclopramide
- Alpha methyldopa
- Clozapine
- Olanzapine
- Flunarizine
- Amoxapine
- Amphetamine derivatives
- Reserpine
- Bupropion
- Buspirone
- Cocaine
- Mazindol
- Methylamphetamine
- Methylphenidate

- Norephedrine
- Phentermine
- Phenylpropanolamine
- Modafinil

6.5.3 Concomitant ST

Investigators will be encouraged to carefully document all changes and dose adaptations, particularly when considering ST initiation, which should always consider the individual participant needs and SoC recommendations.

Levodopa is determined as the first choice for participants who are determined to require ST. Other ST options (ie, dopamine agonists) are only permitted where levodopa has an unsatisfactory effect, where contraindications against levodopa are identified by the Investigator, or where an alternative ST drug is medically indicated for any other reason.

Monoamine oxidase-B inhibitors and their metabolites (amphetamine derivatives) will not be allowed due to their potential impact on disease progression.

The date and time of onset of rescue medication administration, as well as the name and dosage regimen of the rescue medication, must be recorded in the eCRF. Any dose adjustments also need to be recorded. This will enable the calculation of the cumulative LEDD (secondary efficacy endpoint; refer to Section 9.3.2.1).

For all scheduled visits, study participants who start to receive ST in PD0055 will be asked to refrain from taking ST for at least 12 hours before the clinic visit and to bring the medication to the site. A 12-hour Washout Period is considered sufficient to achieve a practically defined "OFF"-state and has proven tolerable in clinical practice (Bloem et al, 2019). All tests which are expected to be sensitive to the effects of ST will take place throughout the first part of the study visit to allow resuming dosing of ST at the earliest possible point. If a participant does not comply with the 12-hour ST Washout Period prior to any visit, this will be recorded.

6.6 Dose modification

There is no dose modification in PD0055 apart from when the best dose is defined based on PD0053 data.

6.7 Criteria for study hold or dosing stoppage

UCB will halt further dosing for all study participants at all sites if the following criteria are met during the course of the study and following case review to confirm causality and seriousness and/or severity of reported events.

Possible reasons for discontinuation or suspension of the study include (but are not limited to):

1. A pattern of adverse events (AEs), abnormal lab results, or other safety findings that would be unacceptable for this patient population.
2. A pattern of hypersensitivity reactions that are considered IMP-related and that would be unacceptable for this patient population.

3. If the Sponsor (or designee) judges it necessary for medical, safety, regulatory, or any other reasons consistent with applicable laws, regulations, and Good Clinical Practices (GCP).
4. Sponsor's decision that continuation of the study is unjustifiable for medical or ethical reasons.
5. Discontinuation of development of the Sponsor's IMP.

If any criterion is potentially met, the SMC will request for the DMC to meet as soon as possible to make a recommendation to the Sponsor as to whether discontinuation, pausing, or suspension of IMP dosing or the study should occur.

Consideration will be given to severity and relatedness of events. Further details on the role and process of ensuring close safety monitoring through the SMC and DMC are provided in the respective charters.

Detailed procedures for reporting SAEs and other safety events which may meet study hold criteria are provided in Appendix 3 (Section 10.3).

6.8 Treatment after the end of the study

Per the current protocol, there is no minzasolmin (UCB0599) treatment planned after the study.

The Investigator will discuss the best treatment option with the study participant after EOT in PD0055, which could include the possibility of extending treatment in this study or joining another study with minzasolmin (UCB0599).

6.9 Digital Health Technology

This study utilizes the Koneksa Neuroscience Toolkit as noninvasive Digital Health Technology for at-home data collection of PD symptoms of motor function, speech, physical activity, and sleep (optional) from study participants. The Koneksa Neuroscience Toolkit is provisioned by Koneksa Health Inc.

Potential risks related to the Digital Health Technology are provided in Section 2.3.2.

Koneksa Neuroscience Toolkit product description

The Koneksa Neuroscience Toolkit consists of the following components:

- The Koneksa Mobile Application for active motor assessments and collection of patient-reported data (Koneksa Health Inc.) integrating the Aural Analytics Speech Module (Aural Analytics Inc.).
- The ActiGraph CPIW (ActiGraph LLC) is a smartwatch that has a Conformité Européenne (CE) Mark and Food and Drug Administration (FDA) 510(k) clearance under K181077; it is routinely used in clinical studies to measure activity and sleep. It is provided together with a Data Hub for data transfer, which has a CE Mark and is FDA 510(k) exempt.
- The Apple iPhone (Apple Inc.) is a smartphone that has a CE Mark and complies with Part 15 of the Federal Communications Commission (FCC) rules.

The mobile software application is executed on the commercially available Apple iPhone and leverages data from the ActiGraph CPIW smartwatch. Smartphone and smartwatch are general purpose platforms and use built-in operating systems and accelerometer sensors as their primary

source of input. Additionally, the ActiGraph CPIW comes with a docking station for charging the wrist-worn smartwatch and data transfer. The accuracy and sensitivity of the accelerometers in the ActiGraph CPIW and Apple iPhone was verified in bench testing across the range of accelerations observed in human motion.

Koneksa Neuroscience Toolkit use in the study

The Koneksa Neuroscience Toolkit is to be used to capture PD motor symptoms in the context of a supervised clinical study. It is not intended as a diagnostic tool and is not used to inform treatment or other medical decisions during the course of the study.

In this study, the Koneksa Neuroscience Toolkit is used for at-home data collection of PD symptoms of motor function, speech, physical activity, and sleep (optional) from study participants. In addition, an electronic version of the MDS-UPDRS Part II (activities of daily living), questions on ST medication intake including ON/OFF status, and sleeping hours of study participants will be captured. Study participant feedback about the usability of the Koneksa Neuroscience Toolkit will be collected via an electronic questionnaire.

Motor function and speech will be assessed through a battery of active tasks using the mobile software application executed on the Apple iPhone. In addition, patient-reported data will be collected via the Apple iPhone as well.

Physical activity and (optional) sleep data will be collected passively using the ActiGraph CPIW.

The data collected by the Koneksa Neuroscience Toolkit is not shared with the study participant or the Investigator and will not be used for medical treatment decision making or for participant management during the study.

The obtained data are assessed only as part of exploratory analyses.

Study participants will be cautioned to follow instructions given in the Digital Health Technology user manuals for appropriate use and storage of the different components of the Koneksa Neuroscience Toolkit.

Study participants are free to withdraw from using the Digital Health Technology at any time during the study without being excluded from study participation.

Screening/Enrollment/Baseline Visit

Study participants will be offered to use the Koneksa Neuroscience Toolkit during the 18-month dose-blinded Treatment Period and will be approached during the Screening Period (or no later than the Baseline Visit) if they are deemed eligible by the Investigator. If participants consent to Koneksa Neuroscience Toolkit use, they will be trained on its proper use prior to or at Visit 2 (Baseline Visit). Training includes a Koneksa Neuroscience Toolkit tutorial and practice using the Koneksa Neuroscience Toolkit under clinical supervision. Following Visit 2 (Baseline Visit), participants will complete the Koneksa Neuroscience Toolkit assessments at home. Proper use of the Koneksa Neuroscience Toolkit will be closely monitored by clinical site staff until Visit 4 (Month 1).

End of Digital Health Technology use

Study participants need to return the Koneksa Neuroscience Toolkit to the clinical site at the next regular site visit after stopping use of the Digital Health Technology (at Month 18).

7 DISCONTINUATION OF STUDY MEDICATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of study medication

Study medication will be stopped if the study participant develops a medical condition (or laboratory abnormality or electrocardiogram [ECG] change) that, in the opinion of the Investigator, compromises the study participant's ability to participate or compromises the study participant's safety.

Any new clinically relevant safety finding should be reported as an AE.

In all cases, the study participant should be followed until the condition has resolved as agreed by the Investigator and the UCB study physician.

See the Schedule of Activities (Section 1.3) for data to be collected at the time of treatment discontinuation and follow up and for any further evaluations that need to be completed.

7.1.1 Hypersensitivity reactions (such as rash, angioedema, or anaphylaxis)

Study participants will be informed that if they develop any symptoms suggestive of a hypersensitivity reaction (eg, rash, angioedema, or anaphylaxis) they should contact the Investigator immediately.

The Investigator should assess the presenting symptoms to determine if this is possibly a hypersensitivity reaction.

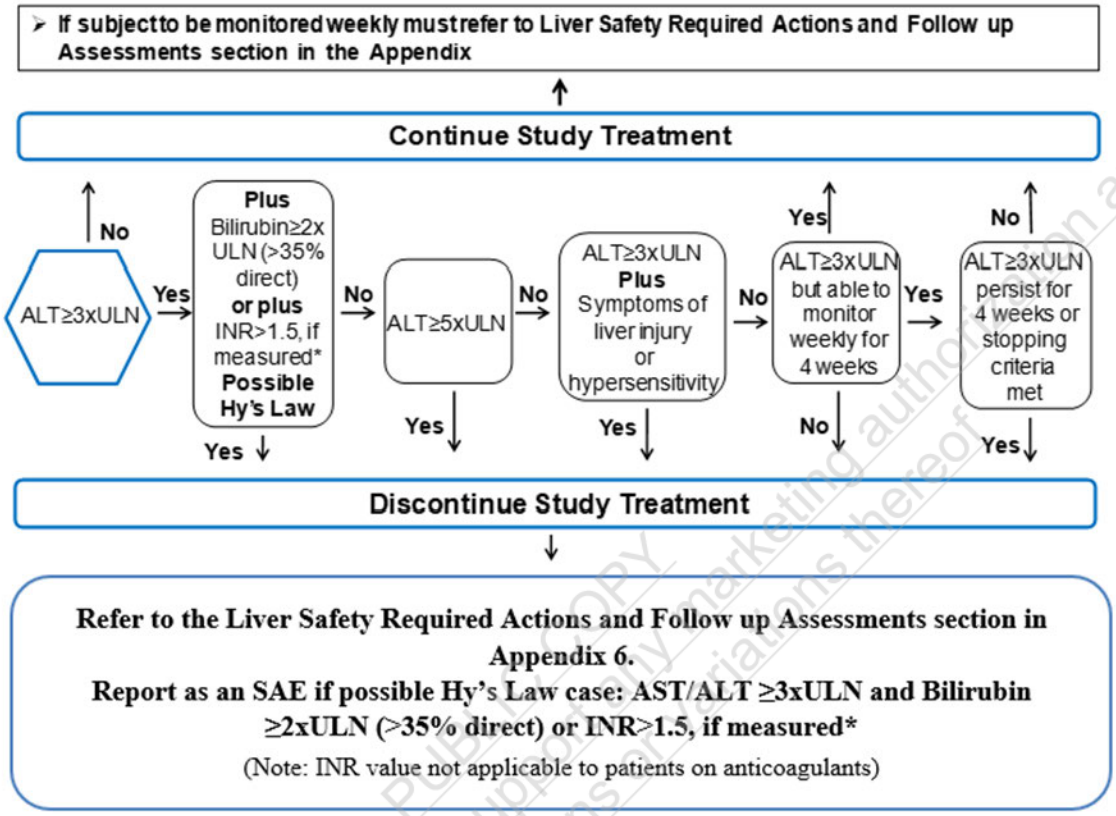
If the event is not considered to be a hypersensitivity reaction (eg, a rash due to another cause) the Investigator should document this, and the participant may continue dosing.

If the event is possibly a hypersensitivity reaction the Investigator should advise the participant to withhold dosing and arrange additional investigations as per Section 8.3.6.1. The event should be reported to UCB as an AESI. In this scenario dosing may only be recommenced following agreement of the Investigator and the SMC.

7.1.2 Liver chemistry stopping criteria

Discontinuation of study treatment for abnormal liver function should be considered by the Investigator when a study participant meets one of the conditions outlined in Figure 7-1 or if the Investigator believes that it is in best interest of the participant.

Figure 7-1: Phase 2 liver chemistry stopping criteria and increased monitoring algorithm



ALT=alanine aminotransferase; AST=aspartate aminotransferase; INR=international normalized ratio; SAE=serious adverse event; ULN=upper limit of normal.

Specific assessments and follow-up actions for potential drug-induced liver injury (PDILI) are provided in Appendix 6 (Section 10.6).

7.1.3 QT corrected stopping criteria

A study participant who meets either bulleted criterion will be withdrawn from IMP. Confirmation of the bulleted criterion should be based on the average of triplicate 12-lead ECG readings.

- QT corrected for heart rate using Fridericia's formula (QTcF) >500ms OR Uncorrected QT >600ms
- Change from Baseline of QTcF >60ms

For participants with underlying bundle branch block, follow the discontinuation criteria listed below:

Baseline QTc with bundle branch block	Discontinuation QTc threshold with bundle branch block
<450ms	>500ms
450 to 480ms	≥530ms

QTc=QT corrected

If a clinically significant finding is identified (including, but not limited to, changes from Baseline in QTcF after enrollment) the Investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented.

7.1.4 Temporary discontinuation

The Investigator, SMC, or DMC may consider temporary discontinuation of dosing of study participants on a case-by-case basis.

7.1.5 Rechallenge

The Investigator after agreement with the SMC (and endorsement by the DMC if requested by the SMC) may consider rechallenge of study participants on a case-by-case basis

7.2 Participant discontinuation/withdrawal from the study

Study participants are free to withdraw from the study at any time, without prejudice to their continued care.

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, SMC, or DMC for safety, behavioral, compliance, or administrative reasons. If a study participant withdraws or is withdrawn, he/she should be encouraged to perform the EOT/Early Termination (ET) Visit and the SFU Visit approximately 30 days after last dose of IMP.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

See the Schedule of Activities (Section 1.3) for data to be collected at the time of study discontinuation and follow up, and for any further evaluations that need to be completed. The DaT-SPECT will occur at EOT, provided that the previous DaT-SPECT occurred more than 6 months prior to EOT Visit.

Participants should be withdrawn from the study if any of the following events occur:

1. Withdrawal of consent by the study participant
2. A regulatory agency requests withdrawal of the participant from the study
3. Loss of ability to freely provide consent through imprisonment or involuntary confinement for treatment of either a psychiatric or physical (eg, infectious disease) illness or throughout quarantine conditions.

Participants must be discontinued from IMP (but not necessarily from the study) if any of the following occurs:

1. Study participant develops an illness that would interfere with his/her continued dosing.
2. Study participant takes prohibited concomitant medications as defined in the protocol. Outcome should be decided on a case-by-case basis.
3. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test.
4. Study participant has actual suicidal ideation since last visit as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "Since Last Visit" version of the Columbia-Suicide Severity Rating Scale (C-SSRS). The study participant should be referred immediately to a mental healthcare professional and must be discontinued from IMP.
5. Study participant is confirmed positive for recreational drug use or for alcohol at the PD0055 Baseline Visit (Day 0), which is deemed significant enough to impair the study participant's safety or the quality of the collected data. Outcome should be decided on a case-by-case basis.
6. Renal toxicity considered possibly related to the IMP. Laboratory tests suggestive of renal toxicity which should trigger further assessment may include:
   - Increase in serum creatinine ≥0.3mg/dL OR
   - Increase in serum creatinine to ≥1.5 times from Baseline OR
   - New persistent albuminuria or clinically significant increase in pre-existing albuminuria, over 6 consecutive weeks

   Any clinically significant findings in laboratory results for renal function will be monitored until resolution or stabilization.
7. The Sponsor requests withdrawal of the participant.
8. Study participant takes part in any other interventional study during the duration of this study.

Investigators should contact the Medical Monitor, whenever possible, to discuss the withdrawal of a participant in advance.

7.3 Lost to follow up

A participant will be considered lost to follow up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (at least 1 phone call and 1 written message to the participant) and document his/her effort (date and summary of the phone call and copy of the written message in the source documents), to complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the reason(s) for removing the participant, must be recorded in the source documents. The eCRF must document the primary reason for withdrawal.

Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow up documented in the eCRF.

7.4 Discontinuation of Digital Health Technology

Study participants can stop using the Koneksa Neuroscience Toolkit at their discretion and without consequences on further study participation at any time during the study.

The Investigator may decide to discontinue use of the Koneksa Neuroscience Toolkit if the study participant develops a medical condition that, in the opinion of the Investigator, compromises the study participant's ability to use the Koneksa Neuroscience Toolkit or compromises the study participant's safety.

A study participant must discontinue use of the Koneksa Neuroscience Toolkit if they initiate use of any kind of implantable active device, including cardiac pacemakers, pumps, and implantable cardioverters.

The reason for discontinuation needs to be documented in the eCRF.

Any newly identified safety information should be documented and reported in line with Section 8.3.7 and Appendix 7 (Section 10.7).

8 STUDY ASSESSMENTS AND PROCEDURES

The order of assessments is optimized for consistency, logistic requirements by the site, and minimized participant burden. Slight variations among the sites do not constitute a protocol deviation, while sites are encouraged to keep the order of assessments consistent over time.

As a general rule, all assessments with a high likelihood of being sensitive to previous intake of ST need to be conducted in a practically defined off-state (as defined in Section 6.5.3) before intake of ST is resumed. The assessments preceding intake of ST should include:

- Patient-reported outcomes (PROs)
- Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (all parts)
- ECGs
- Laboratory blood sampling
- Vital signs

Study procedures and their timing are summarized in the Schedule of Activities (Section 1.3).

Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue IMP.

Adherence to the study design requirements, including those specified in the Schedule of Activities (Section 1.3), is essential and required for study conduct.

All Screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a Screening log to record details of all participants screened and to confirm eligibility or record reasons for Screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for Screening or Baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Activities (Section 1.3).

The maximum amount of blood collected from each participant will not exceed 50mL at any visit and will not exceed 500mL over the duration of the study, including any extra assessments that may be required. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy assessments

Planned time points for all efficacy assessments are provided in the Schedule of Activities (Section 1.3).

8.1.1 Clinical assessments

8.1.1.1 DaT-SPECT

^{123}I-Ioflupane (DaTscan, GE Healthcare) is a radiopharmaceutical approved in the EU, Canada, and US.

Each study participant will receive a maximum of 3 injections of ^{123}I-Ioflupane during the study, according to the approved label. The target single injection dose of 185MBq is estimated to result in a radiation burden of 4.63mSv and the total effective dose for the study will be a maximum of 14mSv. This is categorized as a category III moderate risk level (ICR62), which is balanced by the substantial societal benefit from the results of this clinical study.

On scanning days, study participants will be admitted to the imaging center. A dose of a thyroid-blocking agent will be given before the radiotracer dose. Approximately 4 hours prior to scanning, a venous canula will be inserted into an arm vein and from 111 to 185MBq DaTscan will be injected. Hydration should be encouraged before the injection, as well as good hydration and frequent voiding for 48 hours after the scan.

Approximately 4 hours post injection of DaTscan, study participants will be placed supine in the Single Photon Emission Computed Tomography scanner and positioned with comfortable head fixation. A single scan will be acquired over approximately 30 to 45 minutes.

8.1.1.2 LEDD

The cumulative LEDD will be calculated for each participant at each visit and at the end of study. This is the sum of all the LEDDs taken up to that visit, ie, if a participant is taking 300mg of levodopa a day, their cumulative dose over 10 days would be 3000mg. Any changes in

medication (type, dose, or dosing regimen) should be accounted for when calculating cumulative doses.

Parkinson's disease medication will recorded throughout the study (see Schedule of Activities, Section 1.3), and the LEDD will be calculated as done in the Parkinson's Progression Markers Initiative (Schade et al, 2020; Tomlinson et al, 2010).

8.1.1.3 Nonmotor symptoms

8.1.1.3.1 Movement Disorder Society Non-Motor Rating Scale

The Movement Disorder Society Non-Motor Rating Scale (MDS-NMS; Martinez-Martin et al, 2019) is a revision of the Non-Motor Symptoms Scale. The rater-administered scale measures frequency and severity of 13 non-motor domains (A-M) with over 52 items, covering a range of key non-motor symptoms that are PD and treatment related.

In addition, the scale also includes a new 8-domain Non-Motor Fluctuations subscale to assess changes in non-motor symptoms in relation to the timing of anti-PD medications.

8.1.1.3.2 MDS-UPDRS Part I subscale or selected items

The MDS-UPDRS Part I subscale (non-motor experiences of daily living, Goetz et al, 2008) has 2 components:

- Part IA includes cognitive impairment, hallucinations and psychosis, depressed mood, anxious mood, apathy, and features of dopamine dysregulation syndrome; it is assessed by the rater with all pertinent information from study participants and caregivers (ie, clinician-reported outcome [ClinRO]).
- Part IB includes sleep problems, daytime sleepiness, pain and other sensation, urinary problems, constipation problems, lightheadedness on standing, and fatigue; it is completed by the study participant with or without the aid of the caregiver, but independently of the rater (ie, PRO).

Both sections can be reviewed by the rater to ensure that all questions are answered clearly, and the rater can help explain any perceived ambiguities.

8.1.1.4 Motor symptoms, activities of daily living & QoL

8.1.1.4.1 MDS-UPDRS Part II subscale or selected items

The MDS-UPDRS Part II subscale (motor experiences of daily living, Goetz et al, 2008):

- Is designed to be a self-administered questionnaire like Part IB (ie, PRO), but can be reviewed by the rater to ensure completeness and clarity.
- Includes speech, saliva and drooling, chewing and swallowing, eating tasks (cutting food and handling utensils), dressing, hygiene, handwriting, doing hobbies and other activities, turning in bed, tremor, getting out of bed, a car or a deep chair, walking and balance, and freezing.

8.1.1.4.2 MDS-UPDRS Part III subscale or selected items

The MDS-UPDRS Part III subscale (motor examination, Goetz et al, 2008):

- Has instructions for the rater to give or demonstrate to the study participant; it is completed by the rater (ie, ClinRO).
- Includes speech, facial expression, rigidity, finger tapping, hand movements, pronation-supination movements of hands, toe tapping, leg agility, arising from chair, gait, freezing of gait, postural stability, posture, global spontaneity of movement (body bradykinesia), postural tremor of the hands, kinetic tremor of the hands, rest tremor amplitude, and constancy of rest tremor. Motor function will be measured in an off-state with regard to ST intake (Section 6.5.3; Bloem et al, 2019).

8.1.1.4.3 MDS-UPDRS Part IV subscale or selected items

The MDS-UPDRS Part IV (motor complications, Goetz et al, 2008):

- Includes time spent with dyskinesias, functional impact of dyskinesias, time spent in the "OFF" state, impact of fluctuations, complexity of motor fluctuations, and painful "OFF" state dystonia.
- Has instructions for the rater and also instructions to be read to the study participant. This part integrates study participant-derived information with the rater's clinical observations and judgments and is completed by the rater.

8.1.1.5 Modified Hoehn and Yahr staging

The Hoehn and Yahr (H&Y) scale (Hoehn and Yahr, 1967) describes how the symptoms of PD progress through 5 stages: Stage 1=unilateral disease; Stage 2=bilateral disease without impairment of balance; Stage 3=mild to moderate bilateral disease, some postural instability, physically independent; Stage 4=severe disability, still able to walk or stand unassisted; and Stage 5=wheelchair bound or bedridden unless aided. The H&Y scale has since been modified with the addition of stages 1.5 (unilateral and axial involvement) and 2.5 (mild bilateral disease with recovery on pull test) to account for the intermediate course of PD.

8.1.1.6 Montreal Cognitive Assessment

The Montreal Cognitive Assessment (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.

In a study of 3706 participants aged 63 to 65 years old from the general population of Norway, the mean MoCA score was 25.3 (95% confidence interval [CI]: 25.2 to 25.4), and 49% of the participants scored below the suggested cutoff score of 26 points. The education level had a significant impact on the test results (>12 years education; mean 26.2, 95% CI: 26.1 to 26.3, median 27 versus ≤12 years education; mean 24.4, 95% CI: 24.3 to 24.6, median 25, p<0.001). The authors suggested that the cutoff score of 26 for mild cognitive impairment (MCI) may have been set too high to distinguish normal cognitive function from MCI (Ihle-Hansen et al, 2017).

To decrease the learning effect from multiple administrations of the MoCA over a short period of time, alternate versions have been made available. The full test has also been adapted for people with disabilities including both physical and mental. The latest full version of the test is now available on an iPad (https://www.mocatest.org/about/).

The MoCA will be assessed at the visits specified in the Schedule of Activities (Section 1.3).

8.1.2 Patient-reported outcomes

Patient-reported outcomes must be completed as per time points mentioned in the Schedule of Activities (Section 1.3).

Patient-reported outcomes must be completed by study participants in a quiet place by themselves without the help of a partner or caregiver, before any clinical examination takes place. During the Treatment Period, PROs will be completed prior to dosing with ST.

Study participants should be informed of the importance of the PRO questionnaires and should be instructed to read the PRO items and instructions carefully. They should be informed that there are no right or wrong answers.

Study personnel are not allowed to interpret the items for the participant. If a participant asks for guidance, study personnel should instruct him/her to respond according to their best understanding of the item.

Patient-reported outcomes should only be checked for completeness by study personnel. In the event a few questionnaire items have not been completed, study personnel should merely enquire to the study participant if this results from an omission. Study personnel shall neither complete missing data nor suggest changes to participant responses. Like any other study data, responses to the questionnaire should be treated as confidential information. Data privacy considerations apply.

The PROs should be completed in the following order: Early PD Function Slowness PRO; Early PD Mobility PRO; FATIGUE-PRO; WOQ-9; and Euro Quality of life 5-Dimensions 5-Level (EQ-5D-5L).

Time required to complete the first 3 PROs listed above was tested with a sample of 6 participants with early-stage PD in PD0053 and was approximately 12 to 15 minutes. Completion of EQ-5D-5L requires approximately 10 additional minutes.

8.1.2.1 Early PD Function Slowness PRO

The Early PD Function Slowness PRO instrument consists of 45 items across 4 domains: 19 motor (upper limb) items, 9 motor (complex or lower limb) items, 9 complex activities (motor and cognitive) items and 8 cognitive items. Participants are asked to score each item based on how slow they may have been when performing daily activities over the past 7 days, using a 5-point Likert scale (“Not at all” to “Extremely slow”). Being an exploratory PRO instrument, no scoring algorithm currently exists. Final PRO content and scoring structure will be informed by analyses performed on external data as well as on PD0053 data.

8.1.2.2 Early PD Mobility PRO

The Early PD Mobility PRO instrument consists of 23 items. Participants are asked to score each item based on whether they have experienced any issue with walking and moving over the past

7 days, using a 5-point Likert scale ("Not at all" to "Extremely"). Being an exploratory PRO instrument, no scoring algorithm currently exists. Final PRO content and scoring structure will be informed by analyses performed on external data as well as on PD0053 data.

8.1.2.3 FATIGUE-PRO

The FATIGUE-PRO is a PRO instrument that quantifies fatigue, originally developed for Systemic Lupus Erythematosus. It consists of 31 items across 3 scales: 'physical fatigue' (9 items; 1 to 9), 'mental and cognitive' (11 items; 10 to 20), and 'susceptibility to fatigue' (11 items; 21 to 31). Study participants are asked to rate each item based on how frequently they experienced it over the past 7 days, using a 5-point Likert scale ranging from 'none of the time' to 'all of the time'. The FATIGUE-PRO currently does not translate into a total score summary. Scale scores are transformed into a score ranging from 0 to 100, with higher scores indicating higher levels of fatigue.

8.1.2.4 WOQ-9

The well-described WO phenomenon is the shortening effect of levodopa, which can be managed with dosage adjustment or adjuvant therapy, such as COMT inhibitors (Pahwa and Lyons, 2009).

The questionnaire selected for this study is the WOQ-9 containing the most valuable questions for PD patients of all stages for the following 9 items: 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).

The WOQ-9 has been recognized by a task force of the Movement Disorder Society as a recommended diagnostic screening tool for its ability to detect WO in PD patients (Antonini et al, 2011).

The WOQ-9 defines the presence of WO as the presence of at least 1 symptom with improvement after the next dose of antiparkinsonian medication (Stacy et al, 2008, COMPASS-I study).

The WOQ-9 will be assessed after initiation of ST at the visits specified in the Schedule of Activities (Section 1.3).

8.1.2.5 EQ-5D-5L

The EQ-5D-5L consists of the Euro Quality of life 5-Dimensions descriptive system and the Euro Quality of life 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: no problems, slight problems, moderate problems, severe problems, and extreme problems. These levels are expressed as a 1-digit number, and the digits for the 5 dimensions are combined into a 5-digit number that describes the participant's health state (eg, 13414). The 1-digit numbers for each of the 5 dimensions will be summarized categorically by visit, treatment group, overall and by gender. Shift tables will also be produced by dimension. The 5-digit numbers will be used in the listings.

The EQ-5D-5L allows derivation of utility scores from country-specific value sets that are then incorporated into health economic models (cost-utility analyses) as used in health technology assessments in several countries around the world. The EQ-5D-5L utility weights range from

1.0 (perfect health) to 0 (death) and can even describe health-related QoL states below 0, ie, a state worse than death (this is rare).

The EQ VAS records a patient's self-rated health on a vertical visual analog 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").

8.1.3 In-study patient interviews (US and UK only)

A target of up to 30 in-study patient interviews will be conducted with a sample of US and/or UK study participants mainly to generate additional evidence on the adequacy of UCB's newly developed PRO instruments in early-stage PD.

Interviews will be optional and will be conducted between Baseline and up to 1 month into the study. Participants will be asked to sign the specific informed consent to participate in the interview. Objectives are 3-fold: cognitive debriefing of the Early PD Function Slowness and Mobility PRO items as well as some MDS-UPDRS Part III items, generation of early evidence on clinically meaningful change, and discussion on study participation experience.

Interviews will be organized and conducted by independent specialist qualitative social research scientists (refer to FDA Patient-Focused Drug Development Public Workshop Guidance 2 Discussion Document – Appendices [Appendix 3 Section B]).

8.1.4 Koneksa Neuroscience Toolkit

The Koneksa Neuroscience Toolkit will be used to collect data related to PD motor symptoms and impacts on daily living. In addition, study participant feedback about the usability of the Koneksa Neuroscience Toolkit will be collected via an electronic questionnaire that will be completed during the study at Visit 4 (Month 1), Visit 6 (Month 6), and Visit 8 (Month 18).

The data collected and analyzed do not guide the therapy administered or guide any other medical decisions during this study. The obtained data are assessed only as exploratory endpoints.

Details on active and passive assessments to be performed with the Koneksa Neuroscience Toolkit are summarized in Table 8–1.

Active tests are performed through the iPhone. Specifically, study participants will conduct an "active test" every week at approximately the same time, once in the practically defined "OFF" state and once in the "ON" state. This will be a set of routine, easy-to-perform activities, that reflect how participants are able to perform with regard to motor function and speech. The active test consists of a short, preconfigured schedule of tasks that capture PD symptoms. Study participants who are not on any ST will conduct one assessment upon waking. Smartphone sensor data will be recorded continuously, throughout the active tests.

Passive tests are performed through the CPIW. As part of passive tracking of daily activities and sleep (optional), study participants will be instructed to wear the provisioned smartwatch on their most affected side starting in the evening of the day prior to the active tests and ending in the evening of the active tests day. Smartwatch sensor data will be recorded continuously throughout the active tests. If participants do not want to wear the smartwatch during sleep, they will be asked to wear it from awakening prior to the active assessments to the evening after the active assessments.

In addition, patient-reported data will be collected through the iPhone. These include an electronic version of the MDS-UPDRS Part II (activities of daily living), ST medication intake, sleeping hours, and ON/OFF status of study participants.

Table 8–1: Activities to be performed with the Koneksa Neuroscience Toolkit

	Instrument/Measure	Frequency	Hardware
Active Tests	20-second walk test assessment	1 day/week; for participants on ST medication 2x/day, first in "OFF" state, then in "ON" state; for participants not on ST medication, once per day	iPhone
	Pronation/supination assessment		
	Postural, kinetic, and resting tremor assessments		
	Finger tap assessment		
	Aural Analytics speech assessment		
Passive Tests	Actigraphy device worn for specific monitoring periods; walk periods analyzed for gait and balance features	Passive 12 to 24 hrs, 1 day/week	CPIW
	Total sleep time and # of wake bouts per worn epoch via actigraphy device worn for specific monitoring periods		
	Steps per day		
Patient-Reported Data	Confirm time point of most recent symptomatic treatment intake	Weekly aligned with morning motor assessments	iPhone
	Confirm sleep time	Weekly aligned with morning motor assessments	iPhone
	Electronic MDS-UPDRS Part 2	Weekly aligned with motor assessments in "OFF" state	iPhone
	Usability and Experience Questionnaire	3 times per study	iPhone

CPIW=CentrePoint Insight Watch; MDS-UPDRS=Movement Disorder Society Unified Parkinson's Disease Rating Scale; ST=symptomatic treatment

Study participants will be consented and trained to use the Koneksa Neuroscience Toolkit during the study as described in Section 6.9. The Koneksa Neuroscience Toolkit will be handed over to participants at Visit 2 (Baseline Visit). Following Visit 2 (Baseline Visit), participants will use the Koneksa Neuroscience Toolkit at home.

Baseline assessments will take place from the evening of Day 0 (Visit 2 [Baseline Visit]) to the evening of Treatment Period Day 1. Study participants will be asked to wear the ActiGraph CPIW (ie, smartwatch) as of the evening of Day 0 (Visit 2 [Baseline Visit]).

Active Baseline tests are done on Treatment Period Day 1. "OFF" assessments are done prior to the intake of the first IMP in the morning of Day 1. "ON" assessments are done after the first intake of IMP and intake of ST.

All subsequent active tests will be done on a weekly basis after intake of the morning dose of IMP at approximately the same time.

The Koneksa Neuroscience Toolkit will guide/alert study participants on required activities with regards to passive and active assessments.

Study participants will be encouraged to adhere to the daily schedule of tasks as much as possible; however, participants will not be excluded from the study if they do not adhere to the planned activities.

Detailed instructions concerning the Koneksa Neuroscience Toolkit will be provided to the participating Investigators in a separate manual prior to the start of Koneksa Neuroscience Toolkit deployment in the study.

8.2 Safety assessments

Planned time points for all safety assessments are provided in the Schedule of Activities (Section 1.3).

8.2.1 Physical examination

A complete physical examination will include, at a minimum, general appearance; ear, nose, and throat; eyes, hair, and skin; and assessments of the cardiovascular, respiratory, gastrointestinal, musculoskeletal, and hepatic systems.

Investigators and site staff should pay special attention to clinical signs related to previous serious illnesses and hypersensitivity reaction (such as rash, angioedema, or anaphylaxis). For any emergent lesion or abnormality on the skin, a full examination of skin and close observation is required to exclude possibility of a hypersensitivity reaction as per Section 8.3.6.1.

Clinically relevant findings or worsening of previous findings will be recorded as AEs.

Weight will be measured and recorded at Visit 2 with the study participant wearing light clothing and without wearing shoes; the outcome will be rounded to the nearest 0.1kg.

8.2.2 Neurological examination

The complete neurological examination will include selected assessment of general neurological status (level of consciousness, mental status, speech), cranial nerves, reflexes, motor system (general motor status, muscle strength, muscle tone), coordination/cerebellar function, and sensation. The day before or the day of the lumbar puncture, a complete neurological examination should be performed in accordance with local safety procedures and results should be available prior to performing the lumbar puncture.

Clinically significant neurological examination findings will be recorded as AEs.

8.2.3 Vital signs

Vital signs (to be taken before blood collection for laboratory tests) will consist of 3 pulse and 3 blood pressure (BP) measurements (3 consecutive BP readings will be recorded at intervals of

at least 1 minute). Blood pressure has to be measured in the supine and erect positions to assess autonomous dysregulation (Trendelenburg test).

All pulse and BP readings will be recorded on the eCRF, and the average will be derived for analyses.

8.2.4 ECGs

Electrocardiogram recordings will be obtained as outlined in the Schedule of Activities (Section 1.3).

The study participant should be resting in the supine position for at least 10 minutes before the start of the recordings. Electrocardiogram recordings will be single reads but can be repeated in triplicate if clinically indicated.

The Investigator should review all ECG recordings and, if there are abnormalities that are considered clinically significant for a particular study participant, then the Investigator should initiate a review by a specialist of all ECG data pertaining to that study participant. The following ECG parameters will be recorded in the eCRF: heart rate, PR interval, QRS duration, QT interval, QTcF, and Investigator's conclusion on ECG profile.

8.2.5 Clinical safety laboratory assessments

See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and the Schedule of Activities (Section 1.3) for the timing and frequency.

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of IMP should be repeated until the values return to normal or Baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

If such values do not return to normal/Baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.

All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the Schedule of Activities (Section 1.3).

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE), then the results must be recorded in the eCRF.

8.2.6 Suicidal risk monitoring

Minzasolmin (UCB0599) is a CNS-active IMP. There has been concern that some CNS-active IMPs may be associated with an increased risk of suicidal ideation or behavior when given to some participants with PD.

Suicidality will be assessed by trained site study personnel using the C-SSRS (Posner et al, 2011). This scale will be used to assess suicidal ideation and behavior that may occur during the study. All study participants will complete the "Since Last Visit" version at the visits indicated on the Schedule of Activities (Section 1.3).

Participants being treated with minzasolmin (UCB0599) should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior. Families and caregivers of participants being treated with minzasolmin (UCB0599) should be instructed to monitor participants for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior, and to report such symptoms immediately to the study Investigator. Consideration should be given to discontinuing minzasolmin (UCB0599) in participants who experience signs of suicidal ideation or behavior. Study stopping behavior for study participants with suicidal ideation or behavior is described in Section 7.2.

8.3 Adverse events and serious adverse events

The definitions of an AE or SAE can be found in Appendix 3 (Section 10.3).

Adverse events will be reported by the participant (or, when appropriate, by a caregiver or surrogate).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the IMP or study procedures, or that caused the participant to discontinue minzasolmin (UCB0599) or PD0055 (see Section 7).

On the AE eCRF page, there is the possibility to assess causality to the IMP and to any concomitant medication. If an AE is considered related to COVID-19 vaccine, a causality assessment should be entered in the AE eCRF.

Note that in this case the national recommendation for reporting AEs related to COVID-19 vaccines should be followed.

If an AE is the result of an interaction between a COVID-19 vaccine and IMP in the study, then the clinical study causal association should be for both IMP and COVID-19 vaccine.

For results disclosure on public registries (eg, ClinicalTrials.gov), TEAEs and treatment-emergent SAEs will be published.

8.3.1 Time period and frequency for collecting AE and SAE information

All AEs and SAEs will be collected from the signing of the ICF until the SFU Visit at the time points specified in the Schedule of Activities (Section 1.3).

In order to ensure complete safety data collection, all AEs occurring during the study (ie, after the signing of the ICF), including any pretreatment and posttreatment periods required by the protocol, must be reported in the eCRF even if no IMP was taken but specific study procedures were conducted. This includes all AEs not present prior to the initial visit and all AEs that recurred or worsened after the initial visit.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE data to the Sponsor without undue delay but not later than within 24 hours of it being available.

The Investigator is specifically requested to collect and report to UCB (or its representative) any SAEs (even if the Investigator is certain that they are in no way associated with the IMP), up to 30 days from the end of the study for each participant, and to also inform participants of the need to inform the Investigator of any SAE within this period. Serious AEs that the Investigator thinks may be associated with the IMP must be reported to UCB regardless of the time between the event and the end of the study.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

8.3.2 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and AESIs (as defined in Section 8.3.6) will be followed until resolution, stabilization, the Investigator determines that it is no longer clinically significant, the event is otherwise explained, or the participant is lost to follow up (as defined in Section 7.3). Further information on follow up procedures is given in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of an IMP under clinical investigation are met.

Further to the reporting of an SAE from the Investigator to the Sponsor, an expectedness assessment will be made per the IB, as reference safety information for this study, and relevant Sponsor's SOPs and appropriate reporting of suspected unexpected serious adverse reactions (SUSARs) will be carried out to health authorities as per ICH and local regulatory requirements.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of an IMP under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and Investigators.

An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of IMP and until at least 12 months after the delivery date.

If a pregnancy is reported, the Investigator must immediately inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).

The participant should be withdrawn from the study as soon as pregnancy is known (by positive pregnancy test [ie, a positive urine test confirmed with a blood test]), and the following should be completed:

- The participant should return for an early discontinuation visit.
- The participant should immediately stop the intake of the IMP as instructed at the early discontinuation visit.
- An SFU Visit should be scheduled 14 days after the participant has discontinued her IMP.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6 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:

- Hy's Law
  - 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, with no alternative explanation for the biochemical abnormality (ie, without waiting for any additional etiologic investigations to have been concluded). Follow-up information should be reported if an alternative etiology is identified during investigation and monitoring of the participant.
- Hypersensitivity reactions (such as rash, angioedema, or anaphylaxis)

8.3.6.1 Hypersensitivity reaction monitoring and management

If a study participant experiences a hypersensitivity reaction (such as rash, angioedema, or anaphylaxis), he or she will contact the clinical site immediately (24 hours a day) or seek urgent medical advice in accordance with instructions from the Investigator.

The advice will be based on the clinical presentation and may be to present to the clinical site or seek medical attention in the community.

The study participant should be rapidly and thoroughly assessed in line with the actions below.

Hypersensitivity reactions (such as rash, angioedema, or anaphylaxis) will be AESIs and require expedited reporting to UCB, regardless of seriousness, expectedness, or relatedness in line with Section 8.3.6. This will allow for rapid evaluation.

In case of a suspected hypersensitivity reaction (such as rash, angioedema, or anaphylaxis) or any clinical indication of an unexpected immune response, the points described in Sections 8.3.6.1.1 through 8.3.6.1.4 should be observed.

Consideration for restarting IMP is provided in Section 7.1.1.

8.3.6.1.1 Medical history

Detailed history of the hypersensitivity reaction (eg, rash, angioedema, or anaphylaxis) with onset time of symptoms and signs, location of symptoms and signs, first appearance, its evolution (eg, where the rash appeared and to where it spread), any other symptoms (eg, pruritus, swelling, breathlessness), especially if showing a systemic involvement (anaphylaxis), will be recorded. The criteria for anaphylaxis are described in Section 8.3.6.1.1.1.

The clinical progression of the hypersensitivity reactions symptoms should be recorded and any change in symptoms or severity should also be recorded together with the timing.

All AEs reported concurrently should be included within the review.

It will also be important to investigate any recent intake of new medications, herbs, supplements, or the recent use of any topical substances.

8.3.6.1.1.1 Anaphylaxis

Sampson et al. listed criteria for the diagnosis of anaphylaxis. This was developed at the Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium (Sampson et al, 2006).

Acute onset=minutes to a few hours.

Criteria for diagnosis-1 or more of the following:

- Acute onset of an illness with symptom complex 1 (see below)
- Acute onset of symptom complex 2 (see below) after exposure to a likely allergen
- Acute onset of a reduced systolic blood pressure (SBP) after exposure to a known allergen for the participant.

Symptom complex 1: both of the following:

- At least 1 of the following:
  - Skin involvement (generalized hives, pruritis, flushing)
  - Mucous membrane involvement (swollen lips, swollen tongue, swollen uvula)
- At least 1 of the following:
  - Respiratory compromise (dyspnea, wheezing, bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)

– Reduced SBP, collapse, syncope, incontinence or other symptom of end-organ dysfunction

Symptom complex 2: Two or more of the following:

- Skin or mucous membranes (as above)
- Respiratory compromise (as above)
- Reduced BP (as above)
- Persistent gastrointestinal tract symptoms (cramping, abdominal pain, vomiting)

Reduced SBP is indicated by 1 of the following:

- BP <70% of Baseline SBP
- Age ≥11 years AND <90mmHg

Limitations:

Treudler et al. found that the criteria may not perform as well as others for the recognition of severe, immediate reactions (Treudler et al, 2008).

8.3.6.1.2 Complete physical examination

Evaluation of a possible hypersensitivity reaction (such as rash, angioedema, or anaphylaxis) includes a complete physical examination of the entire body as soon as feasible after reporting by the study participant. The complete physical examination includes a detailed description of the signs such as rash or angioedema, the location of the signs, and an examination for other possible signs, such as:

- Blanched or flushed skin
- Mucous membrane erosions or ulceration
- Maculae
- Papulae
- Blisters
- Confluent erythema
- Angioedema: face, lips, and/or tongue swelling, also back of hands or feet
- Wheeze, stridor, dyspnea
- Palpable purpura
- Lymphadenopathy

An examination of the entire skin surface, not just local to the site of reaction, is required.

Furthermore, a complete physical examination will also include:

- Vital signs (high fever, dyspnea, or hypotension)
  - Vital signs (pulse rate, SBP, diastolic BP, respiratory rate, body temperature, and oxygen saturation) will be taken when the AE of hypersensitivity is reported and at regular intervals (approximately 20 to 30 minutes) for a minimum of 2 hours. The frequency thereafter will be based on clinical judgement. If there is worsening of clinical status, the Investigator will apply the appropriate treatment and safety procedures (eg, call emergency) and contact the UCB study physician.
- Photography of rash and other symptoms at the first opportunity and with reasonable time sequence to document resolution. If timely site visit is not possible the participant may be requested to take photos to ensure photos of active symptoms. If participant is requested to provide photos the Investigator should advise the participant in data protection requirements (eg, avoidance of identifying features such as characteristic tattoos, parts of the face). The Investigator will ensure that identifiable characteristics are removed / hidden before sharing the pictures with the Sponsor.
- Re-examination should the symptoms significantly worsen
- Occurrence of other recent or current symptoms, even if they appear not related

8.3.6.1.3 Additional investigations

Investigators should arrange for the following investigations; further investigations may be requested after consultation with the Medical Monitor:

- Additional blood sampling for extended etiological characterization of the hypersensitivity reaction including:
  - Basophil Activation Test
  - Lymphocyte Transformation Test assays
  - Tryptase
  - Immunoglobulin E
- Rapid referral to experts (ie, dermatologist, allergist, or immunologist)

Additionally, a skin biopsy should be considered following review by expert.

8.3.6.1.4 Treatment

Investigators will administer the appropriate treatment as deemed necessary in cases of hypersensitivity. This includes the use of antihistamines for urticaria and the appropriate management in case of potentially life-threatening events such as anaphylaxis, Stevens-Johnson Syndrome, and toxic epidermal necrolysis.

8.3.6.2 Renal function safety monitoring and management

If a participant develops clinically significant renal dysfunction, repeat laboratory testing should be undertaken as soon as possible and other appropriate investigations may be arranged. An increase in serum creatinine of >25% from the previous value will trigger repeat testing within

48 hours. The Medical Monitor should be notified, and consideration should be given to more frequent monitoring.

Clinically significant renal dysfunction will trigger an SMC and DMC review.

Participants must be discontinued from IMP (but not necessarily from the study) if laboratory tests suggest evidence of renal toxicity (see Section 7.2). Any clinically significant findings in laboratory results for renal function will be monitored until resolution or stabilization.

The SMC and DMC charters will include further details regarding the assessment of renal function.

8.3.7 Digital Health Technology safety reporting

The Koneksa Neuroscience Toolkit is being provided as a noninvasive exploratory tool for assessing motor function, speech, physical activity, and sleep (optional) in study participants who volunteer to use it.

To fulfill regulatory obligations worldwide, the Investigator is responsible for detecting and documenting events associated with the use of the Koneksa Neuroscience Toolkit and notifying Koneksa Health Inc. of such events, if they meet the definitions of incident or malfunction and occur during the study with the Koneksa Neuroscience Toolkit.

The processes for detecting, recording, and reporting of AEs and SAEs are outlined in Section 8.3 and also pertain to any AE or SAE observed during the study and related to the Koneksa Neuroscience Toolkit. The processes outlined below describe additional activities for AEs and SAEs related to the components of the Koneksa Neuroscience Toolkit as well as deficiencies related to the Koneksa Neuroscience Toolkit.

For AEs, SAEs, and deficiencies related to the mobile software application and the Apple iPhone components of the Koneksa Neuroscience Toolkit, the Investigator is responsible for notifying Koneksa Health Inc. (via a message to help@koneksahealth.com).

For adverse device effects (ADEs) related to the ActiGraph CPIW (including its Data Hub) component of the Koneksa Neuroscience Toolkit, the Investigator is responsible for notifying Koneksa Health Inc. (via a message to help@koneksahealth.com). Refer to Appendix 7 (Section 10.7) for definitions of ADE, serious ADE (SADE), and device deficiency.

Of note, events fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 8.3.3 and Appendix 3 (Section 10.3).

Koneksa Health Inc. will support the Sponsor on any follow-up for ADEs/SADEs and deficiencies related to the Koneksa Neuroscience Toolkit that occur during the study.

8.3.7.1 Time period for safety reporting

Adverse events will be collected at the timepoints specified in the Schedule of Activities (Section 1.3; Koneksa Neuroscience Toolkit safety).

Adverse events, ADEs, and device deficiencies will be detected, documented, and reported during all periods of the study in which the Koneksa Neuroscience Toolkit is used.

If the Investigator learns of any safety information or deficiency related to the Koneksa Neuroscience Toolkit at any time after a study participant has been discharged from the study,

and such event(s) is/are considered reasonably related to the Koneksa Neuroscience Toolkit, the Investigator will promptly notify Koneksa Health Inc. (via a message to help@koneksahealth.com) if the study is ongoing. If the Sponsor becomes aware of any ADE/SADE or deficiency related to the use of the Koneksa Neuroscience toolkit after study completion, the Sponsor will inform Koneksa Health Inc.

In all cases, Koneksa Health Inc. will support the Sponsor on any subsequent follow-up.

The process for documentation is provided in Appendix 7 (Section 10.7).

8.3.7.2 Follow-up of AEs, ADEs, and device deficiencies

Follow-up applies to all study participants, including those who discontinue study medication and/or the study.

The Investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the AE, ADE, or deficiency.

New or updated information will be forwarded to Koneksa Health Inc. and documented as per Appendix 7 (Section 10.7).

8.3.7.3 Reporting of AEs, ADEs, and device deficiencies

The Investigator will notify AEs (including SAEs) and deficiencies associated with the mobile software application or the Apple iPhone, as well as ADEs (including SADEs) and device deficiencies associated with the ActiGraph CPIW to Koneksa Health Inc. (via a message to help@koneksahealth.com) within 24 hours after the Investigator determines that the event meets the protocol definition of an event that should be reported. The definitions and the process for documentation are provided in Appendix 7 (Section 10.7).

The Investigator will provide Koneksa Health Inc. (via an attachment to a message to help@koneksahealth.com) with the respective information using the Adverse Event and Device Deficiency Form supplied by the Sponsor. Koneksa Health Inc. is responsible for the subsequent reporting to the respective manufacturers as applicable.

8.3.8 Safety reporting for in-study patient interviews (US and UK only)

Any potential AE reported by participants during a qualitative interview will be reported to the site from which the participant was recruited, and the site will be responsible for checking their records if the AE has already been reported by the participant during the clinical study. If it has already been reported by the participant, the AE will be considered reconciled. If the AE has not been previously reported, the site will be responsible for reporting the AE in the eCRF according to the AE reporting procedures in Appendix 3 (Section 10.3).

8.4 Safety signal detection

Selected data from this study will be reviewed periodically to detect as early as possible any safety concern(s) related to the IMP so that Investigators, clinical study participants, regulatory authorities, and IRBs/IECs will be informed appropriately and as early as possible.

The study physician or medically qualified designee/equivalent will conduct an ongoing review of SAEs and perform ongoing SAE reconciliations in collaboration with the Patient Safety representative.

As appropriate for the stage of development and accumulated experience with the IMP, medically qualified personnel at UCB may identify additional safety measures (eg, AEs, vital signs, laboratory or ECG results) for which data will be periodically reviewed during the course of the study.

8.5 Treatment of overdose

For this study, any administration of minzasolmin (UCB0599) totaling greater than 360mg within approximately a 24-hour time period will be considered an overdose.

Overdose events are only considered AEs or SAEs if there are associated clinical signs and symptoms or if the act of taking the excess IMP itself is an AE or SAE (eg, suicide attempt).

UCB does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator or treating physician should:

- Stop dosing and contact the Medical Monitor immediately.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until minzasolmin (UCB0599) can no longer be detected systemically (approximately 5 days).
- Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.6 Pharmacokinetics

Pharmacokinetic parameters will not be evaluated in this study.

8.7 Genetics

Genetic blood samples were collected in PD0053.

8.8 Pharmacodynamics

DaT-SPECT (Section 8.1.1.1) and CSF ASYN (Section 8.9) will be used as pharmacodynamic biomarkers to evaluate the biological response to minzasolmin (UCB0599) treatment.

8.9 Biomarkers

Imaging biomarker DaT-SPECT assessment is discussed in Section 8.1.1.1. Collection of CSF and blood samples for potential exploratory biomarker research forms part of the study objectives.

The ASYN seeding assay in CSF has been recently demonstrated (Siderowf et al, 2023) to be a robust (qualitative - Yes/No) biomarker of Lewy body pathology in PD. Active and vigorous steps are being taken in the field to develop a quantitative assay of the biomarker. This promising quantitative assay could potentially be a marker of disease progression/response to therapy in the near future for drugs targeting ASYN, including minzasolmin (UCB0599; the active IMP in this study). Since few study participants opted to consent to CSF sampling in PD0053, a renewed attempt (still optional for study participants) will be made in PD0055 to collect CSF samples to serve as a biomarker that may help gain valuable insights for Phase 2 readout and for Phase 3 planning and assay development.

The CSF samples will be collected for assessment of ASYN markers, ie, total ASYN and ASYN oligomerization. Alpha-synuclein oligomerization is believed to result into the toxic species responsible for the neuronal spread of pathology underlying the ASYN pathology in brain and probably also the decrease of total ASYN release into the CSF of patients. Total ASYN levels in CSF will be assessed using a commercially available enzyme-linked immunosorbent assay. Pathological ASYN species (eg, ASYN seeds) may also be assessed.

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

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.

Cerebrospinal fluid and blood samples for measurement of biomarkers will be collected at the time points specified in the schedule of Schedule of Activities (Section 1.3). These samples should be collected only after all other assessments of the visit have been performed. As part of each individual CSF sampling procedure, a maximum of 12mL of CSF during each lumbar puncture will be collected and a CSF quality control check (total cell count and/or hemoglobin measurement) will be done to identify a possible contamination with blood caused by lumbar puncture.

Instructions pertaining to sample collection, processing, storage, labeling, and shipping are provided in the PD0055 Laboratory Manual for this study.

8.10 University of Pennsylvania Smell Identification Test

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. It is a widely used smell test for assessing hyposmia in individuals with PD (Doty, 2012; Doty et al, 1984). The UPSIT will be completed as specified in the Schedule of Activities (Section 1.3) and the User Manual for further characterization of the study population. Site staff will perform the UPSIT with each study participant once during the Treatment Period and record results in the eCRF. Site staff will document if the underlying cause for hyposmia may be due to other underlying conditions than PD, eg, COVID-19. The UPSIT will not be used for medical treatment decision making or for participant management during the study.

8.11 Medical resource utilization and health economics

Not applicable.

9 STATISTICAL CONSIDERATIONS

A description of statistical methods follows and will be described in more detail in the statistical analysis plan (SAP).

9.1 Definition of analysis sets

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 demographic, safety, and efficacy analyses.

For efficacy, analyses will be based on treatment assigned in PD0055; for safety, analyses will be based on treatment actually received in PD0055.

Note: A Full Analysis Set will not be defined in this study.

9.2 General statistical considerations

All analyses will be performed using SAS® version 9.4 or later (SAS Institute, Cary, NC, US).

9.2.1 Descriptive statistics and modeling

For continuous variables, summary statistics will include the number of study participants, mean, median, standard deviation (SD), minimum, and maximum, unless stated otherwise. Categorical endpoints will be summarized using frequency counts and percentages. Further details on which summary statistics will be presented for each variable type will be given in the SAP.

Baseline will refer to PD0053 Baseline Visit data (or Screening Visit data where applicable). Longitudinal analyses will include data from the PD0053 Baseline/Screening Visits (as applicable). All time points will be specified with reference to the PD0053 Baseline/Screening Visits.

The estimations for the treatment of interest for the Primary Efficacy Objective/Estimand and for the Exploratory Efficacy Objective III (dose comparison) can be obtained from a single analysis using a 3-category treatment effect: the "Early-start 360mg/day" arm, the "Early-start 180mg/day" arm, and the "Delayed-start 360mg/day" arm. The estimations will be, respectively:

- Difference at 36 months ("PD0055 Month 18 analysis") and at 78 months ("PD0055 Month 60 analysis") between the Early-start minzasolmin (UCB0599) (360mg/day) arm and the 18-month Delayed-start minzasolmin (UCB0599) (360mg/day) arm, equivalent to half-cumulative dose

  AND
- Difference at 36 months ("PD0055 Month 18 analysis") and at 78 months ("PD0055 Month 60 analysis") between the Early-start minzasolmin (UCB0599) (360mg/day) arm and the Early-start minzasolmin (UCB0599) (180mg/day) arm. Here, the "PD0055 Month 18 analysis" will be a comparison to an equivalent half-cumulative dose, whereas at the "PD0055 Month 60 analysis" the comparison of cumulative doses will depend on the best dose selected.

All analyses will be adjusted for gender and age.

9.2.2 Handling of intercurrent events, protocol deviations, and resulting missing data

The strategies/approaches for handling intercurrent events (ICEs) and protocol deviations 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 occurred (under some hypothetical conditions).

  One such hypothetical condition is that the ICE presented completely at random. In this case, all post ICE data are set to missing (removed) and imputed under the assumption of missing completely at random. 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.

  Alternative imputation approaches will also be considered for ICEs which are considered to be informative with respect to the effect of interest, ie, treatment-related study termination and treatment discontinuation, such as reference-based imputation (RBI) approaches (see SAP for details).

  This approach will reflect the treatment effect had the ICE not occurred.

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

For the primary and secondary Objectives/Estimands, an overview of the handling strategies for ICEs, protocol deviations, study termination/loss to follow up, and resulting missing data is presented in Table 9-1.

Imputation approaches to deal with missing data, censored data, and removed data due to the "Hypothetical" handling strategy will be described in detail in the SAP.

Table 9-1: Overview of handling strategies for ICEs and approach in case of study termination

	DaT-SPECT whole striatum SBR	Cumulative LEDD
Estimand	**Primary**	**Secondary**
	Regardless of ST initiation / type / dose	**ST initiation / type / dose as integral part**
ICE		
ST	Treatment policy (Include post ICE data)	Composite (ICE data incorporated into endpoint)
AE-related treatment discontinuation	Treatment policy (Include post ICE data)	id
Treatment discontinuation (all other causes)	Treatment policy (Include post ICE data)	id
Other protocol deviations - Important	Hypothetical (Impute post ICE data [a])	id
Other protocol deviations - Not important	Treatment policy (Include post ICE data)	id
Death or serious injury (all causes)	Hypothetical (Impute post ICE data [a])	id
Confirmed or suspected cases of COVID-19 without treatment discontinuation or study termination	Treatment policy (Include post ICE data)	id
COVID-19 vaccination	Treatment policy (Include post ICE data)	id
Study termination and loss to follow-up		
Treatment related	Hypothetical (Impute post termination data [a])	id
Other/unknown causes	Hypothetical (Impute post termination data [a])	id

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; WOQ-9=Wearing-Off Questionnaire - 9; SBR=specific binding ratio; SAP=statistical analysis plan; ST=symptomatic treatment

Note: The handling strategies are defined as follows: "Treatment policy" – include post ICE data; "Hypothetical" – remove post ICE data and impute missing data.

[a] Approach to data imputation will be detailed in the SAP.

9.2.2.1 ICEs potentially affecting the interpretation of measurements

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.

9.2.2.1.1 ST initiation

9.2.2.1.1.1 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 9-1). Monoamine oxidase-B inhibitors will not be allowed in this study (see Section 6.5.2 and Section 6.5.3). 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 randomness (MAR) in the primary analysis.

Missing data due to scan not having taken place at the participant's or Investigator's discretion will be treated as MAR.

9.2.2.1.1.2 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.

9.2.2.1.2 Treatment discontinuation (without consent withdrawal)/nonadherence

Participant-led or Investigator-led (see details on stopping criteria in Section 7) treatment discontinuation may be related to assigned investigational treatment (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" handling strategy - see SAP for details).

Minor treatment nonadherence (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" handling strategy – see SAP for details).

Major treatment nonadherence or drug administration error will be considered uninformative with respect to the effect of interest, and the post ICE data will be removed in the analyses and the post ICE missing data will be imputed ("Hypothetical" handling strategy – see SAP for details).

9.2.2.2 ICEs potentially affecting the existence of measurements

In addition, bias may be introduced through drop out, loss to follow up, and dissent to enter the extension study PD0055 following the proof-of-concept study PD0053.

9.2.2.2.1 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 (see Section 7.2).

Where the cause for study termination is known to be unrelated to assigned investigational treatment or unknown (including loss to follow up), study termination will be considered uninformative with respect to the effect of interest, and the post ICE data will be imputed assuming MAR as the default approach ("Hypothetical" handling strategy – see SAP for details).

9.2.2.2.2 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. Study-related death or death due to other causes (including COVID-19) may occur during the study. 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 – see SAP for details).

9.2.2.3 Protocol deviations

Protocol deviations which are not already predefined as ICEs (eg, nonadherence) could also affect the conduct of the study and/or impact study participant safety as well as key efficacy endpoint measurements.

The criteria for identifying important protocol deviations will be defined within the relevant protocol deviation specification document, which is part of the data cleaning plan. All protocol deviations will be reviewed as part of the ongoing data cleaning process and all important deviations will be identified and documented before unblinding to confirm exclusion from analysis sets. Important protocol deviations will be listed and summarized.

Important protocol deviations (not predefined as ICEs) will be considered uninformative with respect to the effect of interest and the post ICE data imputed assuming MAR as the default approach ("Hypothetical" handling strategy – see SAP for details).

Minor protocol deviations (not predefined as ICEs) will be considered not to impact the effect of interest and the post ICE data included in the analyses ("Treatment policy" handling strategy – see SAP for details).

9.2.2.4 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" handling strategy). This is assuming that the participant remains in the study.

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" handling strategy will be used for this ICE where postvaccination data are kept as part of the analyses.

9.3 Planned efficacy/outcome analyses

9.3.1 Primary efficacy objective (and exploratory efficacy objective III): primary efficacy estimand

9.3.1.1 DaT-SPECT

The main analysis will be based on the SBR of whole striatum calculated as the average of the SBR data values for the 4 following "small" regions: "left caudate small," "left putamen small," "right caudate small," and "right putamen small."

For each region, the SBR will be calculated with the occipital cortex as the 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))

The participant-level endpoint will be DaT-SPECT whole striatum SBR at 36 and 78 months post PD0053 Screening, regardless of ST initiation of, type, dose, and/or change in ST. For DaT-SPECT, Baseline is the value recorded at PD0053 Screening.

Descriptive statistics and visualization

Descriptive statistics for observed results and changes from Baseline in DaT-SPECT whole striatum SBR at PD0053 Screening/Baseline and at all available timepointspost PD0053 Baseline will be presented. Summary tables will be produced by treatment group and visit at PD0053 Screening/Baseline and at all available timepoints post PD0053 Baseline), overall and by gender and age at PD0053 Baseline (age categories to be defined in SAP).

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 (Early-start 360mg, Early-start 180mg, and Delayed-start 360mg), gender, and age category at PD0053 Baseline. Trajectories will be color coded to clearly indicate when a participant initiates ST.

In addition to these individual plots, longitudinal plots of mean observed DaT-SPECT whole striatum SBR will be produced by treatment group, overall as well as by gender and/or age category at PD0053 Baseline. These plots will include error bars (±SD) and all treatment groups will be overlaid on the same plot.

Main analytical approach

A linear mixed effects model (LMEM) for analysis of covariance (ANCOVA) for repeated measures will be used to analyze the longitudinal observed data. Treatment, time (visit, categorical) and treatment by time (interaction term between treatment and visit) will be included as fixed effects, and Baseline DaT-SPECT Striatum SBR will be included as a covariate. A variance-covariance matrix structure will be prespecified to account for repeated measures within a participant.

Handling of the main ICE, ie, initiation/intake of ST, will be "Treatment policy" (include post ICE data). Handling of other ICEs and protocol deviations is summarized in Table 9-1.

Month 18 analysis

At the PD0055 Month 18 analysis data cut, the model will be applied to PD0053 Screening and 12-, 18-, and 36-month post-PD0053 Baseline data.

Month 60 analysis

At the PD0055 Month 60 analysis data cut, the model will be applied to PD0053 Screening and 12-, 18-, 36-, and 78-month post-PD0053 Baseline data.

The population-level summary of interest will be the Baseline-adjusted difference in target population mean in DaT-SPECT Striatum SBR at 36 months (PD0055 Month 18 analysis) and at 78 months (PD0055 Month 60 analysis) regardless of ST initiation between:

- Early-start minzasolmin (UCB0599) (360mg/day) arm and 18-month Delayed-start minzasolmin (UCB0599) (360mg/day) arm; and
- Early-start minzasolmin (UCB0599) (360mg/day) arm and Early-start minzasolmin (UCB0599) (180mg/day) arm.

A summary table presenting the estimates of the treatment effects at all available timepoints and corresponding 95% CIs from this model will be presented.

A plot displaying the adjusted mean and 95% CI for each treatment group from this model (LMEM over all available timepoints) will be produced.

The descriptive statistics and analyses will be repeated for the striatal sub-regions.

Sensitivity analyses

For both the PD0055 Month 18 and Month 60 analyses, the main analysis will be repeated after exclusion of Atypical Parkinsonian Disorders participants (see Section 9.3.5).

Supporting analyses (for PD0055 Month 18 analysis only)

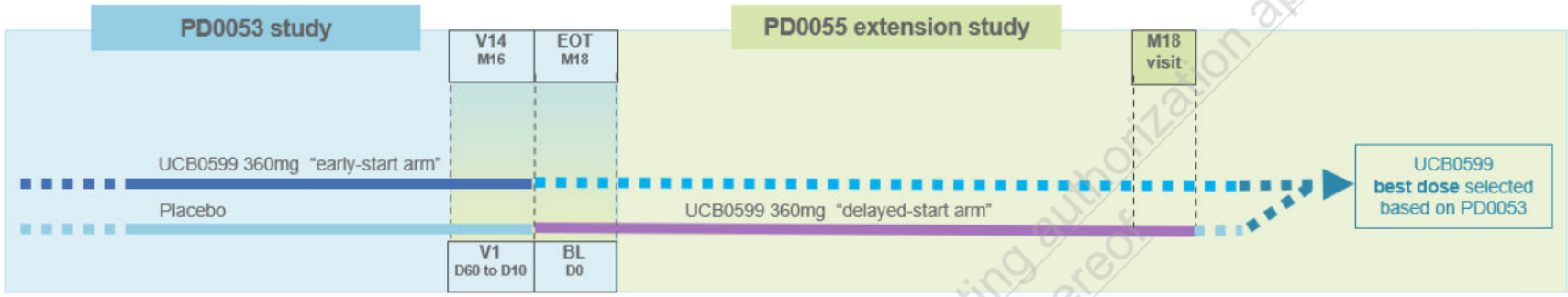
- Observed absolute change from Baseline (mean and SD) over 18 months in DaT-SPECT whole striatum SBR for each of the following groups (see Figure 9-1):
  - 18-month minzasolmin (UCB0599) 360mg/day initiated more than 2 years postdiagnosis (purple line)
  - 18-month minzasolmin (UCB0599) 360mg/day initiated within 2 years of diagnosis (navy line)
  - 18-month placebo arm (participants within 2 years of diagnosis at Baseline) (light blue line)

In addition, participant characteristics such as gender, age at Baseline, and disease duration at Baseline will be summarized for each of the 3 groups.

Exploratory analyses

Exploratory efficacy analyses will be detailed in a PD0055 Exploratory Efficacy Analysis Plan. Any exploratory investigations based on advanced image analysis methods will be detailed in a separate PD0055 Analysis Plan.

Figure 9-1: Delayed-start design (first 18 months)



BL=PD0055 Baseline Visit; D=day; EOT=End of Treatment; M=month; V=visit

9.3.2 Secondary efficacy objective and exploratory efficacy objectives I (III): Secondary estimand

9.3.2.1 LEDD

The participant-level endpoint will be cumulative LEDD up to 78 months post PD0053 Baseline. No Baseline data will be available as participants were "ST-naïve" at PD0053 Baseline.

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 and by gender. Summary statistics will be calculated at Months 12, 18, 24, 36, and 78 post PD0053 Baseline. For participants who have not started ST by a particular visit, their cumulative LEDD will be 0mg 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 individual trajectories of LEDD will be produced by treatment group, gender, and age category at Baseline.

Main analytical approach

An ANCOVA will be used to analyze the 36-month observed data at the PD0055 Month 18 analysis data cut and a separate ANCOVA will be used to analyze the 78-month observed data at the PD0055 Month 60 analysis data cut. Treatment will be included in the model as a categorical fixed effect.

The population-level summary of interest will be the differences in target population mean cumulative LEDD at 36 or at 78 months, depending on the analysis data cut for the treatment comparisons (see Section 9.2.2). Symptomatic treatment dose is an integral part of outcome.

Handling of ICEs and protocol deviations are summarized in Table 9-1.

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.

Sensitivity analyses

For both the PD0055 Month 18 and Month 60 analyses, the main analysis will be repeated after exclusion of Atypical Parkinsonian Disorder participants (see Section 9.3.5).

Exploratory analyses

Exploratory efficacy analyses will be detailed in a PD0055 Exploratory Efficacy Analysis Plan.

9.3.3 Secondary efficacy objective and exploratory efficacy objective I (III): Exploratory estimands/endpoints

9.3.3.1 WOQ-9

For WOQ-9, no Baseline data will be available as participants were "ST-naïve" at PD0053 Baseline.

Descriptive statistics and visualization

Descriptive statistics for observed results at all available timepoints will be presented. Summary tables will be produced by treatment group and visit, overall and by gender and age at PD0053 Baseline (age categories to be defined in SAP).

Details of the plots will be given in the SAP.

Exploratory analyses

Exploratory efficacy analyses will be detailed in a PD0055 Exploratory Efficacy Analysis Plan.

9.3.3.2 MoCA

Descriptive statistics and visualization

Descriptive statistics for observed scores at all available timepoints post PD0053 Baseline will be presented. Summary tables will be produced by treatment group and visit, overall and by gender and age at PD0053 Baseline.

Plots of individual trajectories over time will also be produced. To make these plots interpretable with our large sample size, plots will be produced by treatment group, gender, and age at Baseline. Trajectories will be color coded to clearly indicate when a participant initiates ST.

In addition to these individual plots, longitudinal plots of mean observed MoCA will be produced by treatment group, overall as well as by gender and age at Baseline. These plots will include error bars (±SD) and all treatment groups will be overlaid on the same plot.

Sensitivity analyses

None planned.

Exploratory analyses

Exploratory efficacy analyses will be detailed in a PD0055 Exploratory Efficacy Analysis Plan.

9.3.3.3 FATIGUE-PRO

The participant-level endpoint will be the fatigue subscales score at all available timepoints post PD0053 Baseline. PD0053 Baseline data will be available.

Descriptive statistics and visualization

This PRO will be summarized using continuous summary statistics by visit, treatment group, overall and by gender. The summary will be presented overall and for participants who are not yet on ST. This summary will be repeated for the transformed score, separately for each scale, where transformed score is calculated as:

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

Plots of individual trajectories over time will also be produced based on the raw score of each of the 3 fatigue scales. To make these plots interpretable with our large sample size, plots will be produced by treatment group, gender, and age category (the categories will be defined in the SAP). Trajectories will be color coded to clearly indicate when a participant is and is not on ST. In addition to these individual plots, plots of observed mean and mean change from Baseline will be produced for each fatigue scale, on both the raw and transformed scale, by treatment group

and ST initiation timing category, overall, and by gender. These plots will include error bars (±SD) and all treatment groups will be overlaid on the same plot.

Exploratory analyses

The FATIGUE-PRO is likely to require adaptation to better represent the PD population fatigue-related symptoms.

Exploratory efficacy analyses will be detailed in a PD0055 Exploratory Efficacy Analysis Plan.

9.3.3.4 Nonmotor symptoms

9.3.3.4.1 MDS-NMS

The participant-level endpoint will be MDS-NMS at all available timepoints post PD0053 Baseline. PD0053 Baseline data will be available.

Descriptive statistics and visualization

Continuous summary statistics will be presented for the MDS-NMS total scores (total frequency and total severity scores) by treatment group, gender, and visit. The data listing for MDS-NMS will be grouped by domain, with frequency and severity results appearing side by side.

A plot of individual trajectories over time will be produced for the total score, using the same by variables and color-coding described for the PRO trajectory plots.

Results for the nonmotor fluctuations subscale section will be listed only.

Exploratory analyses

Exploratory efficacy analyses will be detailed in a PD0055 Exploratory Efficacy Analysis Plan.

9.3.3.4.2 MDS-UPDRS Part I subscale or selected items

The participant-level endpoint will be MDS-UPDRS Part I subscore/item score at all available timepoints post PD0053 Baseline. PD0053 Baseline score will be available.

Descriptive statistics

Descriptive statistics and visualizations will be produced for the MDS-UPDRS Part I subscore (as described for MDS-UPDRS Part I-III sum score, Section 9.3.3.5.3). A heat map of the item-level responses will be produced, further details on this heat map and the descriptive statistics will be presented in the SAP.

Exploratory analyses

Exploratory efficacy analyses will be detailed in a PD0055 Exploratory Efficacy Analysis Plan.

9.3.3.5 Motor symptoms, activities of daily living, and QOL

Descriptive statistics and visualizations will be produced for the following endpoints:

9.3.3.5.1 MDS-UPDRS Part II subscale or selected items

The participant-level endpoint will be MDS-UPDRS Part II subscore/item score at all available timepoints post PD0053 Baseline. PD0053 Baseline score will be available.

Descriptive statistics

Descriptive statistics and visualizations will be produced for the MDS-UPDRS Part II subscore (as described for MDS-UPDRS Part I-III sum score, Section 9.3.3.5.3). A heat map of the item-level responses will be produced, further details on this heat map and the descriptive statistics will be presented in the SAP.

Exploratory analyses

Exploratory efficacy analyses will be detailed in a PD0055 Exploratory Efficacy Analysis Plan.

9.3.3.5.2 MDS-UPDRS Part III subscale or selected items

The participant-level endpoint will be MDS-UPDRS Part III subscore/item score at all available timepoints post PD0053 Baseline. PD0053 Baseline score will be available.

Descriptive statistics

Descriptive statistics and visualizations will be produced for the MDS-UPDRS Part III subscore (as described for MDS-UPDRS Part I-III sum score, Section 9.3.3.5.3). A heat map of the item-level responses will be produced, further details on this heat map and the descriptive statistics will be presented in the SAP.

Exploratory analyses

Exploratory efficacy analyses will be detailed in a PD0055 Exploratory Efficacy Analysis Plan.

9.3.3.5.3 MDS-UPDRS Parts I-III sum score

The participant-level endpoint will be MDS-UPDRS Parts I-III sum score at all available timepoints post PD0053 Baseline. PD0053 Baseline score will be available.

Descriptive statistics and visualization

Summary tables presenting the observed mean and mean change from Baseline in MDS-UPDRS Parts I-III sum score by treatment group and visit, overall and by gender will be produced. This summary will be produced overall and by ST status, where ST status is defined as having or not having started ST by each visit. For all summary tables and listings where this ST status flag is used and presented, the assumption is made that once a participant starts ST, they remain on ST for all study visits after their initiation date.

Plots of individual MDS-UPDRS Parts I-III sum scores over time by treatment group and gender will be presented, color coded to clearly indicate when a participant is and is not on ST. These plots will be grouped by ST initiation timing, the categories here will be participants who started ST:

- by Month 12 (inclusive)
- between Months 12 and 18 (inclusive)
- between Months 18 and 24 (inclusive)
- between Months 24 and 30 (inclusive)
- between Months 30 and 36 (inclusive)
- between Months 36 and 42 (inclusive)

- between Months 42 and 48 (inclusive)
- between Months 48 and 54 (inclusive)
- between Months 54 and 60 (inclusive)
- between Months 60 and 66 (inclusive)
- between Months 66 and 72 (inclusive)
- between Months 72 and 78 (inclusive)
- not started by 78 months (if applicable)

In addition to these individual plots, plots of observed mean MDS-UPDRS Parts I-III sum score will be produced by treatment group and ST initiation timing category, overall and by gender. These plots will include error bars (±SD) and all treatment groups will be overlaid on the same plot.

All planned summary tables and plots of MDS-UPDRS Parts I-III sum score will also be produced for the sum scores of each individual subscale (Part I, II, and III).

Exploratory analyses

Exploratory efficacy analyses will be detailed in a PD0055 Exploratory Efficacy Analysis Plan.

9.3.3.5.4 Modified H&Y

The participant-level endpoint will be the H&Y score at 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, and 78 months post PD0053 Baseline. PD0053 Baseline score will be available.

Descriptive statistics and visualization

Modified H&Y staging results will be summarized descriptively using frequency counts and percentages. Scores/ratings will be presented overall and for participants who are not yet on ST at a particular visit (where applicable), by treatment group, gender, and visit.

Exploratory analyses

Exploratory efficacy analyses will be detailed in a PD0055 Exploratory Efficacy Analysis Plan.

9.3.3.5.5 Early PD Function Slowness and Early PD Mobility PROs

The participant-level endpoint will be PRO final score at all available timepoints post PD0053 Baseline. PD0053 Baseline data will be available.

Descriptive statistics and visualization

Data for these PROs will be listed only.

Exploratory analyses

Exploratory efficacy analyses will be detailed in a PD0055 Exploratory Efficacy Analysis Plan.

9.3.3.5.6 CSF ASYN

Total ASYN and ASYN oligomers/seeding capacity will be measured in CSF samples in consenting participants, as well as in CSF samples obtained from PD0055 participants who initially did not consent in PD0053.

<u>Descriptive statistics and visualization</u>

The CSF total ASYN continuous summary statistics will be presented by visit (all available timepoints post PD0053 Screening/Baseline), treatment group, overall, and by gender. A trajectory plot will also be produced. Plots of observed mean will be produced by treatment group, overall, and by gender. These plots will include error bars (±SD) and all treatment groups will be overlaid on the same plot.

Separate tabulated and graphical summaries will be produced for study participants who consented only from PD0055 Baseline.

<u>Exploratory analyses</u>

Exploratory efficacy analyses will be detailed in a PD0055 Exploratory Analysis Plan.

9.3.3.6 Digital Health Technology

The analysis of Digital Health Technology data will be described in a separate PD0055 Digital Analysis Plan (Koneksa Health Inc.). The data will be analyzed separately from the study analysis. Any analysis of data obtained from the Digital Health Technology will be performed after database lock and unblinding of the PD0053 study.

9.3.4 Exploratory Objective II

9.3.4.1 EQ-5D-5L

The participant-level endpoint will be EQ-5D-5L score at all available timepoints post PD0053 Baseline. PD0053 Baseline data will be available. These data allow meeting payer expectations of showing associations between improvements in key clinical outcomes (eg, MDS-UPDRS) and improvements in QoL. Six-monthly collections of these data also align with the cost-utility model cycle lengths commonly used in health economic analyses in PD.

<u>Descriptive statistics and visualization</u>

The EQ VAS scores will be summarized using continuous descriptive statistics presented by visit and treatment group, overall and by gender. For both sets of Euro Quality of life scores/ratings, data will be summarized overall and for participants who are not yet on ST (if applicable).

In addition to the summary table, plots of individual trajectories for the EQ VAS score will be produced by treatment group, gender, and age category.

<u>Exploratory analyses</u>

Exploratory effectiveness analyses will be detailed in a PD0055 Trial Emulation Analysis Plan.

9.3.4.2 Use of external real-world data

An external, real-world comparator arm will be designed to estimate the effectiveness of minzasolmin versus the SoC on clinical and QoL outcomes (limited to MDS-UPDRS Part I-IV, modified H&Y, cumulative LEDD, EQ-5D-5L, MoCA) beyond the 18 months duration of the feeder study PD0053.

Statistical analyses for these data will be described in a PD0055 Trial Emulation Analysis Plan. A detailed feasibility assessment of potential accessible data sources to meet this exploratory objective has been finalized and is available as a separate report.

9.3.5 Exploratory Objective IV: Atypical Parkinsonism

9.3.5.1 Descriptive statistics and visualization

PD0053 Screening/Baseline data for participants not re-confirmed to have a diagnosis of PD will be summarized and plotted (details to be provided in the PD0055 SAP).

To characterize participant response to minzasolmin (UCB0599), data for participants not re-confirmed to have a diagnosis of PD will be colored differentially (details to be specified in the PD0055 SAP).

9.3.5.2 PD0053/PD0055 sensitivity analyses

Selected PD0053/PD0055 analyses will be repeated after exclusion of participants with Atypical Parkinsonian Disorder diagnoses (to be specified in a PD0053 Exploratory Analysis Plan or in the PD0055 protocol/SAP as sensitivity analyses).

9.4 Planned safety and other analyses

9.4.1 Safety analyses

Safety will be assessed by analyzing incidence of any TEAE, SAE, and study participant withdrawals, and changes in different parameters such as vital signs, safety laboratory data, 12-lead ECG assessment, physical examination findings, neurological examination findings, and suicidality using the C-SSRS.

Further details on the planned safety analyses will be given in the SAP.

9.4.2 Other analyses

Analysis of the qualitative data generated as part of the in-study patient interviews described in Section 8.1.3 (**US and UK only**) will follow the guidelines from the mixed-methods analysis protocol for the refinement of the Early PD Function Slowness and Mobility PRO instruments.

9.5 Handling of protocol deviations

Refer to Section 9.2.2 for details of handling of protocol deviations.

9.6 Handling of dropouts or missing data

Refer to Section 9.2.2 for details of handling of missing data.

9.7 Planned analysis and data monitoring

Digital Health Technology will be analyzed as described in Section 9.3.3.6.

The analyses to be performed for the primary and secondary efficacy objectives (delayed-start design), as well as for the exploratory efficacy objective II (dose comparison) use data from the first 18 months of the study (PD0055 Month 18 analysis); therefore, these analyses will be carried out once all participants have completed their Month 18 Visit. This will be a formal analysis but will not be considered an interim analysis as the results will not impact study conduct. Care will be taken to ensure that all study participants and Investigators will remain blinded to treatment/dose received in PD0053 and PD0055, at least until all participants have completed the Month 18 assessments in PD0055.

The analyses for the primary and secondary efficacy objectives (delayed-start design), will be repeated using data from all 60 months of the study (PD0055 Month 60 analysis).

Descriptive statistics and visualizations will be provided at both analysis data cuts for all endpoints, including exploratory endpoints. Further details will be provided in the SAP.

Details of analyses for other exploratory objectives will be provided in the specified analysis plans.

Additional analyses may be conducted for publication purposes and to support regulatory interactions.

DMC and SMC:

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**.

The 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.

9.8 Determination of sample size

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) 360mg/day (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 and 314 participants would be expected to reach PD0055 Month 18 and Month 60, respectively.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1 Regulatory and ethical considerations

The study will be conducted under the auspices of a competent authority (CA) and or IRB/IEC, as defined in local regulations, International Council for Harmonisation (ICH)-GCP, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator/UCB will ensure that a CA and an appropriately constituted IRB/IEC that complies with the requirements of the current ICH-GCP version or applicable country-specific regulations will be responsible for the initial and continuing review and approval of the clinical study. Prior to initiation of the study, the Investigator/UCB will forward copies of the protocol, ICF, IB, Investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other participant-related documents to be used for the study to the CA/IRB/IEC for their review and approval.

Before initiating a study, the Investigator will have written and dated full approval from the responsible CA/IRB/IEC for the protocol.

The Investigator will also promptly report to the IRB/IEC all changes in the study, all unanticipated problems involving risks to participants or others, and any protocol deviations, to eliminate immediate hazards to participants. The Sponsor will submit relevant information to the CA in accordance with regulatory requirements.

The Sponsor will not make any changes in the study or study conduct without CA/IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to the participants. For minor changes to a previously approved protocol during the period covered by the original approval, it may be possible for the Sponsor to obtain an expedited review by the CA/IRB/IEC as allowed.

As part of the CA/IRB/IEC requirements for continuing review of approved studies, the Sponsor will be responsible for submitting periodic progress reports according to regulatory requirements, at intervals appropriate to the degree of participant risk involved, but no less than once per year. The Sponsor should provide a final report to the CA/IRB/IEC following study completion.

UCB (or its representative) will communicate safety information to the CA and all active Investigators in accordance with applicable regulatory requirements. The appropriate IRB/IEC will also be informed by the Investigator or the Sponsor, as specified by the applicable regulatory requirements in each concerned country. Where applicable, Investigators are to provide the Sponsor (or its representative) with evidence of such IRB/IEC notification.

10.1.2 Financial disclosure

Insurance coverage will be handled according to local requirements.

Finance and insurance are addressed in the Investigator and/or CRO agreements, as applicable.

10.1.3 Informed consent process

Participant's informed consent must be obtained and documented in accordance with local regulations, ICH-GCP requirements, and the ethical principles that have their origin in the principles of the Declaration of Helsinki.

Prior to obtaining informed consent, information should be given in a language and at a level of complexity understandable to the participant in both oral and written form by the Investigator (or designee). The participant will be given as much time as needed to decide whether or not they wish to take part in the study. Each participant will have the opportunity to discuss the study and its alternatives with the Investigator or seek additional advice. The amount of time a potential participant takes to decide whether to participate or not will vary per participant. The potential participants will be under no pressure to make a decision.

Prior to participation in the study, the ICF should be signed and personally dated by the participant and by the person who conducted the informed consent discussion (Investigator or designee). The participant must receive a copy of the signed and dated ICF. As part of the consent process, each participant must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB/IEC review, and regulatory inspection. Remote consent (eConsent) is permitted during this study, but not required. For those participants who are assessed as preliminarily eligible per the IRB/IEC-approved preScreening script, contact information will be collected, including a valid email address of the participant.

If the ICF is amended during the study, the Investigator (or the sponsor, if applicable) must follow all applicable regulatory requirements pertaining to the approval of the amended ICF by the IRB/IEC and use of the amended form.

All studies conducted at centers in the US must include the use of a Health Insurance Portability and Accountability Act authorization form.

The participant may withdraw his/her consent to participate in the study at any time. A participant is considered as enrolled in the study when he/she has signed the ICF. The eCRF must not be started, nor may any study specific procedure be performed for a given participant, without having obtained his/her written consent to participate in the study.

10.1.4 Data protection

UCB staff (or designee) will affirm and uphold the participant's confidentiality. Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The Investigator agrees that representatives of UCB, its designee, representatives of the relevant IRB/IEC, or representatives of regulatory authorities will be allowed to review that portion of the participant's primary medical records that directly concerns this study (including, but not limited to, laboratory test result reports, ECG reports, admission/discharge summaries for hospital admissions occurring during a participant's study participation, and autopsy reports for deaths occurring during the study).

The participant will be informed how his/her personal study-related data will be used by the Sponsor and that it will be used in accordance with local data protection law. The level of disclosure will also be explained to the participant.

The participant will be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The contract between UCB and study sites specifies responsibilities of the parties and the timelines related to data protection, including handling of data security breaches and respective communication and cooperation of the parties in order to mitigate the possible deleterious consequences for the participants.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

10.1.5 Committees structures

An independent DMC will conduct safety interim reviews of all available unblinded safety data and an SMC will regularly review the available blinded safety data as described in Section 9.7.

10.1.6 Dissemination of clinical study data

This study will be registered and results posted on public registries as required and in line with UCB policies. A plain language summary of results may also be written. Investigators may request access to anonymized individual participant-level data and redacted study documents after product approval in the United States and Europe. However, once the study completes, if the risk of re-identifying study participants is determined to be too high, then individual participant-level data will not be made available.

For results disclosure on public registries (eg, ClinicalTrials.gov), TEAEs and treatment-emergent SAEs will be published.

A summary of the results is planned to be posted to the EU database within 1 year of study completion, in accordance with international standards and irrespective of the outcome of the clinical study.

10.1.7 Data quality assurance

All participant data relating to the study will be recorded on printed or eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, legible, contemporaneous, original, and attributable from source documents; that the safety and rights of participants are being protected;

and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH-GCP, and all applicable regulatory requirements.

All essential documents must be retained by the Investigator for the minimum retention period mandatory under the applicable local laws and regulations. The Investigator will contact UCB for authorization prior to the destruction of any study records or in the event of accidental loss or destruction of any study records. The Investigator will also notify UCB should he/she relocate or move the study-related files to a location other than that specified in the Sponsor's trial master file.

Quality tolerance limits will be established for the study using parameters related to patient safety reporting and reliability of study results. The parameters will be monitored throughout the study to identify systematic issues. Parameters used, parameter values, important deviations from the quality tolerance limits, and actions taken will be summarized in the clinical study report.

10.1.7.1 eCRF completion

The Investigator is responsible for prompt reporting of accurate, complete, and legible data in the eCRFs and in all required reports.

Any change or correction to the eCRF after saving must be accompanied by a reason for the change.

Corrections made after the Investigator's review and approval (by means of a password/electronic signature) will be reapproved by the Investigator.

The Investigator should maintain a list of personnel authorized to enter data into the eCRF.

Detailed instructions will be provided in the eCRF Completion Guidelines.

10.1.7.2 Apps

Not applicable.

10.1.8 Source documents

All source documents must be accurate, clear, unambiguous, permanent, and capable of being audited. They should be made using some permanent form of recording (ink, typing, printing, optical disc). They should not be obscured by correction fluid or have temporary attachments (such as removable self-stick notes). Photocopies and/or printouts of eCRFs are not considered acceptable source documents.

Source documents are original records in which raw data are first recorded. These may include hospital/clinic/general practitioner records, charts, diaries, x-rays, laboratory results, printouts, pharmacy records, care records, ECG, or other printouts, completed scales, QoL questionnaires, or video, for example. Source documents should be kept in a secure, limited access area.

Source documents that are computer generated and stored electronically must be printed for review by the monitor (eg, ECG reports). Once printed, these copies should be signed and dated by the Investigator and become a permanent part of the participant's source documents. The Investigator will facilitate the process for enabling the monitor to compare the content of the printout and the data stored in the computer to ensure all data are consistent.

Electronic data records, such as Holter monitor records or electroencephalogram records, must be saved and stored as instructed by UCB (or designee).

10.1.9 Study and site start and closure

The start of recruitment

The start of recruitment is the first participant's first visit and is also the start date of the clinical study.

Study/site termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further IMP development

10.1.10 Publication policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical laboratory tests

- The tests detailed in the table below will be performed.
  - Local laboratory results are only required in the event that the central laboratory results are not available in time for either IMP administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be entered into the eCRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and Section 5.2 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Protocol-required Safety Laboratory Assessments

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

Laboratory Assessments	Parameters
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 (Section 10.6). 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

Investigators must document their review of each laboratory safety report.

Laboratory tests that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

10.3 Appendix 3: Adverse events – Definitions and procedures for recording, evaluating, follow-up, and reporting

Definition of AE

AE definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study medication, whether or not considered related to the study medication. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study medication.

Events <u>meeting</u> the AE definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre existing condition, including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study medication administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study medication or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT meeting the AE definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the study participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per definition above, then it cannot be a SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Important medical events: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include, but are not limited to, potential Hy's law, invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and follow-up of AE and/or SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to UCB in lieu of completion of the UCB/AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by UCB. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to UCB.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of a SAE, NOT when it is rated as severe (eg, a severe AE may be either serious or not serious, depending on whether these criteria are also met).

The National Cancer Institute Common Terminology Criteria for Adverse Events should be used as a supportive standardization instrument to evaluate AEs and SAEs but the final intensity grading by the Investigator must be mild, moderate, or severe.

Assessment of causality

- The Investigator is obligated to assess the relationship between study medication and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study medication administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which a SAE has occurred, and the Investigator has minimal information to include in the initial report to UCB. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to UCB.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by UCB to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- An AE should be followed until it has resolved, has a stable sequelae, the Investigator determines that it is no longer clinically significant, or the participant is lost to follow up. This follow-up requirement applies to AEs, SAEs, and AEs of special interest.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide UCB with a copy of any post mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

Reporting of SAEs

SAE reporting to UCB via an electronic data collection tool

- The primary mechanism for reporting a SAE to UCB will be the electronic data collection tool.
- If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section).
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to UCB by telephone.
- Contacts for SAE reporting can be found in SERIOUS ADVERSE EVENT REPORTING.

SAE reporting to UCB via paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to UCB.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in SERIOUS ADVERSE EVENT REPORTING.

10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

Definitions

WOCBP

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. In case of sterilization, it should have taken place before the start of the Screening Period and the medical records of the participant should include the method of sterilization, along with the date of sterilization, as proof of the contraception.

Women in the following categories **are not considered WOCBP**:

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception guidance

Male participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.
- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in the table below when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.

In addition, male participants must refrain from donating sperm for the duration of the study and for 3 months after the last dose of study medication.

Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame and for 3 months after the last dose of study medication.

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the table below.

Highly effective contraceptive methods [a]

Highly effective contraceptive methods that are user dependent [b] Failure rate of <1% per year when used consistently and correctly.
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[c] • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly effective methods that are user independent [c]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system • Bilateral tubal occlusion
Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP, and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study medication. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
NOTES: a) In case of newly started contraception pills/IUDs, the Investigator should consider the correct timing of starting/applying such methods in relation to the menstrual cycle and the manufacturing instruction as to when these newly started methods would become effective. b) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies. c) If oral contraception is used, an additional barrier method will be required during the Treatment Period and for at least 30 days after the last dose of study medication.

Pregnancy testing

- A WOCBP should only be included after a confirmed menstrual period and a negative urine pregnancy test.
- Additional pregnancy testing should be performed at each visit during the Treatment Period and at the SFU Visit and as required locally.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.
- A positive urine test should be confirmed by a blood test with a sensitivity of 25 mIU/mL.

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study medication.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 1 working day of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow up will be at least 12 months after the delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

- Any female participant who becomes pregnant while participating in the study will discontinue study medication.
- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 1 working day of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, the follow-up will be at least 12 months after the delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be a SAE and will be reported as such. Any poststudy pregnancy-related SAE considered reasonably related to the study medication by the Investigator will be reported to the Sponsor as described in Section 8.3.5. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of a SAE through spontaneous reporting.

10.5 Appendix 5: Genetics

Not applicable.

10.6 Appendix 6: Liver safety – suggested actions and follow-up assessments

Participants with potential drug-induced liver injury must be assessed to determine if study medication must be discontinued. In addition, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued.

Investigators should attempt to obtain information on study participants in the case of study medication discontinuation to complete the final evaluation.

Study participants with potential drug-induced liver injury should not be withdrawn from the study until investigation and monitoring are complete. All results of these evaluations and observations, as well as the reason(s) for study medication discontinuation and/or participant withdrawal (if applicable), must be recorded in the source documents. The eCRF must document the primary reason for discontinuation of study medication.

A specific monitoring plan must be agreed between the UCB study physician and the Investigator for study participants who have ALT >5xULN. The monitoring plan should include any necessary follow-up assessments (until resolution of the abnormal lab values).

Phase 2 liver chemistry stopping criteria are designed to assure participant safety and to evaluate liver event etiology (Section 7.1.2).

Table 10-1: Phase 2 liver chemistry stopping criteria and follow-up assessments

Liver Chemistry Stopping Criteria	
ALT-absolute	ALT ≥5xULN
ALT Increase	ALT ≥3xULN persists for ≥4 weeks
Bilirubin[a,b]	ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin)
INR[b]	ALT ≥3xULN **and** international normalized ratio (INR) >1.5, if INR measured
Cannot Monitor	ALT ≥3xULN and cannot be monitored weekly for 4 weeks
Symptomatic[c]	ALT ≥3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
Suggested Actions and Follow-up Assessments	
Actions	**Follow-Up Assessments**
• **Immediately** discontinue study medication. • Report the event to the Sponsor **within 24 hours.** • Complete the liver event eCRF and complete an SAE data collection tool if the event also met the criteria for an SAE. [b] • Perform liver chemistry follow-up assessments.	• Viral hepatitis serology [d] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend

Table 10-1: Phase 2 liver chemistry stopping criteria and follow-up assessments

Liver Chemistry Stopping Criteria	
• Monitor the participant until liver chemistry test abnormalities resolve, stabilize, or return to Baseline (see **MONITORING**). • **Do not restart/rechallenge** participant with study medication unless allowed per protocol and Sponsor approval is granted • If restart/rechallenge **not allowed per protocol or not granted**, permanently discontinue study medication and continue participant in the study for any protocol specified follow-up assessments • Consider the need for a toxicology Screening **MONITORING**: **<u>If ALT ≥3xULN AND bilirubin ≥2xULN or INR >1.5:</u>** • Repeat liver chemistry tests (include ALT, aspartate transaminase [AST], alkaline phosphatase, bilirubin) and perform liver event follow-up assessments within **24 hours.** • Monitor participant twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to Baseline. • A specialist or hepatology consultation is recommended. **<u>If ALT ≥3xULN AND bilirubin <2xULN and INR ≤1.5:</u>** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver chemistry follow-up assessments within **24 to 72 hours.** • Monitor participants weekly until liver chemistry abnormalities resolve, stabilize, or return to Baseline.	• Obtain blood sample for pharmacokinetic (PK) analysis as soon as possible after the most recent dose [e] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH) • Fractionate bilirubin, if total bilirubin ≥ 2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury (eg, fatigue, nausea, vomiting, right upper quadrant pain), or hypersensitivity, on the adverse event (AE) report form • Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) on the concomitant medications eCRF • Record alcohol use on the liver event alcohol intake eCRF • Exclude pregnancy **<u>If ALT ≥3xULN AND bilirubin ≥2xULN or INR >1.5:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins • Serum acetaminophen (EAN paracetamol) • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease; complete liver

Table 10-1: Phase 2 liver chemistry stopping criteria and follow-up assessments

Liver Chemistry Stopping Criteria

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CPK=creatine phosphokinase; EAN=International Article Number; eCRF=electronic case report form; HBcAb=hepatitis B core antibody; HBsAg=hepatitis B virus surface antigen; HPLC=high performance liquid chromatography; IgG=immunoglobin G; IgM=immunoglobin M; INR=international normalized ratio; LDH=lactate dehydrogenase; PBO=placebo; PK=pharmacokinetic; RNA=ribonucleic acid; SAE=serious adverse event; ULN=upper limit of normal.

[a] Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study medication if ALT ≥3xULN **and** bilirubin ≥2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick** which is indicative of direct bilirubin elevations suggesting liver injury.

[b] All events of ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3xULN and INR >1.5 may indicate severe liver injury **(possible 'Hy's Law') and must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**. The INR measurement is not required, and the stated threshold value will not apply to participants receiving anticoagulants.

[c] New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as rash, angioedema, or anaphylaxis)

[d] Includes: Hepatitis A immunoglobulin M (IgM) antibody; HBsAg and HBcAb; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody.

[e] Record the date/time of the PK blood sample draw and the date/time of the last dose of study medication prior to the blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the Study Reference Manual

10.7 Appendix 7: Digital Health Technology AEs, SAEs, ADEs, SADEs, and device deficiencies: Definition and procedures for recording, evaluating, follow-up, and reporting

Throughout the study, safety information will be recorded and reported according to the procedures outlined in Section 8.3, Appendix 3 (Section 10.3), and below for the different components of the Koneksa Neuroscience Toolkit.

10.7.1 Safety reporting for the Koneksa mobile software application and Apple iPhone

10.7.1.1 Adverse events of the Koneksa mobile software application and Apple iPhone

The Investigator is expected to record any AEs and SAEs related to the Koneksa mobile software application and the Apple iPhone in the eCRF. The eCRF page will allow the Investigator to assess causality.

The Sponsor and/or Investigator will send reports of AEs and SAEs related to the Koneksa mobile software application and the Apple iPhone to Koneksa Health Inc. (via a message to help@koneksahealth.com).

10.7.1.2 Deficiencies of the Koneksa mobile software application and Apple iPhone

Deficiencies of the Koneksa mobile software application and Apple iPhone are defined as inadequacies with respect to their identity, quality, durability, reliability, safety, or performance. Upon identification of such deficiencies, study participants will be provided with a replacement. The affected technology will be returned, when possible, to Koneksa Health Inc. for failure analysis investigation.

The Investigator will send reports of deficiencies of the Koneksa mobile software application and Apple iPhone to Koneksa Health Inc. (via a message to help@koneksahealth.com).

10.7.2 Safety reporting for the ActiGraph CPIW and the Data Hub

The ActiGraph CPIW (ActiGraph LLC) is a smartwatch that has a CE Mark and FDA 510(k) clearance under K181077. Therefore, the below safety reporting requirements apply.

For the following subsections, the ActiGraph CPIW and Data Hub are described jointly as the ActiGraph CPIW.

The Investigator must notify ADEs/SADEs/device deficiencies associated with the use of the ActiGraph CPIW directly to Koneksa Health Inc. (via a message to help@koneksahealth.com) using the Adverse Event and Device Deficiency Form.

10.7.2.1 Definition of ADE

ADE definition
• An adverse device effect (ADE) is defined as an AE related to the use of the ActiGraph CPIW. This definition includes any AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the ActiGraph CPIW as well as any event resulting from use error or from intentional misuse of the ActiGraph CPIW.

10.7.2.2 Definition of SADE and USADE

SADE definition
• A serious adverse device effect (SADE) is defined as an adverse effect reported for the ActiGraph CPIW that has resulted in any of the consequences characteristic of an SAE.
USADE definition
• An unanticipated serious adverse device effect (USADE) is a SADE which, by its nature, incidence, severity, or outcome, has not been identified in the current version of the risk analysis report.

10.7.2.3 Definition of device deficiency

Device deficiency definition
• A device deficiency is an inadequacy of the ActiGraph CPIW with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling.

10.7.2.4 Recording and follow-up of ADE/SADE/device deficiency

Recording of ADE/SADE/device deficiency
• When an ADE/SADE/device deficiency occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The Investigator will then record all relevant ADE/SADE/device deficiency information in the participant's medical records in accordance with the Investigator's normal clinical practice. In addition, AE/SAEs will be documented on the appropriate form of the CRF. • It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to UCB or Koneksa Health Inc. in lieu of completion of the ADE/SADE/device deficiency CRF page. • There may be instances when copies of medical records for certain cases are requested by UCB or Koneksa Health Inc. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to UCB or Koneksa Health Inc. • The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the ADE/SADE. • For device deficiencies, it is very important that the Investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.

- A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence. The Investigator should complete a Product Complaint Form (provided by the Sponsor) for all reported device deficiencies.

Assessment of intensity

The Investigator will make an assessment of intensity for each ADE/SADE/device deficiency reported during the study and assign it to one of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An ADE that is assessed as severe should not be confused with a SADE. Severe is a category utilized for rating the intensity of an event, and both ADEs and SADEs can be assessed as severe.
- An event is defined as serious when it meets at least one of the predefined outcomes as described in the definition of a SADE, NOT when it is rated as severe.
- Other measures to evaluate ADEs and SADEs may be utilized (eg, National Cancer Institute - Common Terminology Criteria for Adverse Events).

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each ADE/SADE/device deficiency.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure in his/her assessment.
- For each ADE/SADE/device deficiency, the Investigator **must** document in the medical notes that he/she has reviewed the ADE/SADE/device deficiency and has provided an assessment of causality.
- There may be situations in which a SADE has occurred and the Investigator has minimal information to include in the initial notification to Koneksa Health Inc. (via a message to help@koneksahealth.com). However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SADE data to Koneksa Health Inc.
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SADE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of ADE/SADE/device deficiency
• The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by UCB or Koneksa Health Inc. to elucidate the nature and/or causality of the ADE/SADE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide Koneksa Health Inc. with a copy of any post-mortem findings, including histopathology. • New or updated information will be recorded in the originally completed CRF for ADEs and SADEs. • The Investigator will submit any updated SADE data to Koneksa Health Inc. (via a message to help@koneksahealth.com) within 24 hours of receipt of the information.

10.7.2.5 Reporting of ADE/SADE/device deficiency

Reporting of ADE/SADE/device deficiency to Koneksa Health Inc.
• The Investigator must notify any ADE/SADE/device deficiency to Koneksa Health Inc. (via a message to help@koneksahealth.com) within 24 hours after the Investigator determines that the event meets the definition of an ADE/SADE/device deficiency. • Koneksa Health Inc. will then promptly notify the device vendor for the ActiGraph CPIW, advising them that an ADE/SADE has been reported. • Contacts for ADE, SADE, and device deficiency reporting can be found in REPORTING OF ADVERSE DEVICE EFFECTS (SERIOUS AND NONSERIOUS) AND DEVICE DEFICIENCIES.

10.8 Appendix 8: Rapid alert procedures

Not applicable.

10.9 Appendix 9: Country-specific requirements

10.9.1 Country-specific requirements for US and UK

An optional in-study patient interview was added with protocol amendment 3.2 in the UK and with protocol amendment 3.3 in the US.

The following updates were made in global protocol amendment 4 to implement the country-specific changes in the global protocol:

- Section 1.3: Optional in-study patient interviews and associated informed consent procedure were added in the schedule of activities.
- Section 8.1.3: A description of the optional in-study patient interview was added.
- Section 8.3.8: New section was added to clarify the safety reporting for events reported during in-study patient interviews.
- Section 9.4.2: A note on the handling of the data generated from the optional in-study patient interviews was added.

These changes apply to US and UK sites only, as noted in the respective sections throughout the protocol.

10.10 Appendix 10: Abbreviations and trademarks

ADE	adverse device effect
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ASPS	All Study Participants Set
AST	aspartate aminotransferase
ASYN	alpha-synuclein
ATC	Anatomical Therapeutic Chemical
BID	twice daily
BP	blood pressure
CA	competent authority
CE	Conformité Européenne
CI	confidence interval
ClinRO	clinician-reported outcome
CNS	central nervous system
COMT	catechol-O-methyltransferase
COVID-19	Coronavirus Disease-2019
CPIW	ActiGraph CentrePoint® Insight Watch
CRF	Case Report form
CRO	contract research organization
CSF	cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP3A4	cytochrome P450 3A4
DaT-SPECT	Dopamine Transporter Imaging with Single Photon Emission Computed Tomography
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic Case Report form
EOT	End of Treatment
ET	Early Termination

EQ-5D-5L	Euro Quality of life 5-Dimensions 5-Level
EQ VAS	Euro Quality of life visual analogue scale
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practices
H&Y	Hoehn and Yahr
HRT	hormonal replacement therapy
IB	Investigator's Brochure
ICE	intercurrent event
ICF	Informed Consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IRB	Institutional Review Board
IRT	interactive response technology
IUD	intrauterine device
LEDD	Levodopa Equivalent Daily Dose
LMEM	linear mixed effects model
MAR	missing at random
MCI	mild cognitive impairment
MDS-NMS	Movement Disorder Society Non-Motor Rating Scale
MDS-UPDRS	Movement Disorder Society Unified Parkinson's Disease Rating Scale
MoCA	Montreal Cognitive Assessments
PD	Parkinson's disease
PK	pharmacokinetics
PRO	patient-reported outcomes
QoL	Quality of Life
QTc	QT corrected
QTcF	QT corrected for heart rate using Fridericia's formula
SAE	serious adverse event
SADE	serious adverse device effect
SAP	statistical analysis plan

SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
SBP	systolic blood pressure
SBR	specific binding ratio
SD	standard deviation
SFU	Safety Follow-up
SMC	Safety Monitoring Committee
SoC	standard of care
SS	Safety Set
ST	symptomatic treatment
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
UPSIT	University of Pennsylvania Smell Identification Test
USADE	unanticipated serious adverse device effect
WO	wearing-off
WOCBP	woman/women of childbearing potential
WOQ-9	Wearing-off Questionnaire-9

10.11 Appendix 11: Protocol amendment history

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

10.11.1 Amendment 3 (18 Sep 2023)

Overall Rationale for the Amendment

PD0055 Protocol Amendment 3 was completed to implement Digital Health Technology in the study. In addition, the international nonproprietary name minzasolmin was introduced and further clarification of protocol procedures was provided.

This amendment is considered to be substantial based on the criteria set forth in Article 2(13) of Regulation No 536/2014 of the European Parliament and the Council of the European Union.

Section # and name	Description of change	Brief rationale
Global	UCB0599 was changed to "minzasolmin (UCB0599)" throughout.	To introduce the international nonproprietary name for UCB0599.
REPORTING OF ADVERSE DEVICE EFFECTS (SERIOUS AND NONSERIOUS) AND DEVICE DEFICIENCIES	Table with reporting information for adverse device effects and device deficiencies was added.	To provide contact information for adverse device effects and device deficiencies reporting.
Section 1.1 Synopsis - Objectives and endpoints and Section 3 OBJECTIVES AND ENDPOINTS	In the Exploratory Objectives, the bullet "FATIGUE-PRO (and subscores)" was changed in 2 places to "FATIGUE-PRO."	To remove unnecessary detail; there is no change to the planned analysis.
	In the Exploratory Objectives under I. Methodology, "Koneksa Neuroscience Toolkit" was added as an "Exploratory Endpoint (Other)."	To implement Digital Health Technology in the study.
	In the Exploratory Objectives under IV. Atypical Parkinsonism, the Exploratory Endpoint "Percentage of participants with these diagnoses from PD0053/PD0055 analyses" was changed to an "Exploratory Assessment" of "Re-confirmed PD diagnosis status."	To clarify the assessment.
Section 1.1 Synopsis - Overall design	A precaution to allow a dose switch from 360mg/day to 180mg/day in case of safety concerns at the time the first participant was planned to transition into PD0055 was removed.	To remove information that no longer applies after First Participant First Visit in PD0055; a switch in dose was not required before First Participant First Visit in PD0055 was conducted.

Section # and name	Description of change	Brief rationale
Section 1.1 Synopsis - Number of participants and Section 4.1 Overall design	Number of participants was updated from "All study participants (approximately 450) can roll over from PD0053. Assuming that 60% of PD0053 participants (270) choose to roll over into PD0055, and 15% of the PD0053 participants drop out or are lost to follow up, then 202 participants would be expected to reach End of Treatment (EOT)" to "All study participants (approximately 490) can roll over from PD0053. Assuming that 15% of PD0053 participants drop out or are lost to follow up over 18 months and 90% of the remaining 416 participants who complete PD0053 choose to roll over into PD0055, then 374 participants would be expected to enter the extension study. Assuming that 15% of PD0055 participants drop out or are lost to follow up over 18 months, 318 participants would be expected to reach PD0055 End of Treatment (EOT)."	To update the number of participants expected to roll over from PD0053 based on observations in PD0055.
Section 1.2 Schema	The footnote in Figure 1-1 that the dose may be switched from 360mg/day to 180mg/day was removed.	Based on PD0053 information, a switch in dose was not required before First Participant First Visit in PD0055 was conducted.
Section 1.3 Schedule of Activities	The Early Termination (ET) label was moved from V9 to V10/EOT in the Schedule of Activities to clarify that the EOT Visit procedures apply for study participants who terminate the study prematurely, in line with footnote 'c'. Footnotes 'c' and 'i' were updated to refer to the EOT/ET Visit.	To clarify which procedures apply if participants discontinue or are withdrawn from the study.

Section # and name	Description of change	Brief rationale
Section 1.3 Schedule of Activities	The following assessments were added: • Koneksa Neuroscience Toolkit safety • Koneksa Neuroscience Toolkit consent and training • Deployment of Koneksa Neuroscience Toolkit • Detailed check on Koneksa Neuroscience Toolkit usage and re-training • Active Koneksa Neuroscience Toolkit tests on cell phone at home • Passive Koneksa Neuroscience Toolkit data collection via smartwatch • Return of Koneksa Neuroscience Toolkit	To implement Digital Health Technology in the study.
	Added the early PD function slowness PRO and early PD mobility assessments to V9 (M24) and V10/EOT/ET (M30) and added the FATIGUE-PRO assessment to V9 (M24).	To generate longer term data.
	Added the UPSIT at V4 (M1).	To better characterize the target population.
	Footnote "b" was revised to include text describing CSF sampling at V2 (Baseline Visit) for participants newly consenting to CSF sampling in PD0055.	To clarify procedure for CSF sampling at V2.
	Footnote "l" was revised to allow optional CSF sampling for <u>all</u> participants <u>regardless of their consenting</u> to CSF sampling in PD0053.	To allow CSF sampling for those participants consenting in PD0055, independent of their consent decision in PD0053, in order to increase the number of CSF samples for biomarker analyses, which are considered to provide additional meaningful information.

Section # and name	Description of change	Brief rationale
Section 1.3 Schedule of Activities	New footnote "n" was added to clarify the timing of Koneksa Neuroscience Toolkit consent and training: at any time from V1 to V2, if needed as an unscheduled visit.	To implement Digital Health Technology in the study; to clarify times of procedures.
	New footnote "o" was added to "Return of Koneksa Neuroscience Toolkit" at V8 to clarify that if a study participant stops using the Digital Health Technology prior to V8 the reason needs to be documented in the CRF.	To implement Digital Health Technology in the study; to clarify procedure.
	New footnote "p" was added to the V10/EOT/ET column to clarify that the return of the Koneksa Neuroscience Toolkit only applies at ET.	To implement Digital Health Technology in the study; to clarify occurrence of procedure.
	New footnote "q" was added to clarify that the WOQ-9 will only be completed by participants who have initiated ST.	To clarify use of the WOQ-9 in the study.
	New footnote "r" was added to provide instructions that study participants who have already completed V4 (M1) will complete the UPSIT at the next visit.	To provide instructions for the timing of the UPSIT.
Section 2.3.2 Digital Health Technology benefit/risk assessment	New section was added on potential benefits and risks associated with the Digital Health Technology used in the study (Koneksa Neuroscience Toolkit).	To provide benefit/risk assessment for the Digital Health Technology.
Section 4.2 Scientific rationale for study design	A sentence was added at the end of the third paragraph to introduce the use of Digital Health Technology in the study.	To align with the addition of the Digital Health Technology.
Section 5.1 Inclusion criteria	Inclusion criterion #1 was revised from "PD0055 Baseline Visit needs to be within 4 weeks following the EOT Visit in PD0053" to "PD0055 Baseline Visit should be no later than 4 weeks following the EOT Visit in PD0053. Any delay needs to be justified by the Investigator and approved by the Sponsor."	To clarify the criterion for study entry.

Section # and name	Description of change	Brief rationale
Section 5.2 Exclusion criteria	Exclusion criterion #5 was added: "Study participants wearing any kind of implantable active device, including cardiac pacemakers, pumps, and implantable cardioverters, will be excluded from using the Koneksa Neuroscience Toolkit, but may participate in the main study."	To add exclusion criterion for participants with active implantable devices.
Section 5.2 Exclusion criteria	Exclusion criterion #6 was added: "Study participant does not agree to refrain from donating blood or blood products or other body fluids."	To add exclusion criterion for participants who do not agree to refrain from blood/blood product or other body fluids donation as the product is not yet fully characterized.
Section 6.5.2 Prohibited concomitant treatments (medications and therapies)	Bupropion was added to the list of medications that are not allowed during the 50 days before a DaT-SPECT imaging.	To complete the list of drugs that may affect the DaT-SPECT scan.
Section 6.9 Digital Health Technology	New section was added with product description and use in the study of the Digital Health Technology (Koneksa Neuroscience Toolkit).	To implement Digital Health Technology in the study.
Section 7.2 Participant discontinuation/withdrawal from the study	Reference to EOT Visit was updated to "EOT/Early Termination (ET) Visit."	To clarify which procedures apply if participants discontinue or are withdrawn from the study.
Section 7.4 Discontinuation of Digital Health Technology	New section was added to describe discontinuation of Digital Health Technology.	To reflect the addition of the Digital Health Technology and adapt study procedures.
Section 8.1.1.1 DaT-SPECT	The estimated radiation burden in PD0055 was changed from 13.89mSv to "a maximum of 9.26mSv" reflecting a maximum of 2 scans done in the study with a radiation dose estimate of 4.63mSv per scan (per EU label). Note that this includes the PD0053 Month 18 scan that is used as PD0055 Baseline. The category risk level was changed from "III substantial" to "IIb intermediate."	To correct the estimated radiation burden, which has been calculated based on the approved dose per scan (max 4.63mSv) multiplied by 2 (max 2 scans). Based on this, the category risk level in PD0055 has been adapted.
Section 8.1.1.2 LEDD	Literature references were updated.	To update references for LEDD calculation.

Section # and name	Description of change	Brief rationale
Section 8.1.2 Patient-reported outcomes	The last sentence of the second paragraph was revised to clarify that PROs will be completed prior to dosing with ST.	To clarify the sequence of PRO completion and dosing with ST.
Section 8.1.2.4 WOQ-9	The last sentence was revised to clarify that the WOQ-9 will be assessed after initiation of ST.	To clarify use of the WOQ-9 in the study.
Section 8.1.2.5 EQ-5D-5L	Literature reference was updated.	To update reference for EQ-5D-5L.
Section 8.1.4 Koneksa Neuroscience Toolkit	New section was added to describe assessments performed with the Koneksa Neuroscience Toolkit.	To implement Digital Health Technology in the study.
Section 8.2.1 Physical examination	Reference to a brief neurological examination performed as part of the physical examination was removed because it did not apply (all visits with physical examination also have a neurological examination planned).	To remove redundancy.
Section 8.3.7 Digital Health Technology safety reporting	New section was added to describe the safety reporting associated with the Digital Health Technology (Koneksa Neuroscience Toolkit).	To reflect the addition of the Digital Health Technology and adapt study procedures.
Section 8.9 Biomarkers	Second paragraph was added to provide justification for the collection of additional CSF samples for the assessment of ASYN markers.	To increase meaningfulness of biomarker analysis.
	Last sentence of third paragraph was revised to clarify that pathological ASYN species (eg, ASYN seeds) may also be assessed (in addition to total ASYN levels).	To clarify planned assessment of further ASYN markers in CSF samples.
Section 8.10 University of Pennsylvania Smell Identification Test	New section was added for the UPSIT.	To better characterize the target population.
Section 9.3 Planned efficacy/outcome analyses	Text was revised from "Exploratory analyses" to "Exploratory efficacy analyses" in multiple places. In addition, text was added to clarify details of the exploratory efficacy analyses in multiple places.	Administrative change.

Section # and name	Description of change	Brief rationale
Section 9.3.3.1 WOQ-9	The timepoints at which WOQ-9 will be measured were changed from "26, 30, and 36 months post PD0053 Baseline" to "24, 30, and 36 months post PD0053 Baseline" to align with the Schedule of Activities (2 places).	To correct 1 timepoint for WOQ-9 measurements.
Section 9.3.3.3 FATIGUE-PRO	The timepoints at which the fatigue subscale score will be the participant-level endpoint was changed from "6, 12, 18, 24, 30, and 36 months" to "6, 12, 18, 24, 30, 36, 42, and 48 months" to align with changes made in the Schedule of Activities.	To generate longer term data; to align with changes made in the Schedule of Activities.
Section 9.3.3.5.5 Early PD Function Slowness and PD Mobility PROs	The timepoints at which the PRO final score will be the participant-level endpoint was changed from "6, 12, 18, 24, 30, and 36 months" to "6, 12, 18, 24, 30, 36, 42, and 48 months" to align with changes made in the Schedule of Activities.	To generate longer term data; to align with changes made in the Schedule of Activities.
Section 9.3.3.5.6 CSF ASYN	Text was added to the first sentence to state that total ASYN and ASYN oligomers/seeding capacity will also be measured in CSF samples obtained from PD0055 participants who initially did not consent in PD0053, ie, at PD0055 Baseline (Month 18 post PD0053 Baseline) and Months 18 and 30 post PD0055 Baseline. Text was added under *Descriptive statistics and visualization* to state that separate tabulated and graphical summaries will be produced for study participants who consented only from PD0055 Baseline.	To increase meaningfulness of biomarker analysis.
Section 9.3.3.6 Digital Health Technology	New section was added to describe analyses related to the Digital Health Technology.	To provide information on analysis of Digital Health Technology data.

Section # and name	Description of change	Brief rationale
Section 9.3.5 Exploratory Objective IV: Atypical Parkinsonism	Subsections were revised to clarify the planned analyses and update references to SAPs for further details. Section 9.3.5.1 *Descriptive statistics and visualization* was added. Former Section 9.3.5.1 *PD0053/PD0055 sensitivity analyses* was renumbered to Section 9.3.5.2. Section 9.3.5.3 *Identification of Atypical Parkinsonian Disorder participants' Baseline characteristics* was removed.	To clarify the planned analysis for Exploratory Objective IV.
Section 9.7 Planned analysis and data monitoring	Text was added at the start of the section to provide a reference to the analyses related to the Digital Health Technology described in Section 9.3.3.6.	To provide information on analysis of Digital Health Technology data.
	The sentence "Care will be taken to ensure that the blinded study team remains blinded for the total duration of the study" was revised to "Care will be taken to ensure that all study participants and Investigators will remain blinded to treatment/dose received in PD0053 and PD0055 at least until all participants have completed the Month 18 assessments in PD0055."	To clarify the duration of blinding and align with Sections 4.1 and 6.3.1.1.
Section 9.8 Determination of sample size	The second paragraph was changed from "Assuming that 60% of PD0053 participants (270) choose to roll over into PD0055, and 15% of the PD0053 participants drop out or are lost to follow up, then 202 participants would be expected to reach the EOT" to "All study participants (approximately 490) can roll over from PD0053. Assuming that 15% of PD0053 participants drop out or are lost to follow up over 18 months and 90% of the remaining 416 participants who complete PD0053 choose to roll over into PD0055, then 374 participants would be expected to enter the extension study. Assuming that 15% of PD0055 participants drop out or are lost to follow up over 18 months, 318 participants would be expected to reach PD0055 EOT."	To update the number of participants expected to roll over from PD0053 based on observations in PD0055.

Section # and name	Description of change	Brief rationale
Section 10.7 Appendix 7: Digital Health Technology AEs, SAEs, ADEs, SADEs, and device deficiencies: Definition and procedures for recording, evaluating, follow-up, and reporting	Appendix 7 was added to provide definitions and procedures for safety reporting associated with the Koneksa Neuroscience Toolkit.	To reflect the addition of the Digital Health Technology and adapt study procedures.
Section 10.11 Appendix 11: Protocol amendment history	The Protocol Amendment Summary of Changes Table for the previous amendment was moved to Appendix 11.	Minor administrative change.
Section 11 REFERENCES	The following references were added: • Apple iPhone User Guide • CentrePoint Data Hub User Guide • CentrePoint Insight Watch User Guide • Devlin and Brooks, 2017 • Doty, 2012 • Doty et al, 1984 • Schade et al, 2020 • Siderowf et al, 2023 • Tomlinson et al, 2010	To update references cited in the protocol.
Throughout	Correction of a few typographical and formatting errors.	Minor, therefore have not been summarized.

10.11.2 Amendment 2 (30 Jun 2023)

Overall Rationale for the Amendment

PD0055 Protocol Amendment 2 was enacted to incorporate additional laboratory tests at Day 60, Day 120, and Day 150 in order to allow for close monitoring of liver function test parameters.

This amendment is considered to be substantial based on the criteria set forth in Article 2(13) of Regulation No 536/2014 of the European Parliament and the Council of the European Union.

Section # and name	Description of change	Brief rationale
Section 1.3 Schedule of Activities	In-clinic visits at Day 60 (Month 2), Day 120 (Month 4), and Day 150 (Month 5) (Visits 4a, 5a, and 5b, respectively) were added.	To increase the monitoring of liver function test parameters and align monitoring at treatment start with the feeder study PD0053.

Section # and name	Description of change	Brief rationale
Section 2.3 Benefit/risk assessment	Text was updated to add hepatotoxicity to the list of potential risks, to add that renal laboratory abnormalities are kept under close safety monitoring, and to clarify the measures to mitigate the potential risk of hepatotoxicity.	To align with the warnings and precautions provided in the updated Section 6.3.4 of the Investigator's Brochure.
Section 10.11 Appendix 11: Protocol amendment history	The Protocol Amendment Summary of Changes Table for the previous amendment has been added.	Minor administrative change.
Throughout	Minor editorial and document formatting revisions.	Minor, therefore have not been summarized.

10.11.3 Amendment 1 (07 Nov 2022)

Overall Rationale for the Amendment

PD0055 Protocol Amendment 1 was completed to update the protocol based on Requests for Information received during the initial Clinical Trial Application.

Section # and name	Description of change	Brief rationale
Global	The protocol 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.	To clarify doses administered in PD0055
Section 2.3.1 Coronavirus Disease-2019 benefit/risk assessment	Section 2.3.1 was added to provide a COVID-19 benefit/risk assessment.	To add a benefit/risk assessment for COVID-19
Section 4.1 Overall design	The following sentence was removed as no safety concern was identified in PD0053 prior to the first study participant entering PD0055: "However, in case of safety concerns with respect to the 360mg/day dose at the time the first participant is planned to transition into PD0055, the dose to switch both placebo and UCB0599 360mg/day participants to may be revised to be UCB0599 180mg/day instead."	To remove a precaution that no longer applies

Section # and name	Description of change	Brief rationale
Section 4.3 Justification for dose	The following sentence was removed as no safety concern was identified in PD0053 prior to the first study participant entering PD0055: "In case of safety concerns with respect to the UCB0599 360mg/day dose at the time the first participant is planned to transition into PD0055, the dose to switch placebo participants to may be selected to be UCB0599 180mg/day instead."	To remove a precaution that no longer applies
Section 8.3.1 Time period and frequency for collecting AE and SAE information	Text was updated to clarify that the Investigator will submit any updated SAE data to the Sponsor **without undue delay but not later than** within 24 hours of it being available.	To align protocol wording with Regulation (EU) No. 536/2014 Article 41, No. 2
Section 8.3.3 Follow-up of AEs and SAEs	Text was revised to clarify that follow-up procedures apply to "all AEs, SAEs, and AESIs" (instead of "all SAEs, and nonserious AESIs").	To remove an inconsistency with Appendix 10.3
Section 8.3.4 Regulatory reporting requirements for SAEs	The following sentence was added: "Further to the reporting of an SAE from the Investigator to the Sponsor, an expectedness assessment will be made per the IB, as reference safety information for this study, and relevant Sponsor's SOPs and appropriate reporting of suspected unexpected serious adverse reactions (SUSARs) will be carried out to health authorities as per ICH and local regulatory requirements." In addition, the following sentence was moved up in the section to appear below the new sentence above: "Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary."	To further clarify reporting of SUSARs
Section 9.8 Determination of sample size	The following text was removed: "However, estimates of power will be provided. Details of these will be described in an accompanying white paper entitled "Sample Size Documentation Form" as per sop-af-104040."	To remove text on estimates of power which does not apply for PD0055
Section 10.1.1 Regulatory and ethical considerations	Text was updated with the competent authority wherever applicable.	To clarify responsibilities in different regions

Section # and name	Description of change	Brief rationale
Section 10.1.3 Informed consent process	The following sentence was removed at the end of the second paragraph: "In France, participants will be given at least 3 days of reflection time before signing the ICF."	To remove a country-specific requirement (related to a Part II RFI request received during the initial Clinical Trial Application)
Section 10.1.4 Data protection	Text was updated.	To further clarify personal data protection
Section 10.1.6 Dissemination of clinical study data	The following sentence was added: "A summary of the results is also planned to be posted to the EU database within 1 year of study completion, in accordance with international standards and irrespective of the outcome of the clinical study."	To further clarify results posting following study completion
Section 10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information	The following text was added: "In case of sterilization, it should have taken place before the start of the Screening Period and the medical records of the participant should include the method of sterilization, along with the date of sterilization, as proof of the contraception."	To provide further clarification on sterilization for WOCBP related to a Part II RFI request received during the initial Clinical Trial Application
Section 10.11 Protocol amendment history	A note was added that the Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.	Minor administrative change

11 REFERENCES

Antonini A, Martinez-Martin P, Chaudhuri RK, et al. Wearing-off scales in Parkinson's disease: critique and recommendations. Mov Disord. 2011;26(12):2169-75.

Bloem BR, Marks WJ Jr, Silva de Lima AL, et al. The Personalized Parkinson Project: examining disease progression through broad biomarkers in early Parkinson's disease. BMC Neurol. 2019;19(1):160.

CentrePoint Data Hub User Guide. Pensacola, FL: ActiGraph, LLC; 2023.

CentrePoint Insight Watch User Guide. Pensacola, FL: ActiGraph, LLC; 2023.

Devlin NJ, Brooks R. EQ-5D and the EuroQol Group: Past, Present and Future. Appl Health Econ Health Policy. 2017;15(2):127-37.

Doty RL. Olfaction in Parkinson's disease and related disorders. Neurobiol Dis. 2012;46(3):527-52.

Doty RL, Shaman P, Dann M. Development of the University of Pennsylvania Smell Identification Test: a standardized microencapsulated test of olfactory function. Physiol Behav. 1984;32(3):489-502.

Food and Drug Administration. Patient-Focused Drug Development Public Workshop Guidance 2 Discussion Document - Appendices. Methods to Identify What is Important to Patients & Select, Develop or Modify Fit-for-Purpose Clinical Outcomes Assessments. Workshop Date: 15-16 Oct 2018. Available at: https://www.fda.gov/media/116259/download (accessed 06 Jun 2024).

Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord. 2008 Nov 15;23(15):2129-70.

Gray R, Patel S, Ives N, et al. Long-term effectiveness of adjuvant treatment with catechol-O-methyltransferase or monoamine oxidase b inhibitors compared with dopamine agonists among patients with Parkinson disease uncontrolled by levodopa therapy - The PD MED randomized clinical trial. JAMA Neurol. 2022;79(2):131-40.

Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology. 1967 May;17(5):427-42.

Ihle-Hansen H, Vigen T, Berge T, et al. Montreal Cognitive Assessment in a 63- to 65-year-old Norwegian cohort from the general population: data from the Akershus Cardiac Examination 1950 study. Dement Geriatr Cogn Disord Extra. 2017;7(3):318–27.

Ikeda K, Ebina J, Kawabe K, et al. Dopamine transporter imaging in Parkinson disease: progressive changes and therapeutic modification after anti-parkinsonian medications. Intern Med. 2019;58(12):1665-72.

iPhone User Guide. Apple Inc. https://support.apple.com/guide/iphone/welcome/ios. Accessed 18 Jul 2023.

Martinez-Martin P, Schrag A, Weintraub D, et al. Pilot study of the International Parkinson and Movement Disorder Society-sponsored Non-Motor Rating Scale (MDS-NMS). Mov Disord Clin Pract. 2019;6(3):227-34.

Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53(4):695-9.

Pahwa R, Lyons KE. Levodopa-related wearing-off in Parkinson's disease: identification and management. Curr Med Res Opin. 2009;25(4):841-9.

Poewe W. The natural history of Parkinson's disease. J Neurol. 2006;253(Suppl 7):VII/2-VII/6.

Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2011 Dec;168(12):1266-77.

Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006 Feb;117(2):391-7.

Schade S, Mollenhauer B, Trenkwalder C. Levodopa equivalent dose conversion factors: an updated proposal including opicapone and safinamide. Mov Disord Clin Pract. 2020;7(3):343-45.

Siderowf A, Concha-Marambio L, Lafontant DE, et al. Assessment of heterogeneity among participants in the Parkinson's Progression Markers Initiative cohort using α-synuclein seed amplification: a cross-sectional study. Lancet Neurol. 2023;22(5):407-17.

Stacy M, Hauser R, Oertel W, et al. End-of-dose wearing off in Parkinson disease: a 9-question survey assessment. Clin Neuropharmacol. 2006;29(6):312-21.

Stacy MA, Murphy JM, Greeley DR, et al. The sensitivity and specificity of the 9-item Wearing-off Questionnaire. Parkinsonism Relat Disord. 2008;14(3):205-12.

Tomlinson CL, Stowe R, Patel S, et al. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord. 2010;25(15):2649-53.

Treudler R, Kozovska Y, Simon JC. Severe immediate type hypersensitivity reactions in 105 German adults: when to diagnose anaphylaxis. J Investig Allergol Clin Immunol. 2008;18(1):52-8.

SPONSOR DECLARATION

I confirm that I have carefully read and understand this protocol and agree to conduct this clinical study as outlined in this protocol, according to Clinical Trial Regulation EU 536/2014, and according to current GCP.

Approval Signatures

Name: pd0055-protocol-amend-4-09oct2024

Version: 1.0

Document Number: CLIN-000251651

Title: PD0055 Protocol Amendment 4

Approved Date: 09 Oct 2024

Document Approvals	
Approval Verdict: Approved	Name: [redacted] Capacity: Subject Matter Expert Date of Signature: 09-Oct-2024 09:48:56 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 09-Oct-2024 15:29:26 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Medical Date of Signature: 09-Oct-2024 15:33:59 GMT+0000