A DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED, 18-MONTH PHASE 2A STUDY TO EVALUATE THE EFFICACY, SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF ORAL UCB0599 IN STUDY PARTICIPANTS WITH EARLY PARKINSON'S DISEASE

PROTOCOL PD0053 AMENDMENT 6

PHASE 2A

SHORT TITLE:

A double-blind, placebo-controlled, randomized, Phase 2a study with oral UCB0599 in study participants with early Parkinson's disease

Sponsor:

UCB Biopharma SRL

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Regulatory agency identifying number(s):

Eudra CT Number:	2020-003265-19
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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document History		
Document	**Date**	**Type of amendment**
Amendment 6	21 Mar 2024	Nonsubstantial
Amendment 5	30 Jun 2023	Substantial
Amendment 4	24 Feb 2022	Substantial
Amendment 3	04 Oct 2021	Substantial
Amendment 2.2 UK	04 Jun 2021	Nonsubstantial
Amendment 2.1 France	04 Jun 2021	Nonsubstantial
Amendment 2	21 May 2021	Nonsubstantial
Amendment 1.7 Germany	10 Aug 2021	Substantial[a]
Amendment 1.6 Germany	17 May 2021	Nonsubstantial
Amendment 1.5 Germany	01 Apr 2021	Nonsubstantial
Amendment 1.4 UK	25 Feb 2021	Not applicable
Amendment 1.3 Germany	22 Feb 2021	Not applicable
Amendment 1.2 France	17 Feb 2021	Not applicable
Amendment 1.1 Canada	15 Feb 2021	Not applicable
Amendment 1	29 Oct 2020	Not applicable
Original Protocol	13 Oct 2020	Not applicable

[a] Amendment 1.7 Germany was initially submitted as a nonsubstantial amendment.

Amendment 6 (21 Mar 2024)

PD0053 Protocol Amendment 6 was completed to provide clarification around blinding, the timing of the Month 12 data analysis, and to remove analyses that are no longer needed. In addition, the list of secondary and exploratory efficacy endpoints was updated. The following changes were implemented:

Section # and Name	Description of Change	Brief Rationale
Global	Throughout the protocol, references to PD0055 were updated to clarify that this is a dose-blinded (not an open-label) extension study.	Correction.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis **Objectives and Endpoints** and Section 3 OBJECTIVES AND ENDPOINTS	A new **Secondary Efficacy Endpoint** for the primary efficacy objective was added and replaces the former exploratory endpoint 'MDS-UPDRS selected items' (as described below): • MDS-UPDRS Part III ePD subscore on selected items (timeframe: Baseline to 18 months)	To add a new secondary efficacy endpoint based on the MDS-UPDRS Part III subscale.
	A new **Secondary Efficacy Endpoint** was added for the primary efficacy objective: • Emerging symptoms as measured by MDS-UPDRS Part II (timeframe: Baseline to 18 months)	To add a new secondary efficacy endpoint consisting of an additional analysis of the MDS-UPDRS Part II data already collected in the study.
	The following **Secondary Efficacy Endpoint** for the primary efficacy objective was revised (**bolded** text added): • Time to worsening of the disease **as measured by MDS-UPDRS Part III** (timeframe: Baseline to 18 months)	To further specify the endpoint.
	The following **Exploratory Efficacy Endpoint** for the primary efficacy objective was revised (see strikethrough text): • Time to worsening in MDS-UPDRS Part I ~~and Part II~~ subscale~~s~~	To further specify the endpoint (Part II subscale is removed as it is now part of new secondary emerging symptoms endpoint).
	The following **Exploratory Efficacy Endpoint** for the primary efficacy objective was removed and is now covered by the new secondary endpoint 'MDS-UPDRS Part III ePD subscore (selection of items)': • ~~MDS-UPDRS selected items~~	To modify an exploratory efficacy endpoint: this endpoint is now part of the secondary endpoints.
	A new **Exploratory Efficacy Endpoint** was added for the primary efficacy objective: • Composite endpoint (based on MDS-UPDRS and/or Early PD PROs)	To add an exploratory efficacy endpoint composed of endpoints already included in the study.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis **Objectives and Endpoints**	The Exploratory Efficacy Endpoint 'CSF ASYN oligomers/seeding capacity' was added for the secondary efficacy objective.	To align with Section 3 (implementing a change from Amendment 4 that was missed in Amendment 5).
Section 1.3 Schedule of Activities	Footnote 'b' was removed from V9. Footnote 'b' was added to V16.	Correction. To align with the visits that can be done from the participant's home.
Section 5.2 Exclusion criteria	In exclusion criterion #31b (1) (previously #31a [1]), bupropion was added back.	Correction. Bupropion had inadvertently been removed in Amendment 4.
Section 6.3 Measures to minimize bias: randomization and blinding	In the fifth paragraph, the following bullet was added to further clarify who may have access to the randomization code: • Unblinded pharmacometrics staff and statistical programmers, independent from the study team, who have access to the 12-month data for the preparation of the exposure-response analysis	To add access to the randomization code to independent experts for exposure-response model development, which has no impact on the ongoing study monitoring and conduct.
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 DaT-SPECT imaging.	To complete the list of drugs that may affect the DaT-SPECT scan.
Section 8.1.1.1 MDS-UPDRS	The introductory sentence for the MDS-UPDRS was revised to clarify that the 4 parts are referred to as "subscales."	To clarify terminology.
Section 9.3 Planned efficacy/outcome analyses	Table 9-1 was updated to reflect the updates to secondary and exploratory efficacy endpoints.	To align with updates to the list of exploratory efficacy endpoints in objectives and endpoints table.
	Text below Table 9-1 was updated to clarify that the efficacy data analysis will take place once all participants have completed their 18-month Visit.	To clarify the timepoint of the efficacy analysis.

Section # and Name	Description of Change	Brief Rationale
Section 9.3 Planned efficacy/outcome analyses	Text around sensitivity analyses was removed at the end of the section.	To remove sensitivity analyses that are no longer relevant due to the large proportion of participants having initiated ST during the study, and/or due to the data being unblinded at end of study only and not at Month 12.
Section 9.3.1.1.1 Primary Efficacy Estimand: MDS-UPDRS Parts I-III sum score at 12 months ("De Jure" Estimand) and Section 9.3.1.2.3 Secondary Efficacy Estimand: MDS-UPDRS Part I/Part II/Part III subscales at 18 months ("De Jure" Estimand)	Under ICEs and handling strategies, 'while-on-treatment' was updated to 'hypothetical'.	Updated to use 'hypothetical' in place of 'while-on-treatment' throughout (no change to actual handling of data, post-ICE data will still be set to missing).
Section 9.3.1.1.1.1 Supplementary Efficacy Estimand to MDS-UPDRS Parts I-III sum score at 12 months ("De Facto" Estimand)	Under Estimator, text was updated to refer to Section 9.3.1.2.1.1 (LMEM estimator based on Baseline to Month 18 data).	Separate 12-month analyses will not be performed. Estimates at Month 12 will be generated from the analyses over 18 months.

Section # and Name	Description of Change	Brief Rationale
Section 9.3.1.1.1 Primary Efficacy Estimand: MDS-UPDRS Parts I-III sum score at 12 months ("De Jure" Estimand) and Section 9.3.1.1.2 Key Secondary Efficacy Estimand: MDS-UPDRS Part III subscale at 12 months ("De Jure" Estimand) and Section 9.3.1.1.4 Secondary Efficacy Estimands: MDS-UPDRS Part I/II subscales at 12 months ("De Jure" Estimands) and Section 9.3.1.2.1 Key Secondary Efficacy Estimand: MDS-UPDRS Parts I-III sum score at 18 months ("De Jure" Estimand) and Section 9.3.1.2.5 (previously 9.3.1.2.4) Secondary Efficacy Estimand: MoCA over 18 months	Subheading and text for Sensitivity analyses was removed.	Sensitivity analyses for these estimands are no longer relevant.
Section 9.3.1.1.3 Key Secondary Efficacy Estimand: Worsening on MDS-UPDRS Part III subscale at 12 months ("De Jure" Estimand)	Section was removed.	To remove a time-to-event analysis which has become redundant as unblinding will only occur at end of study.
Section 9.3.1.1.3 Key Secondary Efficacy Estimand: MDS-UPDRS Part III subscale and Part III early-stage PD subscore at 12 months	New section was added.	To align with updates to the list of exploratory efficacy endpoints in objectives and endpoints table.
Section 9.3.1.1.4 Secondary Efficacy Estimands: MDS-UPDRS Part I/II subscales at 12 months ("De Jure" Estimands)	Text under ICEs and handling strategies and Population-level summary was updated.	Correction to handle MDS-UPDRS Part I and Part II in the same way for the secondary estimand, and handle both regardless of ST in the supplementary estimand.

Section # and Name	Description of Change	Brief Rationale
Section 9.3.1.1.4 Secondary Efficacy Estimands: MDS-UPDRS Part I/II subscales at 12 months ("De Jure" Estimands)	Under Estimator, text was replaced to be a reference to Section 9.3.1.2.3 (LMEM estimator based on Baseline to Month 18 data).	Separate 12-month analyses will not be performed. Estimates at Month 12 will be generated from the analyses over 18 months.
Section 9.3.1.1.4.1 Supplementary Efficacy Estimand to MDS-UPDRS Part I/II subscales at 12 months ("De Facto" Estimand)	Under Estimator, estimates, and sensitivity analyses, text was replaced to be a reference to Section 9.3.1.2.1.1 (LMEM estimator based on Baseline to Month 18 data).	Separate 12-month analyses will not be performed. Estimates at Month 12 will be generated from the analyses over 18 months.
Section 9.3.1.1.5 Exploratory Efficacy Endpoints at 12 months and Section 9.3.1.2.6 (previously 9.3.1.2.5) Exploratory Efficacy Endpoints at 18 months	The first Exploratory Efficacy Endpoint in the list was updated (see strikethrough text): • Time to worsening in MDS-UPDRS Part I ~~and Part II~~ subscale~~s~~ The second Exploratory Efficacy Endpoint in the list was removed: • ~~MDS-UPDRS selected items~~ A new Exploratory Efficacy Endpoint was added below the Mobility PRO: • Composite endpoint (based on MDS-UPDRS and/or Early PD PROs)	To align with updates in objectives and endpoints table.
Section 9.3.1.2.3 Secondary Efficacy Estimand: MDS-UPDRS Part I/Part II/Part III subscales at 18 months ("De Jure" Estimand)	Under Sensitivity analyses, text was updated.	To remove sensitivity analyses that are no longer relevant.
Section 9.3.1.2.3.1 Key Secondary Efficacy Estimand: MDS-UPDRS Part III subscale and Part II ePD subscore at 18 months	New section was added.	To align with updates to the list of exploratory efficacy endpoints in objectives and endpoints table.
Section 9.3.1.2.3.2 (previously 9.3.1.2.3.1) Supplementary Efficacy Estimand: MDS-UPDRS Part II/Part III subscales at 18 months ("De Facto" Estimand)	Under Estimator, estimates, and sensitivity analyses, a reference to the SAP for further exploratory analyses was removed.	To remove sensitivity analyses that are no longer relevant.

Section # and Name	Description of Change	Brief Rationale
Section 9.3.1.2.4 Secondary Efficacy Estimand: MDS-UPDRS Part II emerging symptoms over 18 months	New section was added.	To align with updates to the list of exploratory efficacy endpoints in objectives and endpoints table.
Section 9.3.2.1 Secondary Efficacy Estimand: DaT-SPECT mean Striatum SBR at Month 12 and Month 18	Throughout, references to "18 months" have been replaced by "Month 12 and Month 18" for clarity. The text under Sensitivity analyses was updated.	To clarify that separate 12-month analyses will not be performed. Estimates at Month 12 will be generated from the analyses over 18 months.
Section 9.3.2.1.1 Supplementary Efficacy Estimand: DaT-SPECT mean Striatum SBR at 18 months	Section was removed.	To remove a supplementary analysis that is no longer relevant.
Section 9.3.2.2 Other Secondary Efficacy Estimand: DaT-SPECT mean Striatum SBR at 12 months	Section was removed.	Section no longer applies as no separate 12-month analyses will be done. Estimates at Month 12 will be generated from the main analyses over 18 months.
Section 9.3.2.2 (previously 9.3.2.3) Exploratory Efficacy Endpoints at Month 12 and Month 18	In the section title, "at 12 and 18 months" was changed to "Month 12 and Month 18"	Minor editorial change.
Section 9.3.3.1 Secondary Efficacy Estimand: Time to ST initiation over 18 months	The section heading was corrected: "Time to ST ~~intake at~~ **initiation over** 18 months" The subheading Supplementary analyses and reference to the SAP was removed.	To remove supplementary analyses that are no longer relevant.
Section 9.3.3.2 Secondary Efficacy Estimand: Intake of ST at 18 months and Section 9.3.3.3 Other Secondary Efficacy Estimand: Intake of ST at 12 months	The following sentence was removed under Sensitivity analyses: ~~The main model will be adjusted for Baseline predictors of early initiation of ST.~~	To remove sensitivity analyses that are no longer relevant.
Section 9.3.4 Subgroup analyses	Text was updated to clarify that analyses by subgroup will be performed as part of exploratory analyses.	To remove analyses that are no longer planned as part of the main analysis.

Section # and Name	Description of Change	Brief Rationale
Section 9.5 Handling of ICEs, protocol deviations, and resulting missing data	The second bullet for the 'while-on-treatment' strategy was removed. The third bullet for the 'hypothetical' strategy was revised. The overview of handling strategies for MDS-UPDRS ICEs and study termination was updated (Table 9-2 and associated text).	To remove the 'while-on-treatment' strategy and align with updates to efficacy endpoints throughout the protocol.
Section 9.5.1 ICEs potentially affecting the interpretation of measurements	Under MDS-UPDRS, the description of how the post-ICE data will be censored was updated. Under DaT-SPECT, the description of the supplementary analysis was removed. Under Treatment discontinuation/nonadherence, 'while-on-treatment' strategy was replaced with 'hypothetical' strategy.	To remove the DaT-SPECT supplementary analysis which was no longer relevant and to align with other changes made throughout the protocol, eg, to reflect change in wording of handling strategy from 'while on treatment' to 'hypothetical'.
Section 9.5.3 Other protocol deviations	In the fourth paragraph, 'while-on-treatment' strategy was replaced with 'hypothetical' strategy. The eighth paragraph on the 'while-on-treatment' strategy was removed.	To replace the 'while-on-treatment' strategy with 'hypothetical' strategy throughout and align with other changes made throughout the protocol.
Section 9.6 Planned analysis at 12 months and data monitoring	The first paragraph was revised to clarify that the analyses of Month 12 data will be carried out at study end. A paragraph was added to describe that a limited team of independent pharmacometricians and statistical programmers with access to the 12-month data will be unblinded to prepare for the exposure-response analysis.	To clarify that no primary analysis at Month 12 will be done, and to describe the unblinding of an independent expert group to develop the exposure-response model which has no impact on the study monitoring or conduct.
Section 10.6 Appendix 6: Liver safety – suggested actions and follow-up assessments	In Table 10-1 (Phase 2 Liver Chemistry Stopping Criteria and Follow-up Assessments), GGT was added as an optional follow-up assessment.	To better characterize the important potential UCB0599 risk of transaminases elevation in case of potential drug-induced liver injury.

Section # and Name	Description of Change	Brief Rationale
Section 11 REFERENCES	The following reference was added: Tosin et al, 2022. The following references were removed: Mehrotra et al, 2017; Parashos et al, 2009; Simuni et al, 2016.	To add a new reference and to remove references that are no longer cited.
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)

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol title:

A double-blind, placebo-controlled, randomized, 18-month Phase 2a study to evaluate the efficacy, safety, tolerability, and pharmacokinetics of oral UCB0599 in study participants with early Parkinson's disease

Short Title:

A double-blind, placebo-controlled, randomized, Phase 2a study with oral UCB0599 in study participants with early Parkinson's disease

Rationale:

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.

Nonclinical and in vivo pharmacology studies have provided scientific evidence suggesting that UCB0599 may slow disease progression in PD, which remains the main unmet medical need in this condition. A first-in-human (FIH) study using UCB0599, UP0030, was conducted in healthy elderly participants. UP0030 provided the safety, tolerability, and pharmacokinetic (PK) information for single dose exposures up to 450mg and multiple dose exposures of 180mg/day for up to 21 days in healthy elderly participants (defined as ≥55 to ≤75 years of age). 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. UP0077 also provided information for the design of the current proof-of-concept (POC) study in study participants with early stage PD. PD0053 is designed to provide proof of concept for the efficacy of the synuclein misfolding inhibitor UCB0599 in reducing disease progression in study participants with early-stage PD and to instruct later stage development.

Objectives and Endpoints

Objectives	Endpoints
Primary Efficacy Objective	
To demonstrate the superiority of UCB0599 over placebo with regard to clinical symptoms of disease progression over 12 and 18 months in participants diagnosed with early-stage PD	**Primary Efficacy Endpoint** • MDS-UPDRS Parts I-III sum score (timeframe: Baseline to 18 months) **Secondary Efficacy Endpoints** • MDS-UPDRS Part III subscale (timeframe: Baseline to 18 months) • MDS-UPDRS Part III ePD subscore on selected items (timeframe: Baseline to 18 months)

Objectives	Endpoints
	• MDS-UPDRS Part II subscale (timeframe: Baseline to 18 months) • MDS-UPDRS Part I subscale (timeframe: Baseline to 18 months) • Emerging symptoms as measured by MDS-UPDRS Part II (timeframe: Baseline to 18 months) • Time to worsening of the disease as measured by MDS-UPDRS Part III (timeframe: Baseline to 18 months) • MoCA (timeframe: Baseline to 18 months) **Exploratory Efficacy Endpoints** • Time to worsening in MDS-UPDRS Part I subscale • Modified Hoehn and Yahr staging • CGII • CGIS • Fatigue-PRO • Early PD Function Slowness PRO • Early PD Mobility PRO • Composite endpoint (based on MDS-UPDRS and/or Early PD PROs) • PGIS, overall and fatigue-specific • PGIC, overall and fatigue-specific • SE-ADL • HADS • MDS-NMS • Starkstein Apathy Scale • EQ-5D-5L • Wearable sensor

Objectives	Endpoints
Secondary Efficacy Objectives	
To demonstrate the superiority of UCB0599 over placebo with regard to neurodegeneration of dopaminergic neurons over 12 and 18 months in participants diagnosed with early-stage PD	**Secondary Efficacy Endpoints** • Change from Baseline (Screening) in DaT-SPECT mean Striatum SBR (timeframe: Screening to 18 months) **Exploratory Efficacy Endpoints** • DaT-SPECT mean SBR in striatal subregions • CSF total ASYN • CSF ASYN oligomers/seeding capacity
To assess the effect of UCB0599 vs placebo with regard to intake of ST over 18 months in participants diagnosed with early-stage PD	**Secondary Efficacy Endpoints** • Time to start of ST (timeframe: Baseline to 18 months) • ST intake (timeframe: Baseline to 18 months) **Exploratory Efficacy Endpoints** • Levodopa cumulative daily dose
Primary Safety Objective	
To assess the safety and tolerability of UCB0599 in participants diagnosed with early-stage PD	**Secondary Safety Endpoints** • Incidence of TEAEs • Incidence of SAEs • Incidence of TEAEs leading to participant withdrawal **Other Safety Endpoints** • Change from Baseline in clinical laboratory values (chemistry, hematology, and urinalysis) • Change from Baseline in vital signs • Change from Baseline in physical examination • Change from Baseline in neurological examination findings • C-SSRS findings • ECG findings
Exploratory PK Objective	
To assess the PK of UCB0599 and its N-oxide metabolite in participants diagnosed with early-stage PD	**Exploratory PK Endpoint** • UCB0599 and N-oxide metabolite plasma and CSF concentrations

ASYN=alpha-synuclein; CGII=Clinical Global Impression of Improvement; CGIS=Clinical Global Impression of Severity; CSF=cerebrospinal fluid; C-SSRS=Columbia-Suicide Severity Rating Scale; DaT-SPECT=Dopamine Transporter Imaging with Single Photon Emission Computerized Tomography; ECG=electrocardiogram; ePD=early-stage PD; EQ-5D-5L=EuroQol-5-dimension-5-level; HADS=Hospital Anxiety and Depression Scale; MDS-NMS=Movement Disorder Society-Non-motor Scale; MDS-UPDRS=Movement Disorder Society-Unified Parkinson's Disease Rating Scale; MoCA=Montreal Cognitive Assessment; PD=Parkinson's disease; PGIC=Patient Global Impression of Change; PGIS=Patient Global Impression of Severity; PK=pharmacokinetic; PRO=Patient-Reported Outcome; SAE=serious adverse event; SBR=specific binding ratio; SE-ADL=Schwab and England Activities of Daily Living; ST=symptomatic treatment; TEAE=treatment-emergent adverse event

Overall Design

PD0053 is a randomized, double-blind, placebo-controlled, 18-month Phase 2a study to evaluate the efficacy, safety, tolerability, and PK of orally administered UCB0599 in study participants with early-stage PD who are not treated with symptomatic medications targeting motor symptoms of PD at the time of inclusion. The primary objective of the study is to demonstrate the superiority of UCB0599 over placebo with regard to clinical symptoms of disease progression over 12 and 18 months in this patient population. The difference between UCB0599 and placebo will be evaluated for both the low and high doses of UCB0599 (180mg/day and 360mg/day). The comparison of the high dose of UCB0599 with placebo will be considered as the primary evaluation. Oral UCB0599 capsules or matching placebo capsules will be administered twice per day (BID), approximately 12 hours apart.

PD0053 includes a Screening Period (including, where available, a wearable sensor familiarization period for those participants who consent to its use), an 18-month Treatment Period (including, where available, a wearable sensor familiarization period for those participants who consent to its use after the Screening Period), and a Safety Follow-up (SFU) Period. Study participants who complete the Treatment Period will have the option to transition into a dose-blinded extension study, PD0055. In this case, participants will not enter the SFU Period of PD0053.

The outcomes of this study will inform the design and dose selection for confirmatory studies, and help to further validate novel endpoints and technologies and support strategic development program decisions.

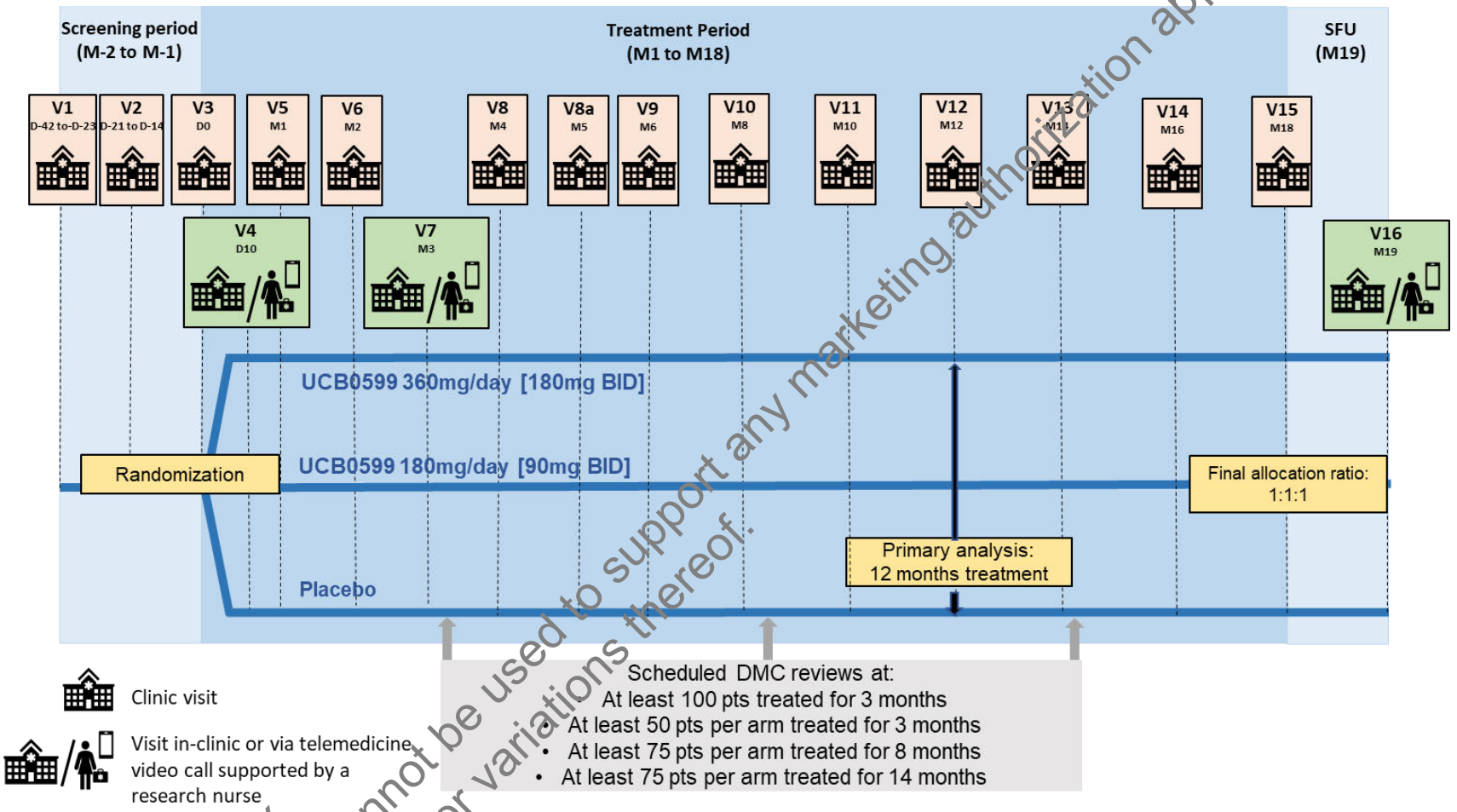
Number of Participants

Approximately 645 participants will be screened to achieve 450 participants randomly assigned to study medication and 429 evaluable participants, for an estimated total of 143 evaluable participants per treatment group.

Treatment Groups and Duration

PD0053 includes a Screening Period of 3 to 6 weeks, an 18-month Treatment Period, and an SFU Period of 1 month, for a total duration of approximately 21 months. PD0053 starts with participants randomized 1:1 to either UCB0599 360mg/day or placebo. Participants will be randomized to either UCB0599 360mg/day (180mg BID), UCB0599 180mg/day (90mg BID), or placebo when the IMP for low dose UCB0599 180mg/day (90mg BID) will be available to supply sites so that the final allocation ratio is 1:1:1.

1.2 Schema



BID=twice per day; D=day; DMC=Data Monitoring Committee; M=month; pts=participants; SFU=Safety Follow-up; V=Visit
Note: All visits are in-clinic visits in France.
Note: Visit 8a will be conducted as an unscheduled visit.

1.3 Schedule of Activities

	Screening		Treatment														SFU
	V1	V2[a]	V3	V4[b]	V5	V6	V7[b]	V8	V8a[w]	V9	V10	V11	V12	V13	V14	V15	V16[b]
			BL		M1	M2	M3	M4	M5	M6	M8	M10	M12	M14	M16	M18 EOT	M19
	🏠	🏠	🏠	🏠/🧍	🏠	🏠	🏠/🧍	🏠	🏠	🏠	🏠	🏠	🏠	🏠	🏠	🏠	🏠/🧍
Day	-42 to -23	-21 to -14	0	10 +/-1	30 +/-1	60 +/-3	90 +/-3	120 +/-5	150 +/-5	180 +/-5	240 +/-5	300 +/-5	360 +/-5	420 +/-5	480 +/-5	540 +/-5	570 +/-5
Written Informed Consent incl. genetics ICF and wearable sensor ICF	X																
Demographics, PD history	X																
General medical and procedure history	X																
Inclusion/Exclusion criteria	X	X	X														
Withdrawal criteria[c]				X	X	X	X	X	X	X	X	X	X	X	X	X	
Participant identification card assignment			X														
Prior and concomitant medications and procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X																

	Screening		Treatment														SFU
	V1	V2[a]	V3	V4[b]	V5	V6	V7[b]	V8	V8a[w]	V9	V10	V11	V12	V13	V14	V15	V16[b]
			BL		M1	M2	M3	M4	M5	M6	M8	M10	M12	M14	M16	M18 EOT	M19
Day	-42 to -23	-21 to -14	0	10 +/-1	30 +/-1	60 +/-3	90 +/-3	120 +/-5	150 +/-5	180 +/-5	240 +/-5	300 +/-5	360 +/-5	420 +/-5	480 +/-5	540 +/-5	570 +/-5
Vital signs, weight[d]	X	X	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
Physical examination	X		X			X							X			X	
Brief physical examination[f]		X		X	X		X	X		X	X	X		X	X		X
Neurological examination (incl. modified H&Y)	X	X[g]				X							X			X	
Brief neurological examination (incl. modified H&Y) [h]			X	X	X		X	X		X	X	X		X	X		X
MRI		X[i]															
DaT-SPECT		X[j]											X[k]			X	
CSF sampling[l]		X											X			X	
12-lead ECG [m]	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
Cystatin C	X		X	X	X	X	X	X		X	X	X	X	X	X	X	X

	Screening		Treatment														SFU
	V1	V2[a]	V3	V4[b]	V5	V6	V7[b]	V8	V8a[w]	V9	V10	V11	V12	V13	V14	V15	V16[b]
			BL		M1	M2	M3	M4	M5	M6	M8	M10	M12	M14	M16	M18 EOT	M19
Day	-42 to -23	-21 to -14	0	10 +/-1	30 +/-1	60 +/-3	90 +/-3	120 +/-5	150 +/-5	180 +/-5	240 +/-5	300 +/-5	360 +/-5	420 +/-5	480 +/-5	540 +/-5	570 +/-5
Urinalysis	X		X	X	X	X	X	X		X	X	X	X	X	X	X	X
Blood sampling for serology (HIV, hepatitis B&C)	X																
Blood sampling for PK[n]			X	X	X	X		X			X		X		X	X	
Blood sampling for genetic biomarkers (DNA)[o]		X															
Blood sampling for genomic biomarkers (RNA)[o]		X											X			X	
Blood sampling for other biomarkers[o]		X											X			X	
Serum pregnancy test[p]	X																
Urine pregnancy test[p]		X	X[q]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
FSH + estradiol	X																
HbA1c	X																
IgE	X																

	Screening		Treatment														SFU
	V1	V2[a]	V3	V4[b]	V5	V6	V7[b]	V8	V8a[w]	V9	V10	V11	V12	V13	V14	V15	V16[b]
			BL		M1	M2	M3	M4	M5	M6	M8	M10	M12	M14	M16	M18 EOT	M19
Day	-42 to -23	-21 to -14	0	10 +/-1	30 +/-1	60 +/-3	90 +/-3	120 +/-5	150 +/-5	180 +/-5	240 +/-5	300 +/-5	360 +/-5	420 +/-5	480 +/-5	540 +/-5	570 +/-5
Urine drug and alcohol screen	X																
Optional participant experience survey			X													X	
Issuance of and instruction on use of wearable sensor and Wearable Sensor Hub, including Virtual Motor Exam training[r]		X															
At-home Virtual Motor Exam on wearable sensor[s]			X (daily for 2 to 3 weeks, then weekly)														
Clinical tagging of Virtual Motor Exam on Study Watch [t]			X			X		X		X	X	X	X	X	X	X	
Return of wearable sensor and wearable sensor hub [r]																X	

	Screening		Treatment														SFU
	V1	V2[a]	V3	V4[b]	V5	V6	V7[b]	V8	V8a[w]	V9	V10	V11	V12	V13	V14	V15	V16[b]
			BL		M1	M2	M3	M4	M5	M6	M8	M10	M12	M14	M16	M18 EOT	M19
Day	-42 to -23	-21 to -14	0	10 +/-1	30 +/-1	60 +/-3	90 +/-3	120 +/-5	150 +/-5	180 +/-5	240 +/-5	300 +/-5	360 +/-5	420 +/-5	480 +/-5	540 +/-5	570 +/-5
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	X
MDS-UPDRS Part III (facilitated by Investigator on the wearable sensor UPDRS firmware)			X			X		X		X	X	X	X	X	X	X	X
MDS-UPDRS Part IV			X										X			X	
Randomization[u]			X														
Contact IRT[r]	X		X		X	X		X			X		X	X		X	
Handing out and/or return of study medication			X[v]		X	X		X			X		X	X		X	
Suicidality questionnaire (C-SSRS)	X		X	X	X	X	X	X		X	X	X	X	X	X	X	X
MoCA	X															X	
SE-ADL			X			X		X		X	X	X	X		X	X	

	Screening		Treatment														SFU
	V1	V2[a]	V3	V4[b]	V5	V6	V7[b]	V8	V8a[w]	V9	V10	V11	V12	V13	V14	V15	V16[b]
			BL		M1	M2	M3	M4	M5	M6	M8	M10	M12	M14	M16	M18 EOT	M19
Day	-42 to -23	-21 to -14	0	10 +/-1	30 +/-1	60 +/-3	90 +/-3	120 +/-5	150 +/-5	180 +/-5	240 +/-5	300 +/-5	360 +/-5	420 +/-5	480 +/-5	540 +/-5	570 +/-5
HADS			X										X			X	
Fatigue PRO			X	X						X			X			X	
Early PD Function Slowness PRO			X	X						X			X			X	
Early PD Mobility PRO			X	X						X			X			X	
Starkstein Apathy Scale			X										X			X	
MDS-NMS			X										X			X	
EQ-5D-5L			X							X			X			X	
PGIC (overall & fatigue-specific)				X						X			X			X	
PGIS (overall & fatigue-specific)			X	X						X			X			X	
CGIS			X	X						X			X			X	
CGII				X						X			X			X	

	Screening		Treatment														SFU
	V1	V2[a]	V3	V4[b]	V5	V6	V7[b]	V8	V8a[w]	V9	V10	V11	V12	V13	V14	V15	V16[b]
			BL		M1	M2	M3	M4	M5	M6	M8	M10	M12	M14	M16	M18 EOT	M19
Day	-42 to -23	-21 to -14	0	10 +/-1	30 +/-1	60 +/-3	90 +/-3	120 +/-5	150 +/-5	180 +/-5	240 +/-5	300 +/-5	360 +/-5	420 +/-5	480 +/-5	540 +/-5	570 +/-5

BL=Baseline; BP=blood pressure; C-SSRS=Columbia Suicide Severity Rating Scale; CGII=Clinical Global Impression of Improvement; CGIS=Clinical Global Impression of Severity; COVID-19=coronavirus disease-2019; CSF=cerebrospinal fluid; D=Day; DaT-SPECT=Dopamine Transporter Imaging With Single Photon Emission Computed Tomography; DNA=deoxyribonucleic acid; ECG=electrocardiogram; EDC=electronic data capture; EQ-5D-5L=Euro Quality of life 5-Dimensions 5-Level; EOT=End of Treatment; FSH=follicle stimulating hormone; H&Y=Hoehn and Yahr; HADS=Hospital Anxiety and Depression Scale; HbA1c=hemoglobin A1c; HIV=human immunodeficiency virus; ICF=Informed Consent form; IgE=Immunoglobulin E; IRT=interactive response technology; M=Month; MDS-NMS=Movement Disorder Society Non-motor Scale; MDS-UPDRS=Movement Disorder Society-Unified Parkinson's Disease Rating Scale; MoCA=Montreal Cognitive Assessment; MRI=magnetic resonance imaging; PD=Parkinson's Disease; PGIC=Patient Global Impression of Change; PGIS=Patient Global Impression of Severity; PK=pharmacokinetic(s); PRO=patient-reported outcomes; RNA=ribonucleic acid; SE-ADL=Schwab and England Activities of Daily Living; SFU=Safety Follow-up; ST=symptomatic treatment; V=Visit; VME=Virtual Motor Exam

Telemedicine video call with attending research nurse at the participant's home

Clinic visit

[a] Visit 2 should be conducted only when Visit 1 assessment results are available. Visit 2 assessments can be conducted on 2 consecutive or nonconsecutive days.

[b] Visits are in-clinic only in France. Therefore, details on telemedicine visits are not implemented (for **France**-specific requirements, please refer to Section 10.9, Appendix 9).

[c] All study participants prematurely terminating from the study should be encouraged to undergo final evaluation procedures in accordance with the EOT 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 supine and erect 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 reaction (such as rash, angioedema, or anaphylaxis), hepatic and/or renal dysfunction, signs and symptoms of COVID-19, and adverse events pertaining to the wearable sensor.

[f] Please refer to Section 8.2.1 for a description of the brief physical examination performed at the clinic vs at home.

[g] Prior to lumbar puncture, a neurological examination should be conducted in accordance with local safety procedures and results should be available prior to the lumbar puncture.

[h] Please refer to Section 8.2.2 for a description of the brief neurological examination performed at the clinic vs at home.

[i] Only for participants without an adequate historical MRI scan within the previous 6 months before Screening Visit 1.

[j] Only for participants without an adequate historical DaT-SPECT scan within the previous 3 months before Screening Visit 1, as determined by the central reader.

[k] In case of early termination of study medication, the DaT-SPECT will occur at EOT (End of Treatment), provided that the previous DaT-SPECT occurred more than 6 months prior to the EOT. There will be no DaT-SPECT assessment at M12 in Germany (for German-specific requirements, please refer to Section10.9, Appendix 9).

[l] Participants have the opportunity to opt out of CSF sampling; however, the aim is to collect samples from at least 50 participants/arm. For those participants undergoing CSF sampling at Visit 2, sampling at M12 is mandatory, while sampling at EOT is optional. The CSF sampling should all occur at the same time of the day and should be timed with blood sampling. These samples should be collected only after all other assessments of the visit have been performed.

[m] All ECG recordings will be performed in triplicate with no more than 2 minutes separating recordings, and the study participant should be resting in the supine position for at least 10 minutes before recording.

[n] The visits at Days 0, 10, 30, 60, 120, 240, 360, 480, and 540 require blood sampling for the purpose of UCB0599 concentration determination. In case the visit is scheduled for up to 11:00 in the morning, study participants will be asked to take their study medication during the site visit after the first blood sample is collected, measuring trough drug concentration. Importantly, 2 blood samples must be collected: one immediately prior to study medication intake (maximum of 15 minutes) and 1 sample between 1 to 6 hours after study medication intake. Clinical staff is encouraged to take the blood samples for PK analysis at the scheduled time window; however, deviations from the scheduled sample times are not considered protocol deviations. The exact time and date of the blood draw as well as study medication intake must be recorded using an unambiguous format such as DD MON YYYY and HH:MM using a 24-hour clock. Ideally, sampling should be conducted on the same day of each week at approximately the same time after study medication.

[o] In case the visit is scheduled before 11:00am, study participants will be asked to take their study medication during the site visit after the blood sample is collected. Blood samples will be drawn at the same time of the sampling for clinical laboratory tests. The time and date of collection will be recorded in the eCRF.

[p] Pregnancy test only for women of child-bearing potential (for **France**-specific requirements, please refer to, Section 10.9 Appendix 9).

[q] The Visit 3 pregnancy test must be performed before the study participant receives study medication.

[r] Monitored by Sponsor/clinical site but not captured in the EDC.

[s] Participants consenting to its use will receive the wearable sensor for 2 to 3 weeks for familiarization at home to address potential technical issues and to collect stable Baseline data. The frequency of the Virtual Motor Exam will be changed thereafter to weekly on the wearable sensor by the Investigator at the next visit. Please refer to Section 8.1.3 for further guidance on the wearable sensor. These data will be entered into the EDC system.

[t] To be performed after MDS-UPDRS Part III (applicable only to the participants wearing the sensor).

[u] Randomization should only occur after all results from Visit 1 and Visit 2 are available and assessed.

[v] First day of UCB0599 administration will be the evening of the BL Visit (Day 0); last administration will be in the morning of the EOT Visit (Day 540).

[w] Visit 8a will be conducted as an unscheduled visit.

2 INTRODUCTION

2.1 Study Rationale

UCB0599 is an orally available inhibitor of 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 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 UCB0599 may slow disease progression in PD, which remains the main unmet medical need in this condition. A FIH study using UCB0599, UP0030, was conducted in healthy elderly participants. UP0030 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 in healthy elderly participants (defined as ≥55 to ≤75 years of age). 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. UP0077 also provided information for the design of the current POC study in study participants with early-stage PD. PD0053 is designed to provide proof of concept for the efficacy of the synuclein misfolding inhibitor UCB0599 in reducing disease progression in study participants with early PD and to instruct later stage development.

2.2 Background

Parkinson's disease is a progressive neurodegenerative disorder that presents with a spectrum of motor and non-motor signs and symptoms. The mean age at onset is 60 years. The incidence of PD is approximately 20/100,000 persons per year, however, it is much higher in the population aged 65 years or older (>100/100,000 persons per year) (Twelves et al, 2003). Similarly, the prevalence of PD increases with age. It is estimated to be 1.4% in the population aged 55 years or older and 4.3% in the population aged 85 years and older (de Rijk et al, 1995).

The clinical diagnosis of PD relies on the presence of the cardinal motor signs: bradykinesia, rigidity, tremor, and postural instability. However, non-motor 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 symptomatic treatment (ST), or that show a good response to levodopa, which represents the standard of care. Other commonly used standard of care medications include dopamine agonists, monoamine oxidase B inhibitors, and catechol-O-methyl transferase inhibitors. As PD progresses, the motor and non-motor 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 non-motor 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). Although the majority of PD cases are sporadic, a small proportion are caused by mutations in PD-related genes, including copy number variations and point mutations of the ASYN-coding gene (*SNCA*) (Siddiqui et al, 2016). The gene copy number variations are of particular interest, as they indicate that an increased frequency of the wild-type ASYN is sufficient to cause PD. This is further reinforced by the observations in families with *SNCA* copy number variations where the pathogenic effect depends on the gene dosage (Devine et al, 2011). Furthermore, single nucleotide polymorphisms in *SNCA* that have been associated with PD in genome-wide association studies have been shown to increase ASYN expression, highlighting the relevance of genetic variation in *SNCA* in sporadic PD (Soldner et al, 2016; Nalls et al, 2014). The 140-amino acid ASYN protein is highly expressed in the brain but is also found in the cerebrospinal fluid (CSF) and periphery (ie, red blood cells and plasma). As an intrinsically disordered protein, ASYN exists in a soluble monomeric form in the cytoplasm and in the extracellular compartment. When it adopts a partially ordered, extended helical structure, ASYN also has a natural affinity for membranes, such as synaptic vesicles. Under certain conditions, ASYN can convert into oligomeric, beta-sheet rich structures where such aggregation is driven through the central region of the molecule, rich in hydrophobic residues (residues 61 to 95) known as the nonamyloid beta component region. These oligomeric structures are believed to be the toxic species responsible for the spread of pathology from neuron to neuron (Chen et al, 2015). 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.

UCB0599 is an orally available inhibitor of ASYN misfolding and downstream ASYN aggregation. Nonclinical pharmacology studies have provided evidence that UCB0599 inhibits ASYN misfolding in the presence of lipid membranes. In vivo pharmacology studies demonstrated that UCB0599 reduced total brain ASYN levels as well as proteinase K-resistant (ie, aggregated) ASYN in a transgenic mouse model overexpressing *SNCA*. Moreover, it reduced glial fibrillary acidic protein, a marker of neuroinflammation, and normalized dopamine transporter loss observed in this model, which are both considered a functional consequence of ASYN aggregation. These data suggest UCB0599 may slow neurodegeneration in PD, resulting in slower disease progression, thus providing a therapeutic benefit to patients with PD. To date, slowing PD disease progression remains the main unmet medical need in PD.

UCB0599 has not been approved by any health authorities worldwide as of the date of this document. UCB has conducted five Phase 1 clinical studies to support the development of UCB0599: 1 study, conducted with the UCB1332 racemate and a single microdose of the UCB0599 R-enantiomer (UP0023), and 4 studies with UCB0599 administration at clinically relevant doses (UP0030, TM0017, UP0077, and UP0078).

In the UCB0599 Phase 1 clinical development program, UP0023, UP0030, TM0017, and UP0077 demonstrated that UCB0599 has good PK properties (dose-exposure linearity, rapid absorption, $t_{½}$ of approximately 11 to 13 hours, and no time-dependent PK behavior observed) and an acceptable safety and tolerability profile for further clinical development. UP0078 demonstrated that food had a minimal effect on the PK profile for UCB0599. Coadministration of the strong cytochrome P450 3A4 (CYP3A4) inhibitor, itraconazole, had a significant effect on UCB0599 disposition, demonstrating a strong drug-drug interaction effect. Further information

regarding UP0023, UP0030, TM0017, UP0077, and UP0078 is provided in the Investigator's Brochure (IB). UP0030, UP0077, and UP0078 provide the primary UCB0599 clinical safety and clinical pharmacology data to date.

2.3 Benefit/Risk assessment

To date, there are no approved 'neuroprotective' and/or 'disease-modifying' treatments to stop or slow disease progression of PD, which remains a large unmet medical need.

UCB0599 acts at an early-stage of ASYN aggregation by inhibiting the initial nucleation event or seed formation by inhibiting misfolding; therefore, it may halt the progression of PD vs only treating the symptoms. The outcome of this study will support the development of a medication that may provide a potential benefit for patients with PD.

Drug hypersensitivity is an important identified risk. Other potential risks include: hepatotoxicity (based on clinical data) and cardiac effects. Renal laboratory abnormalities are also kept under close safety monitoring.

In Phase 1 development of UCB0599, 5 studies (UP0030, TM0017, UP0023, UP0077, and UP0078) demonstrated that UCB0599 has acceptable safety, PK, and tolerability profiles for further clinical development. Overall, the majority of treatment-emergent adverse events (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 UCB0599 in UP0077. A causal relationship between the reported events of drug hypersensitivity and UCB0599 is considered plausible. The hypersensitivity reactions are further described in the IB.

There have been no reports of anaphylaxis in the UCB0599 clinical program.

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 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 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, 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.

2.3.1 Coronavirus Disease-2019 benefit/risk assessment

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 UCB0599 administration. No such risks have been identified through regular review of published literature. PD0053 will include study participants with early-stage PD from 40 up to and including 75 years of age (the mean age of onset of PD is 60 years of age). A similar population was exposed to UCB0599 in the Phase 1 clinical program.

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 UCB0599 will have any substantial effect to worsen a Coronavirus Disease-2019 (COVID-19) disease 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 UCB0599 may enhance the infection risk or the disease manifestation.

Therefore, 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 other risk mitigation, the risk from COVID-19 vaccination to study participants in PD0053 is not expected to be significantly different from the general population of individuals with PD. The benefit-risk profile of UCB0599 in PD0053 in the context of COVID-19 vaccination remains positive.

Consequently, there are no restrictions on COVID-19 vaccination during PD0053 (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.
- This study will commence enrollment only when the Sponsor and contract research organization (CRO) both deem it is safe to do so. UCB is conducting ongoing assessments to approve which countries are suitable to conduct studies based on pandemic infection rates, country-level governmental status, Health Authority requirements, patient safety, study medication supply, CRO and site staff availability, local site level restrictions or guidance, and laboratory services. Individual sites in approved countries will be activated based upon a site-level review conducted by the study team. This review will confirm that these sites can conduct the study as per protocol and allow on-site monitoring or make remote monitoring feasible.
- 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).
- To reduce the risk of exposure during the study, consideration will be given to replace more site visits with telemedicine and home visits when feasible (eg, when only blood tests, physical examinations, and the collection of adverse events (AEs) are planned).
- 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 UCB0599, the inclusion and exclusion criteria, and the measures to mitigate risks described in this protocol, the risk to study participants in PD0053, 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 Wearable sensor regulatory classification

In the EU and Canada, the wearable sensor is an investigational product exclusively for research use in this clinical trial. It is manufactured by Verily Life Science LLC, and is not intended to be used to make any diagnosis or treatment decisions or for any individual benefit of the participant during the course of the PD0053 study.

In the US, the wearable sensor is considered to be exempt from Investigational Device Exemption regulations as the data from the wearable sensor is not shared with the study participant or study investigator. Further, this classification assumes that the data generated by the wearable sensor is used for exploratory/research hypothesis generating purposes only and not used during patient clinical management. Moreover, the wearable sensor does not pose significant health risks to study participants (please refer to Section 2.3.3.2 for further details).

2.3.3 Wearable sensor benefit/risk assessment

2.3.3.1 Potential benefits

The wearable sensor may make an evaluation of digital measurements for aspects of motor function, sleep, and neurovegetative parameters in real life possible, without requiring study participants to visit a clinical site. The wearable sensor in PD0053 is a noninvasive watch that will not guide diagnosis or therapy.

2.3.3.2 Potential risks of the wearable sensor

Sensor electrodes on the wearable sensor are made with stainless steel to minimize potential skin reaction. Some parts of the sensor have a small amount of nickel which could irritate the skin due to nickel or metal jewelry allergy. Participants with known severe allergies to nickel or metal jewelry should not wear the wearable sensor.

The electronic case report form (eCRF) requires the Investigator to indicate whether there is a likely causal relationship between the wearable sensor and an AE.

The types of risks the study participants will encounter from wearing the wearable sensor are similar to those of wearing commercially available smart watches. These may include:

- Pruritus
- Dry skin
- Mild redness
- Mild rash
- Swelling at the site of the sensor

These risks are considered anticipated sensor-related AEs that will also be collected as part of the PD0053 clinical study.

The wearable sensor may generate electromagnetic interference because of static magnetic fields, radio frequency emissions, and applied voltages, and the sensor's charging dock contains small magnets that could potentially affect implantable medical electronic devices such as cardiac pacemakers, implantable defibrillators, and medical pumps. The wearable sensor (while not worn on the wrist), the charging dock, and the wearable sensor hub should be kept at least 6 inches from any implantable device. Study participants with any implantable medical device are excluded from wearing the wearable sensor. This information is also relevant for people living in the same place as the study participant. People living in the same place should follow the wearable sensors instructions for use and should contact their healthcare provider if they have concerns regarding their implanted device during the study.

The wearable sensor display is made of glass and may break under significant impact or falls.

If participants experience discomfort, they should be instructed to stop wearing the wearable sensor and contact the study team. Any skin irritation should be allowed to clear up before returning the sensor (at the discretion of the Investigator) to the same wrist.

Participants should be instructed to clean the wearable sensor bands often to remove any perspiration that may build up on the bands. Minimizing moisture on the bands may reduce the potential for skin complications such as irritation or rash.

The wearable sensor is not waterproof. Participants should not soak or submerge the wearable sensor to avoid dysfunction.

2.3.3.2.1 Potential Wearable Sensor Hub risks

The Wearable Sensor Hub is a connectivity bridge that allows compatible wearable sensor devices to upload user data to the Sensor Suite. The Wearable Sensor Hub does not control or alter the functions or parameters of the connected wearable sensor. The participant risks arising from potential breaches in data privacy and cybersecurity during data transfer from the wearable sensor to the Wearable Sensor Hub and then to the Verily Cloud Server have been mitigated through a Privacy Impact Analysis and Web Application Security (Penetration) testing.

The Wearable Sensor Hub has been tested and found to comply with the limits for a Class B digital sensor, pursuant to Part 15 of the Federal Communications Commission Rules. For people

with a cardiac pacemaker, implantable defibrillator, medical pump, or other implantable medical electronic device who live in the same place as a study participant, it is important to be aware that the Wearable Sensor Hub may use wireless signals like Bluetooth, Wi-Fi, and cellular connections that could potentially affect their implantable medical electronic device. Participants with any implantable medical device are excluded from using the wearable sensor.

The Wearable Sensor Hub is not waterproof. To avoid dysfunction, participants should not soak or submerge the Wearable Sensor Hub.

The Wearable Sensor Hub may overheat at high temperatures. Participants should keep the Wearable Sensor Hub out of direct heat and in a well-ventilated environment.

2.3.3.3 Wearable sensor benefit/risk conclusion

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 wearable sensor in PD0053 is considered positive. Considering the risk mitigation measures in place, the wearable sensor does not pose significant risks to study participants. Risks are similar to those of commercially available smart watches. The overall residual risk is acceptable for the sensor's intended use in investigational clinical studies.

2.3.4 Overall benefit/risk conclusion

The Sponsor will immediately notify the Investigator and Regulatory Agencies if any important clinically relevant information becomes available during the study.

Given the current evidence, based on the scientific rationale, nonclinical data, and limited human data, the important unmet medical need in patients with PD, and the appropriate risk communication, monitoring, and minimization measures to be implemented, the Sponsor considers the benefit-risk profile for UCB0599 to be acceptable for further clinical development.

More detailed information about the known and expected benefits and risks and expected adverse events of UCB0599 may be found in the IB and ICF.

3 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary Efficacy Objective	
To demonstrate the superiority of UCB0599 over placebo with regard to clinical symptoms of disease progression over 12 and 18 months in participants diagnosed with early-stage PD	**Primary Efficacy Endpoint** • MDS-UPDRS Parts I-III sum score (timeframe: Baseline to 18 months) **Secondary Efficacy Endpoints** • MDS-UPDRS Part III subscale (timeframe: Baseline to 18 months) • MDS-UPDRS Part III ePD subscore on selected items (timeframe: Baseline to 18 months)

Objectives	Endpoints
	• MDS-UPDRS Part II subscale (timeframe: Baseline to 18 months) • MDS-UPDRS Part I subscale (timeframe: Baseline to 18 months) • Emerging symptoms as measured by MDS-UPDRS Part II (timeframe: Baseline to 18 months) • Time to worsening of the disease as measured by MDS-UPDRS Part III (timeframe: Baseline to 18 months) • MoCA (timeframe: Baseline to 18 months) **Exploratory Efficacy Endpoints** • Time to worsening in MDS-UPDRS Part I subscale • Modified Hoehn and Yahr staging • CGII • CGIS • Fatigue-PRO • Early PD Function Slowness PRO • Early PD Mobility PRO • Composite endpoint (based on MDS-UPDRS and/or Early PD PROs) • PGIS, overall and fatigue-specific • PGIC, overall and fatigue-specific • SE-ADL • HADS • MDS-NMS • Starkstein Apathy Scale • EQ-5D-5L • Wearable sensor

Objectives	Endpoints
Secondary Efficacy Objectives	
To demonstrate the superiority of UCB0599 over placebo with regard to neurodegeneration of dopaminergic neurons over 12 and 18 months in participants diagnosed with early-stage PD	**Secondary Efficacy Endpoints** • Change from Baseline (Screening) in DaT-SPECT mean Striatum SBR (timeframe: Screening to 18 months) **Exploratory Efficacy Endpoints** • DaT-SPECT mean SBR in striatal subregions • CSF total ASYN • CSF ASYN oligomers/seeding capacity
To assess the effect of UCB0599 vs placebo with regard to intake of ST over 18 months in participants diagnosed with early-stage PD	**Secondary Efficacy Endpoints** • Time to start of ST (timeframe: Baseline to 18 months) • ST intake (timeframe: Baseline to 18 months) **Exploratory Efficacy Endpoints** • Levodopa cumulative daily dose
Primary Safety Objective	
To assess the safety and tolerability of UCB0599 in participants diagnosed with early-stage PD	**Secondary Safety Endpoints** • Incidence of TEAEs • Incidence of SAEs • Incidence of TEAEs leading to participant withdrawal **Other Safety Endpoints** • Change from Baseline in clinical laboratory values (chemistry, hematology, and urinalysis) • Change from Baseline in vital signs • Change from Baseline in physical examination • Change from Baseline in neurological examination findings • C-SSRS findings • ECG findings
Exploratory PK Objective	
To assess the PK of UCB0599 and its N-oxide metabolite in participants diagnosed with early-stage PD	**Exploratory PK Endpoint** • UCB0599 and N-oxide metabolite plasma and CSF concentrations

ASYN=alpha-synuclein; CGII=Clinical Global Impression of Improvement; CGIS=Clinical Global Impression of Severity; C-SSRS=Columbia-Suicide Severity Rating Scale; CSF=cerebrospinal fluid; DaT-SPECT=Dopamine Transporter Imaging with Single Photon Emission Computerized Tomography; ECG=electrocardiogram; ePD=early-stage PD; EQ-5D-5L=EuroQol-5-dimension-5-level; HADS=Hospital Anxiety and Depression Scale; MDS-NMS=Movement Disorder Society Non-motor Scale; MDS-UPDRS=Movement Disorder Society-Unified Parkinson's Disease Rating Scale; MoCA=Montreal Cognitive Assessment; PD=Parkinson's disease; PGIC=Patient Global Impression of Change; PGIS=Patient Global Impression of Severity; PK=pharmacokinetic; PRO=Patient-Reported Outcome; SAE=serious adverse event; SBR=specific binding ratio; SE-ADL=Schwab and England Activities of Daily Living; ST=symptomatic treatment; TEAE=treatment-emergent adverse event

4 STUDY DESIGN

4.1 Overall design

PD0053 is a randomized, double-blind, placebo-controlled, 18-month Phase 2a study to evaluate the efficacy, safety, tolerability, and PK of orally administered UCB0599 in study participants with early PD who are not treated with symptomatic medications targeting motor symptoms of PD at the time of inclusion. Oral UCB0599 capsules or matching placebo capsules will be administered BID, approximately 12 hours apart. The primary objective of the study is to demonstrate the superiority of UCB0599 over placebo with regard to clinical symptoms of disease progression over 12 and 18 months in this patient population. The difference between UCB0599 and placebo will be evaluated for both the low and high doses of UCB0599 (180mg/day and 360mg/day). The comparison of the high dose of UCB0599 with placebo will be considered as the primary evaluation. If the comparison of the low dose and placebo gives a positive result on the primary estimand but the comparison of the high dose and placebo does not, these results will have to be interpreted with caution. In all analyses, the 2 dose levels will be assessed separately against placebo, there will be no pooling of the 2 dose levels, and they will not be compared to each other.

PD0053 includes a Screening Period of 3 to 6 weeks (including where available, a wearable sensor familiarization period for those participants who consent to its use), an 18-month Treatment Period (including, where available, a wearable sensor familiarization period for those participants who consent to its use after the Screening Period), and an SFU Period of 1 month. Study participants who complete the Treatment Period will have the option to transition into a dose-blinded extension study (PD0055). In this case, participants will not enter the SFU Period of PD0053.

The outcomes of this study will inform the design and dose selection for confirmatory studies, and help to further validate novel endpoints and technologies and support strategic development program decisions.

4.1.1 Decentralized model

The study will be conducted utilizing a partly decentralized model, ie, study visits may be composed of a combination of onsite visits and remote visits (except in France; for **France**-specific requirements, please refer to Section 10.9 Appendix 9). During remote visits, study assessments will be conducted with the study participant from his/her home. This is offered in order to reduce study participant burden and encourage greater study participation.

In a decentralized model, video communication technology will be integrated into the clinical research process to support management of research activities, including data collection, and

providing study participants with a channel for direct feedback. Qualified and trained mobile healthcare personnel (ie, a qualified research nurse) may visit the study participant's/caregiver's home to complete certain study assessments (refer to the Schedule of Activities in Section 1.3). Some of the assessments performed during the remote visits may be conducted without direct observation by the Investigator; these are standard examinations and sampling for analysis that will be performed by the research nurse. The other assessments that are important for the evaluation of efficacy endpoints in the study require direct observation and instruction by the Investigator through the use of telemedicine technology. Please refer to Section 8 for specifications of all assessments planned in the study. The research nurse and Investigator will discuss all observations and findings during the remote visits. In case an observation (eg, an AE) requires follow up at the clinic, an unscheduled visit should be performed. Also, in case a research nurse is not available to perform a scheduled remote visit, eg, due to COVID-19 related contact and transportation restriction or other circumstances, a remote visit may be changed to a clinic visit. In addition, clinic visits can be changed to remote visits for reasons noted in Section 4.1.2.

Video and communication technology will be provided for interactions among the Investigator, mobile healthcare personnel (research nurse), and study participants/caregivers for remote visits. The technology will allow for direct communication of the participant with the site staff.

Where feasible, all data will be collected electronically using purpose-built technology and will be monitored remotely by clinical research associates while complying with all data privacy standards. Original paper source, eg, electrocardiogram (ECG) readings, will be provided to the clinical site for the source document filing shortly after completion of the remote visit.

4.1.2 Study conduct due to COVID-19

The protocol-mandated visit schedule (Section 1.3) should be followed to the extent possible, considering the individual benefit-risk assessment by the Investigator. Where adherence to the protocol schedule of assessments is not possible, the Sponsor should be made aware of the details. If necessary, and after discussion with the Sponsor, clinic visits may be turned into remote visits and/or the study participants or caregivers will be contacted by telephone or videoconference. Ad hoc study participant contact may be warranted to understand the current health status of the study participants, to follow up on AEs, and inform them of any protective measures taken by the clinical site as a result of the COVID-19 pandemic (eg, any measures that may limit access to the site or may require additional actions by the study participant prior to entry to the site).

Investigators and study coordinators may use discretion when determining the need to perform a home visit (safety laboratory parameters, PK samples), but will need to inform the Sponsor.

If a participant needs to be discontinued and cannot come into the clinic, then appropriate instructions will be provided, and a visit will be scheduled to perform safety assessments as soon as possible.

In situations where a study participant is unable to return to the study site, Investigators will assess and document the study participant's safety via telephone contact and/or videoconference. Based on information gathered from the telephone contact, Investigators will confirm whether the participant could continue the current study medication based upon the outcome of the safety assessment. Study participants' agreement to implement this procedure should be obtained and

documented prior to implementing any changes. Changes in the study medication supply in this situation are described in Section 6.2.

If a study participant visits another facility for a medical issue (or has to switch sites for a COVID-19-related reason), the Investigator should request contact with the physician providing care to provide a detailed explanation of the study participant's condition and his/her participation in the clinical study. Study participants or caregivers shall be reminded to collect and keep complete records of this visit.

If laboratory assessments cannot be conducted via the central laboratory vendor due to restricted site access and home visits by study health care providers are not an option, local laboratory safety assessments may need to be conducted in a format that allows the Investigator to receive/review these results and include them as source documentation.

Deviations to data collection including inability to perform any assessments, such as ECG, blood collection for safety laboratory assessments and PK, or alternative methods of assessment, such as phone calls, should be recorded in the source documentation and notated as "not done" in the eCRF.

4.2 Scientific rationale for study design

The main objective of PD0053 is to provide POC for the efficacy of the ASYN misfolding inhibitor UCB0599 in reducing disease progression in study participants with early-stage PD, and to instruct later stage development. The ultimate goal is to provide novel treatment options to PD patients which have the potential to modify the progression of the disease.

Two types of data supporting an intervention as a Disease Modification Therapy have been identified (Cummings, 2017):

1. The intervention produces a significant drug-placebo difference on accepted clinical outcome(s), AND has a consistent effect on (fluid or imaging) biomarkers considered reflective of the fundamental pathophysiology of a neurodegenerative disease (NDD), ie, neurodegeneration.
2. The intervention produces a positive outcome on a randomized-start clinical study design consistent with an enduring (positive) change (ie, treatment effect) in the clinical course of disease.

In both cases, slowing of disease progression on clinical measures is evident; in the former, biological evidence of disease modification (DM) supports the clinical measures.

To this aim, the proposed study, PD0053, is a Phase 2a study with a double-blind parallel-group, placebo-controlled design and a treatment duration of 18 months.

Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Parts I-III sum score, the primary clinical outcome, is the best-established functional scale to evaluate disease progression in PD populations and to assess the effect of STs. In the case of drugs with the potential of slowing disease progression in this population, MDS-UPDRS would have considerable limitations if applied as a solitary and standalone endpoint. As it is currently the best characterized and most widely used scale, MDS-UPDRS will have a prominent role in this study to assess the effect of UCB0599 in delaying the progression of clinical symptoms; however, it is understood that it almost exclusively captures neuromotor dysfunction and thus in

isolation would not have the bandwidth to provide a holistic picture of disease progression. To address this limitation and to ensure a more holistic view, the suggested POC study incorporates multiple measures and scales capturing non-motor domains (including cognition and neurovegetative function).

Evaluation of how study participants feel and function through the use of patient-reported outcome (PRO) measures has become an increasingly important component of therapeutic assessment. In an effort to best measure the patient perception of motor and non-motor signs and their impact in early-stage PD, UCB, together with the patient organizations Parkinson's UK and Parkinson Foundation USA, has collaborated on large patient-centered research to define an optimized PRO strategy for the context of use of early-stage PD. Research findings across over 50 patients and 10 caregivers highlighted that bradykinesia (particularly function slowness), tremor, rigidity/stiffness, mobility (particularly gait and upper limb issues), and fatigue are the cardinal concepts of interest in early-stage PD. Research outcomes also suggested that the legacy PROs traditionally used in clinical research may not be fit for purpose in early-stage PD, as most of them were developed for use in later stages of disease. As a result, UCB developed with patients an exploratory set of novel PROs for early-stage PD, composed of: the Early Parkinson's Disease Function Slowness PRO, the Early Parkinson's Disease Mobility PRO, and Fatigue-PRO. UCB hypothesizes that this exploratory PRO strategy will generate interpretable PRO data for the demonstration of treatment benefit in early-stage PD patients and adequately complement MDS-UPDRS evidence. It is intended to test the new UCB PRO strategies in PD0053 as exploratory endpoints.

Rescue medication currently available for PD patients, namely levodopa and other dopamine agonists, will interfere with motor symptoms and therefore bias any MDS-UPDRS measures collected postinitiation of rescue medication. The intention with this study is to provide a measure of the effect of UCB0599 on the MDS-UPDRS clinical scale, free of confounding by rescue medication. However, for all scheduled visits, study participants that do start to receive ST over the study observation period 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. Please refer to Section 6.5.3 for further details.

To assess neurodegeneration, the biomarker Dopamine Transporter Imaging with Single Photon Emission Computed Tomography (DaT-SPECT) will be used, which 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 the ST (Ikeda et al. 2019). Therefore, DaT-SPECT will be used as an assessment in the study to identify the effect of UCB0599 treatment. Moreover, DaT-SPECT at Screening will allow identification of the relevant target population by identifying patients without evidence of dopaminergic deficit.

Identifying participants with early motor deficits in conjunction with confirming reduction of dopamine transporter levels has been shown to be a useful and EMA-qualified means of selecting participants who will have detectable progression rates over the course of clinical studies (EMA/CHMP/SAWP/765041/2017). In this study, DaT-SPECT will be used at Screening as a means to confirm dopamine transporter level reduction.

Previous studies that have attempted to demonstrate efficacy of nonsymptomatic treatments for PD in early-stage populations have failed to show DM. Among the reasons for failure,

insufficient treatment duration to detect delayed treatment effect and the high variability of disease progression have been identified. An 18-month duration was chosen because it is expected to be sufficient time for UCB0599 to reveal a disease modifying effect and to differentiate from ST.

In addition, the impact of UCB0599 on time-to-initiation and overall intake of rescue medication will be investigated. Since UCB0599 treatment is expected to slow disease progression and disease progression is directly linked to onset of ST, UCB0599 would be expected to delay the time until the study participants require initiating ST, which therefore can be utilized as an event.

The treatment duration of up to 18 months means that treatment effects of UCB0599 on the need for initiation of rescue medication will be able to be assessed in the majority of study participants.

As UCB0599 has potential to slow disease progression in the non-motor domain, which prominently encompasses cognitive functioning, there is a need to include instruments which may capture a signal in this area. The Montreal Cognitive Assessments ([MoCA]; Nasreddine et al, 2005) will be used to complete the main assessments, as it covers different cognitive domains (visuospatial/executive, naming, memory, attention, language, abstraction, delayed recall, and orientation). Practice effects have been observed on repeating MoCA assessments (Wong et al, 2018) and therefore parallel versions are available which can be utilized for longitudinal observations. Furthermore, the MoCA will play a role in Screening, to exclude participants with a pronounced cognitive impairment, which specifically in younger participants could be indicative of a neurodegenerative disorder other than PD.

For each efficacy objective, the precise treatment effect of interest is defined on the selected endpoints referred to as the estimands. As this is a Phase 2 study, we will focus on estimands which measure efficacy (as opposed to effectiveness).

4.3 Justification for dose

The rationale for testing the proposed clinical dose levels of UCB0599 180mg/day (90mg BID) and 360mg/day (180mg BID) in PD0053 is based on (1) the safety margin estimates comparing systemic exposures at the no observed adverse effect level (NOAEL) 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 (SNCA) in the CNS.

Potential food effect, as well as potential drug-drug interaction with itraconazole, a strong CYP3A4 inhibitor, were evaluated in UP0078 after UCB0599 single dose (180mg). Data from UP0078 confirmed that no food restriction is needed in PD0053. However, strong CYP3A4 inhibitors (and inducers) should not be co-administered with UCB0599 (see Section 6.5.2).

4.3.1 Safety-based dose levels

UCB0599 exposure data in the most sensitive nonclinical species (monkey) are presented in Table 4-1. The UCB0599 C_{max} and $AUC_{0\text{-}24h}$ following daily dosing of 60mg/kg/day for 39 weeks in male monkeys were 4090ng/mL and 28000h*ng/mL, respectively. These PK parameters were used to determine the human safety margins, comparing nonclinical exposures with human observed exposures.

Across the dose range tested, UCB0599 behaved approximately linearly when relating dose and exposure; therefore, the projected equivalent $AUC_{0\text{-}24h}$ at steady state at (180mg/day [90mg BID]) is 8072h*ng/mL (mean $AUC_{0\text{-}12h,ss}$ 4036h*ng/mL multiplied by 2; and at 360mg/day [180mg BID]) is 15908h*ng/mL (mean $AUC_{0\text{-}12h,ss}$ 7954h*ng/mL multiplied by 2) (Table 4-1).

Table 4-1: C_{max} and AUC and unbound ($C_{max[u]}$ and $AUC_{[u]}$) UCB0599 exposures calculated on measured plasma protein binding in monkey or human plasma samples

	C_{max} ng/mL	$C_{max(u)}$ ng/mL	$AUC_{0\text{-}24h}$ h*ng/mL	$AUC_{0\text{-}24h(u)}$ h*ng/mL
Male monkey (39-week) (at 60mg/kg/day)	4090	200.4	28,000	1372.0
Observed human exposures (90mg BID, 180mg/day)	730	6.6	8072	72.6
Observed human exposures (180mg BID, 360mg/day)	1330	12	15,908	143.2

BID=twice per day
Note: Mean $AUC_{0\text{-}24h}$, calculated as 2x the measured $AUC_{0\text{-}12h}$, in UP0077 (Investigator Brochure Table 4-7 and 4-8).
Note: Plasma unbound fraction in monkeys and humans are 4.9% and 0.9%, respectively (Study NCD2777).

Comparing these human observed C_{max} and AUC parameters with the nonclinical data (Table 4-1) indicates that mean expected drug exposures remain below the observed mean NOAEL levels obtained in the 39-week monkey study. To further provide reassurance on the safety exposures, Table 4-1 also provides calculated unbound PK parameters, ie, $C_{max(u)}$ and $AUC_{(u)}$, based on the concept of unbound drug being a pharmacologically active moiety. In monkey plasma, the mean bound percentage was 95.1±3.4% at 37°C. The protein binding in human plasma was 99.1±0.1% at 37°C (UCB study number NCD2777). Using the unbound fraction to convert to unbound (pharmacologically active) drug comparing the average exposure in human study participants vs the observed monkey exposure data, a safety margin of >15 is to be expected on the basis of this calculation.

4.3.2 Pharmacology-based dose levels

The projected exposures in humans at UCB0599 180mg/day (90mg BID) and 360mg/day (180mg BID) are predicted to correspond to efficacious CNS exposures in the transgenic mouse model overexpressing human wildtype ASYN gene (*SNCA*). Therefore, UCB0599 dose selection for UP0030 was projected to achieve systemic exposures in humans that were comparable to the efficacious exposures obtained in the pharmacological animal model (transgenic mice overexpressing *SNCA*), and, in particular, a range of exposures encompassed within those

expected after chronic administration at UCB0599 1mg/kg and UCB0599 5mg/kg. The AUC and C_{max} exposures (expressed as total and unbound) estimated after administration at UCB0599 1mg/kg were 308ng*h/mL (unbound: 6.5h*ng/mL) and 332ng/mL (unbound: 7.0ng/mL), respectively (Table 4-2). AUC and C_{max} exposures (total and unbound) estimated after administration at UCB0599 5mg/kg were 1648ng*h/mL (unbound: 34.6h*ng /mL) and 1317h*ng/mL (unbound: 27.7ng/mL), respectively.

Table 4-2: UCB0599 exposure at pharmacological dose

Dose (mg/kg/day)	Gender	AUC_{0-24} (h*ng/mL)	C_{max} (ng/mL)	Unbound AUC_{0-24} (h*ng/mL)	Unbound C_{max} (ng/mL)
1	Male	308	332	6.5	7.0
5	Male	1648	1317	34.6	27.7

At UCB0599 180 or 360mg/day in UP0077, the projected exposure (AUC_{0-24h}) in humans at these doses were 8072 and 15908h*ng/mL, respectively (unbound: 72.6 and 143.2h*ng/mL, respectively), and the C_{max} were 730 and 1330ng/mL, respectively (unbound: 6.6 and 12ng/mL, respectively), at steady state. This exposure covers the range of both C_{max} and AUC exposure in mice at the highest pharmacological dose of UCB0599 5mg/kg.

4.4 End of study definition

Participants are considered to have completed the study if they have completed all phases of the study, including the SFU Visit (30 days after the End of Treatment [EOT] Visit). Participants opting to enter PD0055 will not enter the SFU Period of PD0053, and are considered to have completed the study if they have completed all visits up to and including EOT.

The 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:

Age

1a. Study participant must be 40 to 75 years of age inclusive, at the time of signing the informed consent.

Type of participant and disease characteristics

2a. Study participant has PD, with a diagnosis made by a neurologist according to the 2015 Movement Disorder Society criteria within 2 years of Baseline Visit (including diagnosis during Screening).

3. The following diagnostic criteria must be met: bradykinesia AND at least ONE of the following: muscular rigidity, or resting tremor.

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

5a. Criterion removed.

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

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

   a. Levodopa
   b. Catechol-O-methyltransferase (COMT) inhibitors
   c. Dopamine agonists
   d. Monoamine oxidase-B (MAO-B) inhibitors
   e. Anticholinergic drugs
   f. Trihexyphenidyl
   g. Amantadine
   h. Safinamide

   Exceptions to the above would be the following:

   i. Acute pharmacological testing for diagnostic purposes is allowed until 1 week before first Screening Visit.
   ii. Historical treatment with symptomatic treatment (ST) for a duration of up to 1 month is allowed until 3 months before first Screening Visit (refer to details in exclusion criterion #26a).

8. Study participant has never taken part in disease-modifying treatment studies directed at NDD.

9. Study participant does not take N-acetyl cysteine or other cysteine donors or glutathione precursors on a regular basis as a food supplement.

10. Study participant is willing, competent, and able to comply with all aspects of the protocol, including follow-up schedule and biospecimen collection.

Weight

11. Study participant has a body mass index (BMI) of 16 to 34kg/m² (inclusive).

Sex

12. Contraception

- A male 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 study medication and refrain from donating sperm during this period.
- A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one 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 in Appendix 4 (Section 10.4) during the Treatment Period and for at least 1 month after the last dose of study medication. The study participant must have a negative serum pregnancy test at Screening (Visit 1), which is to be confirmed negative by urine testing prior to the first dose of study medication at Baseline (Visit 3). If oral contraception is used, an additional barrier method will be required during the study as a study medication related-gastrointestinal upset or a drug interaction by CYP3A4 induction could interfere with efficacy.

Informed consent

13. 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 current or past medical or psychiatric condition that, in the opinion of the Investigator, could jeopardize or would compromise the study participant's safety or ability to participate in this study.
2. Study participant has a current history of alcohol or drug use disorder, as defined in the Diagnostic and Statistical Manual of Mental Disorders V, within the previous year before Screening.
3. Study participant has a known hypersensitivity to any components (and/or its excipients) of the study medication or comparative drugs as stated in the protocol.

4a. Study participant has a known relevant allergy (not including mild seasonal hay-fever and/or conjunctivitis or low-grade food intolerances), a pre-existing history of a relevant and clinically significant allergic condition, or a predisposition for an allergic reaction (eg, total immunoglobulin E value above normal range according to the study's central laboratory reference range) at Screening in the opinion of the Investigator.

5. Study participant wearing any kind of implantable device, including cardiac pacemakers, pumps, and implantable cardioverters, will be excluded from wearing the wearable sensor, but may participate in the main study.

6. Study participant with a known nickel allergy severe enough to preclude 24 hours a day/7 days a week wearing of a sensor device with a nickel alloy-containing housing will be excluded from wearing the wearable sensor, but may participate in the main study.

7. Study participants with any condition or in any circumstances that in the opinion of the Investigator, makes the participant inappropriate for wearing of the wearable sensor. These study participants will be excluded from wearing the wearable sensor but may participate in the main study.

8. Study participant has a brain magnetic resonance imaging (MRI) scan performed during Screening indicative of a clinically significant abnormality or a historical MRI scan during the 6 months before Screening Visit 1 of sufficient quality to show such abnormalities. In case of doubt, the significance is determined on a case-by-case basis in close collaboration with the Medical Monitor and should not include abnormalities like age-appropriate brain atrophy, minor white matter signals, or mild vasculopathy.

9. Study participant has any contraindication for the brain MRI or DaT-SPECT imaging.

10. Study participant has ongoing significant inflammatory gastrointestinal disorders and/or clinical signs of significant gastrointestinal problems at Screening. Study participants with PD-associated gastrointestinal motility problems need not be excluded.

11. Study participant has a MoCA score less than 23, indicating mild cognitive impairment or other significant cognitive impairment or clinical dementia at Screening that, in the opinion of the Investigator, would interfere with study evaluation.

12. Study participant has a lifetime history of suicide attempt (including an actual attempt, interrupted attempt, or aborted attempt), or has suicidal ideation in the past 6 months as indicated by positive responses ("Yes") to either Question 4 or Question 5 of the Columbia-Suicide Severity Rating Scale (C-SSRS) at Screening.

13. Study participant has a diagnosis of a significant CNS disease other than PD or history of epilepsy or seizure disorder other than febrile seizures as a child.

14a. Study participant has abnormalities in lumbar spine previously known or determined by a Screening lumbar X-ray (if conducted) that could preclude lumbar puncture, in the opinion of the Investigator. The participant must be excluded from lumbar puncture but not from study participation.

15a. Study participant has a history of clinically significant back pain, back pathology, and/or back injury (for example, degenerative disease, spinal deformity, or spinal surgery) that in the opinion of the Investigator is sufficiently severe as to potentially predispose participant to complications or technical difficulty with lumbar puncture. The participant must be excluded from lumbar puncture but not from study participation.

16a. Evidence or history of significant active bleeding or coagulation disorder or use of drugs that affect coagulation or platelet function within 14 days prior to lumbar puncture. The participant must be excluded from lumbar puncture but not from study participation.

17a. Allergy to lidocaine (Xylocaine®) or its derivatives. The participant must be excluded from lumbar puncture but not from study participation.

18a. Medical or surgical conditions which in the opinion of the Investigator represent a contraindication for lumbar puncture. The participant must be excluded from lumbar puncture but not from study participation.

19. Total bilirubin >upper limit of normal (ULN) (≥1.5xULN total bilirubin if known Gilbert's syndrome). If study participant has elevations in total bilirubin that are >ULN and <1.5xULN, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%).

20. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).

    a. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) are >1.5xULN.

    b. For randomized study participants with a Baseline result >ULN for ALT, AST, ALP, or total bilirubin, a Baseline diagnosis and/or the cause of any clinically meaningful elevation must be understood and recorded in the eCRF.

    c. If the study participant has >ULN ALT, AST, or ALP that does not meet the exclusion limit at Screening, repeat the tests, if possible, prior to dosing to ensure there is no further ongoing clinically relevant increase. In case of a clinically relevant increase, inclusion of the study participant must be discussed with the Medical Monitor.

    d. Tests that result in ALT, AST, or ALP up to 25% above the exclusion limit may be repeated for confirmation. This includes reScreening.

21. Study participant has a history or present condition of respiratory or cardiovascular disorders at Screening (eg, cardiac insufficiency, coronary heart disease, uncontrolled hypertension, arrhythmia, tachyarrhythmia, or myocardial infarction) which is considered clinically significant by the Investigator.

22a. Study participant has medical history or current diagnosis of Type 1 diabetes or uncontrolled Type 2 diabetes. Well controlled type 2 diabetes in line with local clinical practice is acceptable.

23a. Study participant has clinically significant ECG abnormality at Screening, in the opinion of the Investigator. In addition, any study participant with any of the following findings will be excluded:

    a. QT corrected for heart rate using Fridericia's formula (QTcF) interval >450ms (in males) or ≥470ms (in females) in 2 of 3 ECGs.

    b. Bundle branch blocks (complete bundle branch block with QRS>120ms), marked right or left axis deviation or second and third degree atrioventricular block are excluded. Mild first degree atrioventricular block (defined as PR interval ≤230ms) is acceptable. Mild axis deviation, incomplete right bundle branch block (QRS≤120ms), or left anterior hemiblock is acceptable if no underlying disease is suspected by the Investigator.

c. Irregular rhythms other than sinus arrhythmia or occasional, rare supraventricular or rare ventricular ectopic beats.

d. In the judgment of the Investigator, T-wave configurations that are not of sufficient quality for assessing QT interval duration.

24. Study participant has a history of recurrent unexplained syncopes or a family history of sudden death due to long QT syndrome.

25a. Study participant has had significant blood loss or has donated or received 1 or more units (450mL) of blood within 30 days prior to Baseline Visit, or has donated plasma or platelets within 14 days prior to Baseline Visit.

Prior/Concomitant therapy

26a. Study participant has past history of use of medications for the treatment of motor symptoms of PD. Short (up to 4 weeks) past use of medications for the treatment of motor symptoms is permitted following a sufficient washout period. Medications included are: levodopa (maximum 400mg per day), dopamine agonists, MAO-B inhibitors, anticholinergics, or amantadine. A sufficient washout period is at least 3 months prior to the Baseline Visit.

27. Study participant received an investigational medicinal product (IMP), or has participated in another study of an IMP within a period of 90 days (or 5 half-lives of the drug, whichever is longer) before Baseline.

28. Study participant has had prior treatment with an investigational medical device, or participated in a study of an investigational medical device within a period of 90 days before Baseline.

29. Study participant has had prior treatment with an investigational vaccine, gene therapy, or stem cell therapy for PD (including active immunization or passive immunotherapy with monoclonal antibodies).

30a. Criterion removed.

31b. (1) Study participant has prior use of any of the following (drugs that may affect DaT-SPECT scan) within 50 days prior to Baseline: metoclopramide, alpha methyldopa, olanzapine, flunarizine, amoxapine, reserpine, bupropion, buspirone, cocaine, mazindol, methamphetamine, methylphenidate, norephedrine, phentermine, phenylpropanolamine, modafinil, clozapine.

(2) Study participant has prior use of any of the following (drugs with possible Parkinson's disease-modifying effects) within 5 days prior to Baseline: pioglitazone, ambroxol, nilotinib, inosine, deferiprone, liraglutide, lixisenatide, N-acetylcysteine, phenylbutyrate, transdermal nicotine, exenatide, and isradipine.

32. Study participant has had prior treatment of PD involving intracranial surgery or implantation of a device (including deep brain stimulation).

33. Study participant has received prohibited prescription or nonprescription medicines (Section 6.5.2) (including over-the-counter medicines and herbal and dietary supplements [including St John's Wort]) that have been taken within 14 days prior to Baseline.

Prior/Concurrent clinical study experience

34. Participant has previously participated in this study or participant has previously been assigned to treatment in a study of the medication under investigation in this study.

Diagnostic assessments

35a. Positive prestudy medication/alcohol/recreational drug screen, unless reasonably explained by concomitant use of a medication.

36. Positive human immunodeficiency virus antibody test.

37. Presence of hepatitis B surface antigen at Screening.

38. Positive hepatitis C antibody test result at Screening or within 3 months prior to starting study medication. NOTE: Participants with positive hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative hepatitis C ribonucleic acid (RNA) test is obtained.

39. Positive hepatitis C RNA test result at Screening or within 3 months prior to first dose of study medication. NOTE: Test is optional and participants with negative hepatitis C antibody test are not required to also undergo hepatitis C RNA testing.

    a. The hepatitis C antibody test is a standard test used at Screening to determine eligibility, and hepatitis C RNA testing is optional and only performed when the antibody test is positive in order to consider participants with positive hepatitis C antibody test for enrollment into the study. Where hepatitis C RNA testing is unavailable, a positive hepatitis C antibody test will be used for exclusion.

    b. NOTE: Stable chronic liver disease (including Gilbert's syndrome and asymptomatic gallstones) is acceptable if the participant otherwise meets entry criteria.

40b. Study participant has medical history or current diagnosis of renal impairment and/or Screening laboratory results show any of the following confirmed by repeat test:

    a. Criterion removed.

    b. Abnormal urinalysis considered clinically significant by the Investigator, eg, red cell casts or hematuria in microscopy.

       Abnormal urinalysis may be treated during the Screening Period and retested prior to Baseline, providing that study participants are still within the Screening Period window and the treatment medication is stopped 14 days prior to Baseline.

    c. Results for urine test of albumin/creatinine ratio of ≥30mg/mmol.

    d. Study participants with evidence of urinary tract infection during the Screening Period.

       Urinary tract infection may be treated during the Screening Period and retested prior to Baseline, providing that study participants are still within the Screening Period window and the treatment medication is stopped 14 days prior to Baseline.

e. The estimated glomerular filtration rate of <45mL/min/1.73m^2 (using the Chronic Kidney Disease Epidemiology Collaboration formula).

f. Clinically significant electrolyte abnormalities.

41. History of significant renal disease.

Other exclusions

42a. The study participant must not ingest grapefruit, starfruit, or pawpaw (as beverage, fruit or supplements) within 72 hours before the study medication administration or be under treatment with any known strong CYP3A4 inhibitor or inducer within 72 hours before study drug administration or throughout the entire study period (Section 6.5.2).

43a. Vulnerable participants (eg, participants kept in detention, soldiers, adults with legally authorized representative, employees of the Sponsor or the CRO with direct involvement in the proposed study or other studies under the direction of the Investigator or the CRO, as well as family members of the employees or the Investigator. In France, another example of vulnerable participants includes participants who do not benefit from social security schemes such as health insurance. (For specific requirements in France, please refer to Section 10.9, Appendix 9.)

44. A female study participant who tests positive for pregnancy, plans to get pregnant during the participation in the study, or who is breastfeeding.

45. Study participant with hypokalemia, defined as a serum potassium level below the lower limit of the laboratory's reference range.

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) within 72 hours before the study medication administration and 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 is an exclusion criterion, and study participants are requested to practice only 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 study medication. 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 serious adverse event (SAE).

For study participants otherwise fully eligible but not able to be randomized as planned for personal reasons, rescreening may be allowed once per participant at the discretion of the Investigator, following discussion with the Medical Monitor. If Visit 2 was completed during screening, only Visit 1 needs to be completed for rescreening. However, the maximum period between DaT-SPECT, MRI assessment, and V1 need to be adhered to as per inclusion criteria. Rescreened participants will be assigned a new participant number.

Rescreening in case of abnormal laboratory results can be considered only in case of test results for which there are strong reasons to be considered transitory and/or without clinical safety significance. In these cases, the assessments might be repeated after consultation with the Medical Monitor.

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	UCB0599 180mg/day	UCB0599 360mg/day	Placebo
Intervention name	UCB0599	UCB0599	Placebo
Type	Drug	Drug	Placebo
Dose formulation	Granules in capsules and matching placebo capsules	Granules in capsules	Matching placebo capsules
Unit dose strength(s)	90mg and 0mg	90mg	0mg
Dosage level(s)[a]	180mg/day [90mg BID]	360mg/day [180mg BID]	NA, BID intake
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	Oral – 4 matching placebo capsules per day BID approximately 12 hours apart
Use	Experimental	Experimental	Placebo-comparator
IMP and NIMP	IMP	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.	IMP will be supplied by UCB Clinical Trial Supply or designee.
Packaging and labeling	UCB0599 and placebo capsules are manufactured, packaged, and labeled according to Good Manufacturing Practice guidelines and applicable laws or regulations.	UCB0599 and placebo capsules are manufactured, packaged, and labeled according to Good Manufacturing Practice guidelines and applicable laws or regulations.	UCB0599 and placebo capsules are manufactured, packaged, and labeled according to Good Manufacturing Practice guidelines and applicable laws or regulations.
Current/Former name(s) or alias(es)	NA	NA	NA

BID=twice per day; IMP=investigational medicinal product; NA=not applicable

[a] Participants will be randomized to either UCB0599 360mg/day (180mg BID), UCB0599 180mg/day (90mg BID), or placebo to achieve a final randomization ratio of 1:1:1 when the IMP for low dose UCB0599 180mg/day (90mg BID) will be available to supply sites.

6.2 Preparation, handling, storage, and accountability requirements

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

Only participants enrolled in the study may receive study medication, and only authorized site staff may supply or administer study medication. All study medications 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 study medication 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 study medication following the instructions on the label.

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

6.2.1 Drug accountability

A Drug Accountability form will be used to record study medication dispensing and return information on a by-participant basis and will serve as source documentation during the course of the study. Details of any study medication 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 study medication 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 study medication 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 study medication must be reconciled and either destroyed at the site according to local laws, regulations, and UCB standard operating procedures 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

Interactive response technology (IRT) will be used for assigning eligible participants to a treatment regimen (as applicable) based on a predetermined production randomization and/or packaging schedule provided by UCB (or designee). The randomization schedule will be produced by the IRT vendor. The IRT will generate individual assignments for kits of study medication, as appropriate, according to the visit schedule.

To enroll a study participant (Visit 1), the Investigator or designee will contact the IRT and provide brief details about the participant to be enrolled. Each participant will receive a 5-digit number assigned at Screening that serves as the participant identifier throughout the study. 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. Enrolled participants who withdraw from the study prior to randomization will retain their participant number without receiving a randomization number (ie, participant numbers will not be reassigned).

To randomize a participant, the Investigator or designee will contact the IRT and provide brief details about the participant to be randomized. The IRT will automatically inform the Investigator or designee of the participant's randomization number. 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 eCRF.

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

- Designated CRO bioanalytical staff analyzing PK samples
- Sponsor clinical study supply staff
- Interactive response technology 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 Data Monitoring Committee (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
- Unblinded pharmacometrics staff and statistical programmers, independent from the study team, who have access to the 12-month data for the preparation of the exposure-response analysis

To balance prognostic factors across treatment groups, randomization of study participants will be stratified using permutation blocks by gender.

In the Parkinson Progression Markers Initiative (PPMI) database, variability in MDS-UPRDS was observed to differ between male and female PD patients. Men and women also behave differently with respect to start of ST. Therefore, the study will balance treatment groups according to gender.

In the three-arm study, only participants who are recruited after the introduction of the randomization schedule which include the low-dose arm will have a chance of being assigned to low-dose UCB0599, causing a small time bias. This time bias will be considered to have no impact on how the participants respond to their assigned treatment, ie, the data collected from participants assigned to the placebo and high-dose arms prior to the introduction of the full randomization schedule will be assumed comparable to the data collected from participants assigned to the placebo and high-dose arms after the introduction of the full randomization schedule.

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.

6.3.1.2 Breaking the treatment blind in an emergency situation

In the event of an emergency, it will be possible to determine to which treatment arm and dose the participant has been allocated by contacting the IRT. All sites will be provided with details of how to contact the system for code breaking at the start of the study.

The Clinical Project Manager will be informed immediately via the IRT when a code is broken, but will remain blinded to specific treatment information. Any unblinding of the study medication performed by the Investigator must be recorded in the source documents and on the Study Termination eCRF page.

6.4 Treatment compliance

At each in-clinic visit after study medication is dispensed, participants must return all unused study medication and empty study medication containers. Drug accountability must be done in the participant's presence in order to obtain explanations regarding discrepancies in compliance with the 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)

DaTSCAN tracer for DaT-SPECT imaging will be sourced from GE-Healthcare via Invicro. The tracer is approved for commercial use in Europe, the US, and Canada and will be used according to the product label. Approximate radioactivity per dose is 185 MBq.

Thyroid-blocking agents such as lugol must be applied before DaT-SPECT.

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)

No concomitant medications for the treatment of motor symptoms of PD or medications with PD disease modifying effect will be allowed at inclusion (eg, levodopa, COMT inhibitors, dopamine agonists, MAO-B inhibitors). 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:

- Metoclopramide
- Alpha methyldopa

- Clozapine
- Olanzapine
- Flunarizine
- Amoxapine
- Amphetamine derivatives
- Reserpine
- Bupropion
- Buspirone
- Cocaine
- Mazindol
- Methylamphetamine
- Methylphenidate
- Norephedrine
- Phentermine
- Phenylpropanolamine
- Modafinil

6.5.3 Rescue medication

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 standard of care recommendations. Guidance on the initiation of rescue medication will be provided in a separate manual.

The study site will supply rescue medication that will be obtained locally.

Levodopa is determined as first choice for participants who are determined to require ST. Other ST options are only permitted in exceptional cases, 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 Type B inhibitors will not be allowed.

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.

For all scheduled visits, study participants that start to receive ST over the study observation period 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 is considered sufficient to achieve a practically defined off-state for the range of STs specified in this section 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 prior to any visit, the data from that particular visit will be censored.

6.6 Dose modification

There is no dose modification allowed in PD0053.

6.7 Criteria for study hold or dosing stoppage

UCB will halt further dosing for all study participants at all sites if any of 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 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 study medication-related and that would be unacceptable for this patient population.

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 DMC are provided in the DMC charter.

3. If the Sponsor or its designees 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 study medication.

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

Study participants who complete the Treatment Period will have the option to transition into a dose-blinded extension study (PD0055). In this case, participants will not enter the SFU Period of PD0053. For those participants who do not roll over to PD0055, the study ends with an SFU Visit (Visit 16) approximately 30 days after the last dose. In case of early termination of a participant's study medication, the participant will be asked to attend the EOT and the SFU Visit (30 days after the last dose) and will not be eligible for PD0055.

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 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 reaction (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.

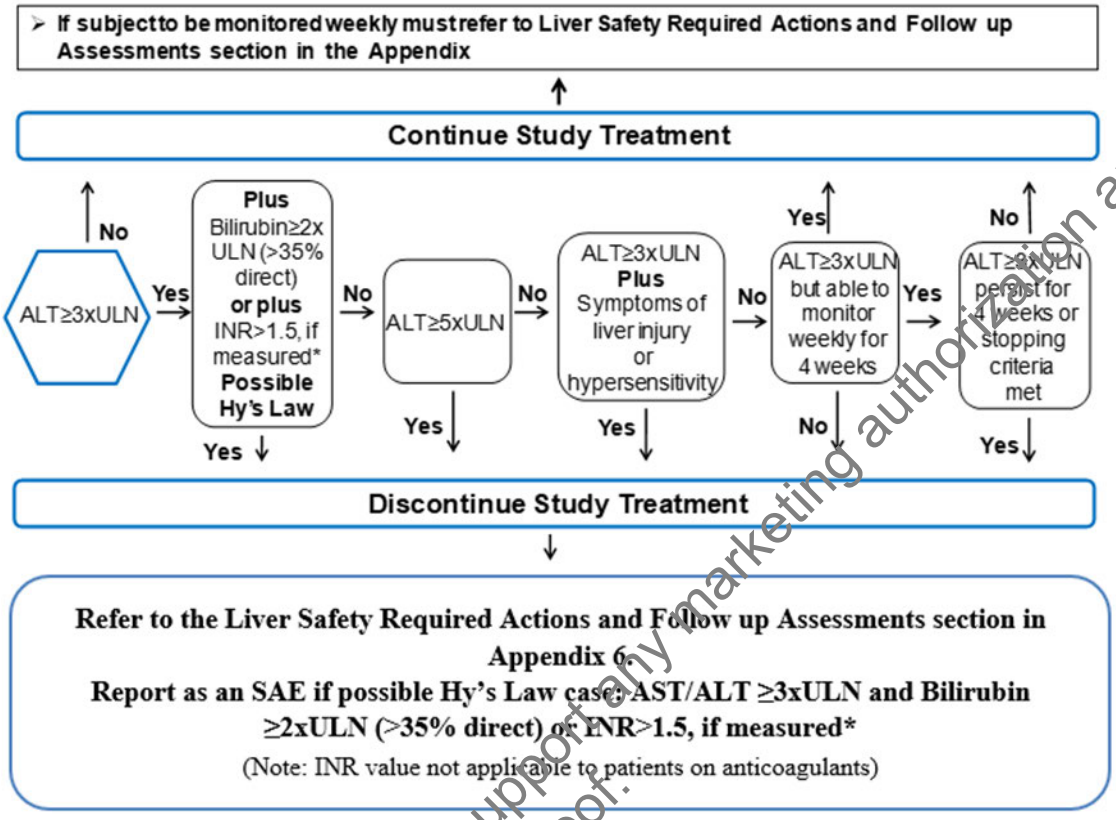
If the event is not considered to be a hypersensitivity reaction (eg, a rash due to another cause) the Investigator should document this and the participant may continue dosing.

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 medication for abnormal liver function should be considered by the Investigator when a 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 are provided in Appendix 6 (Section 10.6).

7.1.3 QTc Stopping Criteria

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

- 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

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

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 the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

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 (End of Treatment), 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 involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness or throughout quarantine conditions.

Participants must be discontinued from study medication (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 C-SSRS. The study participant should be referred immediately to a mental healthcare professional and must be discontinued from study medication.
5. Study participant is confirmed positive for recreational drug use or for alcohol at a 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 attend scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to attend 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.

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. To avoid bias and to maintain consistency over time, this rule should also apply to participants not (yet) on ST. The assessments in the timeslot preceding intake of ST should comprise:

- PROs (at home prior to a clinic visit or first assessments at the clinic)
- MDS-UPDRS (all parts)
- Virtual Motor Exam (VME) (after a period of rest)
- ECGs
- Laboratory and PK 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 study medication.

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.

The maximum amount of blood collected from each participant will not exceed 50mL at any visit and will not exceed 510mL 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

8.1.1 Clinical assessments

8.1.1.1 MDS-UPDRS

The primary efficacy objective will be assessed by comparing the mean slope of progression of the MDS-UPDRS Parts I-III sum score estimated using all available data during the Treatment Period, from Baseline to Month 12 or up to intake of ST (Primary Estimand) between UCB0599 and placebo. The difference in population means between treatment groups at 18 months or up to intake of ST will also be estimated (Key Secondary Estimand). In addition, the treatment difference in population mean slope of progression in MDS-UPDRS Part III subscale and in time to 5-point increase in MDS-UPDRS Part III will be estimated (Key Secondary Estimands). See Section 9.3 for more information on the planned efficacy analyses.

The MDS-UPDRS (Goetz et al, 2008) will be completed according to the Schedule of Assessments (Section 1.3).

The MDS sponsored a new version of the UPDRS in 2003 consisting of 4 parts (subscales):

- Part I (non-motor experiences of daily living) 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.
  - 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.

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.

- Part II (motor experiences of daily living):
  - 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.
  - Is designed to be a self-administered questionnaire like Part IB, but can be reviewed by the rater to ensure completeness and clarity.
- Part III (motor examination)
  - 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).

  - Has instructions for the rater to give or demonstrate to the study participant; it is completed by the rater.

- Part IV (motor complications)
  - 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.

Where possible, the same person should assess the study participant at each time point to avoid inter-individual rating differences. Study participants who do start to receive ST during the study Treatment period will be asked to refrain from taking ST for at least 12 hours before clinic visits and to bring the medication to the site. A 12-hour washout is considered sufficient to achieve a practically defined "off" state (please refer to Section 6.5.3 for further details). If a participant does not comply with the 12-hour ST washout prior to any visit, the data from that particular visit will be censored.

8.1.1.2 Modified Hoehn and Yahr staging

The Hoehn and Yahr 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 Hoehn and Yahr 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.

8.1.1.3 Dopamine Transporter Imaging with Single Photon Emission Computed Tomography

Dopamine Transporter Imaging with Single Photon Emission Computed Tomography will be conducted at the visits specified in Section 1.3.

^{123}I-Ioflupane (DaTSCAN®, GE Healthcare) is a radiopharmaceutical approved in the EU, Canada, and U.S.

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 13.89mSv. This is categorized as a category III substantial 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 SPECT scanner and positioned with comfortable head fixation. A single scan will be acquired over approximately 30 to 45 minutes.

At Screening, the DaTSCAN imaging data will be transferred to a central imaging lab and analyzed visually to determine the status of dopamine deficit.

For the Screening, Month 12 (no scan will be performed at Month 12 for participants in Germany [please see Appendix 9, Section 10.9]), and Month 18 scans; DaTSCAN imaging data will be analyzed quantitatively using region of interest analysis methods to determine tracer uptake and the mean striatum specific binding ratio. Other exploratory analysis may also be done.

A historical DaT-SPECT scan within the previous 3 months before Screening Visit 1 is acceptable if the same specifications as in protocol were followed and if scan quality is acceptable by central imaging (InVicro).

The DaTSCAN tracer for DaT-SPECT imaging must be sourced from GE-Healthcare, the participant must have avoided the medications listed in Section 6.5.2 which are not allowed during the 50 days before DaT-SPECT imaging and the DaTSCAN imaging data will be transferred to the central imaging lab (InVicro) and analyzed visually for dopamine deficit status (Baseline) and quantitatively for mean striatum specific binding ratio at Baseline, 12 months, and 18 months.

8.1.1.4 ST intake

Differences in ST intake between UCB0599 and placebo will be assessed at 12 and 18 months regardless of assigned study medication (Secondary efficacy estimand).

For details on ST initiation, see Section 6.5.3.

8.1.1.5 Montreal Cognitive Assessment

The difference between UCB0599 and placebo in target population mean (measured at Screening) in Montreal Cognitive Assessment (MoCA) at 18 months regardless of concomitant ST intake is a secondary efficacy endpoint.

The MoCA (Nasreddine et al, 2005) assesses different cognitive domains (visuospatial/executive, naming, memory, attention, language, abstraction, delayed recall, and orientation). Participants are assessed on a 30-point scale. A score of 26 or above is considered normal.

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

8.1.1.6 Clinical Global Impression of Improvement

For the Clinical Global Impression of Improvement (CGII), the Investigator will assess change observed in the study participant's condition compared with his/her condition at Baseline. Response options include: 0=not assessed; 1=very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6= much worse; 7=very much worse.

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

8.1.1.7 Clinical Global Impression of Severity

With the Clinical Global Impression of Severity (CGIS), the Investigator will assess the current overall severity of Parkinson's Disease observed in the study participant. Response options include: 0=not assessed; 1=normal, not at all ill; 2=borderline ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; and 7=among the most extremely ill participants.

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

8.1.1.8 Movement Disorder Society Non-motor symptom scale

The Movement Disorder Society Non-motor symptom 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 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.

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

8.1.1.9 Schwab and England Activities of Daily Living Scale

The Schwab and England Activities of Daily Living (SE-ADL) is a short assessment of an individual's level of functional independence. In PD patients, the SE-ADL is typically assessed in conjunction with the MDS-UPDRS. For the SE-ADL, the examiner prompts the individual to select the rating that most accurately describes their level of functional independence. The SE-ADL scoring ranges, in 11 steps, from 100% (Completely independent; able to do all chores without slowness, difficulty, or impairment; Essentially normal; unaware of any difficulty) to 0% (Vegetative functions such as swallowing; Bladder and bowel functions are not functioning; Bedridden).

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

8.1.1.10 Starkstein Apathy Scale

The Starkstein Apathy Scale (Starkstein et al, 1992) is a 14-item questionnaire to assess the severity of apathetic symptoms. The questions are read aloud to the participant by the examiner. For questions 1 to 8, each item is scored on a 4-point scale: “not at all” (3 points), "slightly" (2 points), "some" (1 point) and “a lot” (0 points). For questions 9 to 14, response options are: “not at all” (0 points), "slightly" (1 point), "some" (2 points), and “a lot” (3 points).

The Starkstein Apathy Scale will be assessed at the visits specified in 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.

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.

In the specific context of telemedicine visits, an automatic alert mechanism should be put in place to remind study participants to complete the PROs prior to any interactions with study personnel. Date and time of completion of the PROs will be recorded electronically.

In the event study personnel finds out that the PROs have not been completed before the visit, study participants should be allowed to complete before any study related assessment is initiated.

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: Fatigue-PRO; Early PD Function Slowness PRO; Early PD Mobility PRO; Patient Global Impression of Severity (PGIS) on Symptoms and Fatigue; Patient Global Impression of Change (PGIC) on Symptoms and Fatigue; Hospital Anxiety and Depression Scale (HADS); Euro Quality of life 5-Dimensions 5-Level (EQ-5D-5L).

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

8.1.2.1 Fatigue PRO

Fatigue PRO consists of 31 items across 3 domains: 9 ‘physical fatigue’ domain items, 11 ‘mental and cognitive’ domain items, and 11 ‘susceptibility to fatigue’ domain items. Participants are asked to score each item based on how frequently they experienced the fatigue item over the past 7 days, using a 5-point Likert scale (“none of the time” to “all of the time”). Domain scores range from 0 to 100, with higher scores indicating higher levels of fatigue. Fatigue-PRO translates into 3 domain scores: 'Physical Fatigue', 'Mental Fatigue' and 'Fatigability' scores. It currently does not include a total score summary.

8.1.2.2 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 generated data in the future.

8.1.2.3 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 generated data in future.

8.1.2.4 PGIS

The PGIS is a 2-item, self-report measure that rates a participant's severity of their PD symptoms and overall fatigue over the past week. The PGIS is a 4-point scale ("none," "mild," "moderate," "severe").

8.1.2.5 PGIC

The PGIC is a 2-state, self-report measure that reflects a participant's assessment of overall change in their PD symptoms and overall fatigue since they started taking the study medication. The PGIC is a 7-point scale ("much improved," "moderately improved," "a little bit improved," "no change," "a little bit worse," "moderately worse," "much worse").

8.1.2.6 HADS

The Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983) is a patient-administered questionnaire that consists of 2 subscales for anxiety and depression. Each subscale consists of 7 items which are scored separately on a 4-point (0–3) scale, leading to a total score range from 0 to 21 for each of the 2 subscales.

8.1.2.7 EQ-5D-5L

The EQ-5D-5L consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ-VAS).

The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: "no problems," "slight problems," "moderate problems," "severe problems," and "extreme problems". The study participant is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the 5 dimensions can be combined into a 5-digit number that describes the study participant's health state.

The EQ VAS records the study participant's self-rated health on a vertical visual analogue scale, where the endpoints are labeled 'The best health you can imagine' and 'The worst health you can imagine'. The VAS can be used as a quantitative measure of health outcome that reflects the study participant's own judgement.

8.1.3 Wearable sensor

Data generated from the wearable sensor will be included within the panel of exploratory assessments and comprise changes in objective measures of motor function, sleep, and selected neurovegetative parameters assessed with a customized, wrist-worn digital sensor (hereinafter referred to as "wearable sensor," which will be worn on the usual wristwatch side for comfort,

even if it is not the most affected side). The multisensor unit will continuously collect physiological and environmental data, including acceleration/orientation, pulse rate, skin impedance, ambient pressure, ambient temperature (in device chamber), and ambient light level.

Digital data collection is initiated during an approximately 2-week adaptation period (Section 1.3) to address technical issues and handling errors and to ensure robust Baseline data before initiation of dosing. Where it is not possible to access the sensor during the Baseline period, participants may start wearing it until Visit 8 (M4). To yield a solid Baseline for the VMEs, these home-based structured activities will be conducted every day throughout the familiarization period. If necessary, the frequency will be adjusted on an individual basis. Study participants will be encouraged to identify a most appropriate time-window in their daily schedule, where the home-based structural activities should be placed. This routine should be maintained until the end of the study. In case of initiation of symptomatic treatment, the home-based VME should be conducted in the practically defined off-state (typically before the intake of the morning medication). Throughout the first 12 months of the study, spontaneous activity data coming from the various sensors included in the wearable sensor will be continuously (up to 23 hours/day) collected in a usual home-setting (or work setting, if applicable) and throughout all non-home-based activities. Even though the laterality of the most pronounced motor symptoms should shift to the contralateral side over time, the wearable sensor will continue to be worn on the initially selected side. In addition to the continuous data collection, a series of 8 simple structured motor tasks will be performed on a weekly basis in the study participant's home environment.

Screening Period (Visit 2 to Visit 3):

During the Screening Period between Visit 2 and Visit 3 (or any 2-week period before Visit 9 [M6] for participants consenting to using the wearable sensor after having completed the Screening Period), one VME per day will be performed by the participants at home to familiarize themselves with the wearable sensor. Participants will rate their individual performance of each VME Skill Check directly on the wearable sensor after each task (5-option smiley face scale, with description provided in the VME training guide).

Baseline (Visit 3):

During the Baseline Visit (Visit 3), participants will perform the VME in the clinic before the first dose of the study treatment, following the MDS-UPDRS Part III assessments. Investigators will rate participant performance of each VME Skill Check following the Investigator Rating Scale (refer to Section 10.12 [Appendix 12]).

The frequency of the VME will be changed after the familiarization period to weekly on the wearable sensor by the Investigator at the next clinical study visit. Participants will be requested to select the day of the week and the time to plan the VME Skill Check Schedule.

Treatment Period:

At in-clinic visits and during telemedicine visits when MDS-UPDRS is assessed, the participants will perform 1 VME, back-to-back after their MDS-UPDRS Part III assessments. Each VME task will be scored by the Investigator.

The participant will also be asked to perform 1 VME per week at home, first thing in the morning before intake of any PD treatment.

The wearable sensors will be finally returned by the participant to the site on Visit 15 (M18) or Early Termination Visit in case of early study termination).

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

Physical examinations will be performed at the scheduled time points presented in the Schedule of Activities (Section 1.3). 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, hepatic, and neurological systems (including sensation, muscle strength, reflexes, balance, and mental state) (a brief neurological exam will only be performed as part of the physical assessment on days when the full neurological exam is not already scheduled).

A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen. A physical examination of the skin will include, at a minimum, a visual check of the skin (including an inspection of the oral cavity), and may be conducted by a nurse or physician. 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.

During telemedicine video call visits, physical examinations will be limited to focused body examinations performed by research nurses. These will include, at a minimum, an assessment of the cardiovascular system (absence/presence of swelling of feet/ankles, absence/presence of pallor), respiratory system (absence/presence of cyanosis), gastrointestinal system (absence/presence of ulcers, rash, lumps, or exudate in the mouth, absence/presence of jaundice, absence/presence of abdominal pain on palpitation), and skin (absence/presence of rash, ulcers, lumps). The examination by the nurses will be guided and assessed by the Investigator via telemedicine video call.

Any abnormal finding from the focused body examinations by the research nurses will be highlighted to the Investigator. The research nurses should pay special attention to clinical signs related to previous serious illnesses and hypersensitivity reaction (such as rash, angioedema, or anaphylaxis). Any abnormal findings, specifically skin changes potentially related to hypersensitivity reaction (such as rash, angioedema, or anaphylaxis) (Section 8.3.6.1), should be highlighted to the Investigator and should be photographically documented, if the participant provides consent. The Investigator will provide instructions regarding further activities. Any abnormal finding from the focused body examinations by the research nurses will be highlighted to the Investigator.

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

Height and weight will be measured and recorded at the Screening Visit, and the study participant's BMI will be calculated. Height will be measured with the study participant not wearing shoes and the outcome will be rounded to the nearest 1cm. Body weight will be

measured with the study participant wearing light clothing and without wearing shoes; the outcome will be rounded to the nearest 0.1kg. The BMI will be calculated (weight [kg]/[height (m^2)]) and will be reported to 1 decimal place.

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 are to be reported as AEs.

A brief neurological exam will include, at a minimum, assessment of the general neurological status (level of consciousness, mental status, speech), reflexes, and motor system (general motor status, muscle strength, muscle tone).

During telemedicine video call visits, neurological examinations will be limited to focused neurological examinations performed by the research nurses. These will include, at a minimum, determination of the level of consciousness, major psychopathological abnormalities, motor function, sensation, cerebellar function, muscle reflexes, and cranial nerve function. Study participants will be actively encouraged to verbally describe any neurological changes they have experienced since the last visit. This information will be captured by the nurse. Any significant new abnormal findings emerging on the brief neurological examination may entail a more formal investigation by a trained neurologist for accurate characterization and determination of the level of consciousness, major psychopathological abnormalities, motor function, sensation, cerebellar function, muscle reflexes, and cranial nerve function. The examination by the nurses will be guided and assessed by the Investigator via telemedicine video call.

8.2.3 Vital signs

Vital signs, including pulse rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), respiratory rate, and tympanic body temperature will be measured with a completely automated device after 5 minutes of rest in supine position (in a quiet setting without distractions such as a television or cell phones) and erect to assess autonomous dysregulation. Manual techniques will be used only if an automated device is not available. Any observation by the research nurse will be discussed with the Investigator during the video communication part of the remote visit. Any clinically significant abnormality in the view of the Investigator will be recorded as an AE.

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

8.2.4 Electrocardiograms

Triplicate 12-lead ECGs will be obtained as outlined in the Schedule of Activities (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR,

QRS, QT, and QTcF intervals. Refer to Section 7.1.3 for QTcF withdrawal criteria and any additional QTc readings that may be necessary.

The study participant should be resting in the supine position for at least 10 minutes before the start of the recordings. At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 10 minutes. Electrocardiograms will be obtained by the research nurse during remote visits. Any observation by the research nurse will be discussed with the Investigator during the video communication part of the remote visit.

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. Blood/urine sampling and urine pregnancy testing will be performed by the research nurses during remote visits.

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 study medication 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

UCB0599 is a CNS-active study medication. There has been concern that some CNS-active study medications 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). During remote visits, the assessment will be performed remotely via telemedicine. This scale will be used for Screening as well as to assess suicidal ideation and behavior that may occur during the study. All study participants will complete the "Baseline/Screening" version of the C-SSRS at Visit 1 (assessing the past 6 months), followed by the "Since Last Visit" version at the visits indicated on the Schedule of Activities (Section 1.3).

Participants being treated with 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 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 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.

8.2.7 MRI assessments

Structural brain MRIs will be performed at the Screening Visit (Visit 2) for study participants without an acceptable historical scan within 6 months before this visit, on an MRI scanner of at least 1.5 Tesla, using a standardized acquisition protocol and without contrast. At a minimum, the following sequences will be performed per local standard practice: T1, T2, and T2 FLAIR.

8.2.8 Wearable sensor data

Physiological and environmental data obtained from the wearable sensor will not be used for safety monitoring and reporting of UCB0599 because the sensor is unvalidated for this purpose and will be only used for exploratory endpoints in this study.

The Investigator is expected to record any AEs in the eCRF and assess causality as it might relate to the wearable sensor. The eCRF page will allow the Investigator to assess causality in relation to the wearable sensor.

Serious adverse events should be reported in the eCRF and expedited to the Sponsor according to Appendix 3 (Section 10.3).

The Sponsor will send reports of SAEs relating to the wearable sensor to Verily so that the manufacturer can comply with its reporting obligations.

See Appendix 7 (Section 10.7) for more information about sensor deficiencies, accountability, handling and discontinuation.

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 study medication or study procedures, or that caused the participant to discontinue UCB0599 or PD0053 (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 study medication 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 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 study medication), 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 study medication 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 non-leading 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 SAEs, and nonserious 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 a study medication under clinical investigation are met.

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

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

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 study medication 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), and the following should be completed:

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

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

8.3.6 Adverse events of special interest

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

- Hy's Law
  - Potential Hy's Law, defined as ≥3xULN ALT or AST with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality (ie, without waiting for any additional etiologic investigations to have been concluded). Follow-up information should 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 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 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 study medication is provided in Section 7.1.1.

8.3.6.1.1 Medical history

Detailed history of the hypersensitivity reaction (such as 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, etc), 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 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: 2 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:

- Blood pressure <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, DBP, respiratory rate, body temperature, and oxygen saturation) will be taken when the AE of hypersensitivity is reported and at regular intervals (approximately 20-30 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
  - IgE
- 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 study medication (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 Anticipated serious adverse events

The following Anticipated SAEs are anticipated to occur in the population studied in this protocol at some frequency that is independent of drug exposure.

This list does not change the Investigator's obligation to report all SAEs (including Anticipated SAEs) as detailed in Section 8.3.1 and Appendix 3 (Section 10.3).

Table 8-1: Anticipated serious adverse events for Parkinson's disease population

MedDRA System Organ Class	MedDRA Preferred Term
Nervous system disorders	Syncope
Psychiatric disorders	Hallucination

MedDRA=Medical Dictionary for Regulatory Activities

8.3.8 Wearable sensor – adverse events (adverse sensor effects, unanticipated adverse sensor effects, SAEs, serious adverse drug events, and unanticipated serious adverse drug events) and sensor deficiencies

The wearable sensor is being provided as a noninvasive exploratory tool for use in this study for the evaluation of digital measurements for aspects of motor function, sleep, and neurovegetative parameters.

In order to fulfill regulatory reporting obligations worldwide, the Investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with the wearable sensor.

Adverse Events associated with the wearable sensor will be reported to the appropriate regulatory agencies and sensor developer. Adverse event reporting will be conducted as per the specific laws, regulations, directives, standards and/or guidelines as appropriate and as required by the countries in which the clinical investigation is conducted.

The definition of a sensor deficiency can be found in Appendix 7 (Section 10.7).

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).

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 study medication 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 study medication, 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 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 study medication 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 UCB0599 can no longer be detected systemically (approximately 5 days).
- Obtain a plasma sample for PK analysis within 3 days from the date of the last dose of study medication if requested by the Medical Monitor (determined on a case-by-case basis).
- 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

Whole blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of UCB0599 and its N-oxide metabolite as specified in the Schedule of Activities (Section 1.3). A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and the Sponsor. Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Participant confidentiality will be maintained. At visits during which plasma samples will be taken for the determination of UCB0599 and its N-oxide metabolite concentrations, Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Samples will be used to evaluate the PK of UCB0599 and its N-oxide metabolite. One sample of sufficient volume can be used. Each plasma sample will be divided into 2 aliquots (1 each for PK and a back-up). Samples collected for analyses of UCB0599 and its N-oxide metabolite concentrations may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Cerebrospinal fluid samples will be taken at 12 months and EOT to measure concentrations of UCB0599 and metabolites. Timing of CSF sampling will be done close to blood sampling time.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the Sponsor and site study files, but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

8.7 Genetics

Refer to Section 8.9 for more information.

8.8 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.9 Biomarkers

Genetic sampling will be mandatory for study participation. Collection of samples for potential exploratory biomarker research forms part of the study objectives (where biomarkers can include, but are not limited to, deoxyribonucleic acid (DNA), RNA, protein, and metabolites). Instructions pertaining to sample collection, processing, storage, labeling, and shipping are provided in the PD0053 laboratory manual for this study. 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, study medication treatment and response, and/or mechanism of action of the study medication treatment. The following samples will be collected and stored from all participants in this study to support potential future exploratory biomarker research. These samples are a required component of the protocol as specified in the Schedule of Activities (Section 1.3).

- Blood samples for DNA specified in the Schedule of Activities (Section 1.3). See Appendix 5 (Section 10.5) for information regarding genetic research.
- 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). Candidate biomarkers might include, but are not limited to: monomeric, oligomeric ASYN, pS129-ASYN, and total ASYN. At dosing visits, blood samples will be drawn prior to dosing, and will be drawn at the same time of the sampling for clinical laboratory tests. The time and date of collection will be recorded in the eCRF.
  - 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.
- All samples collected may be used for exploratory purposes.

These samples will only be used to further understanding of PD and/or how biomarkers, including genetic variation, may affect response or be affected by treatment with UCB0599 in the treatment of PD.

8.10 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: All study participants who sign the ICF
- Randomized Set (RS): All study participants who are randomized
- Safety Set (SS): All randomized study participants who receive at least a partial dose of study medication. The SS will be used for demographic and safety analyses and analyses will be based on treatment received.
- Full Analysis Set (FAS): All randomized study participants who receive at least a partial dose of study medication and who have at least 1 post-Baseline assessment. The FAS will be used for all efficacy analyses, and analyses will be conducted based on randomized treatment.
- Pharmacokinetic Set (PKS): All study participants in the Safety Set who have at least 1 observable PK measurement. The PKS will be used for PK analyses.

For all analyses, the target population will be the 'entire study population' as selected according to the inclusion/exclusion criteria described in Section 5.

The FAS will be used for all analyses with intercurrent events (ICEs) and other protocol deviations to be handled according to the policy specified for each estimand (Section 9.3).

9.2 General statistical considerations

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

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.

9.3 Planned efficacy/outcome analyses

An overview of the planned efficacy analyses is presented in Table 9-1. For all estimands, the difference between UCB0599 and placebo will be evaluated for both the low and the high doses of UCB0599 (180mg/day and 360mg/day). The comparison of the high dose of UCB0599 with placebo will be considered as the primary evaluation. If the comparison of the low dose and placebo gives a positive result on the primary estimand but the comparison of the high dose and placebo does not, these results will have to be interpreted with caution. In all analyses, the 2 dose levels will be assessed separately against placebo, there will be no pooling of the 2 dose levels, and they will not be compared to each other.

Table 9-1: Overview of planned efficacy analyses

Objectives	Estimands
Primary Efficacy Objective	**Target population: Entire study population**
To demonstrate the superiority of UCB0599 over placebo with regard to **clinical symptoms of disease progression** over 12 and 18 months in participants diagnosed with early-stage PD	**Primary Efficacy Estimand** • Difference between UCB0599 and placebo in target population mean slope of progression in **MDS-UPDRS Parts I-III sum score** over 12 months in the absence of concomitant ST intake **Key Secondary Efficacy Estimands** • Difference between UCB0599 and placebo in target population mean in **MDS-UPDRS Parts I-III sum score** at 18 months in the absence of concomitant ST intake • Difference between UCB0599 and placebo in target population mean slope of progression in **MDS-UPDRS Part III subscale** score over 12 months in the absence of concomitant ST intake

Table 9-1: Overview of planned efficacy analyses

	• Difference between UCB0599 and placebo in target population mean in **MDS-UPDRS Part III ePD subscore** at 12 months in the absence of concomitant ST intake • Difference between UCB0599 and placebo in target population RMET, in this case, time to worsening of the disease as defined by a **5-point increase in MDS-UPDRS III**, within the 18-month period, in the absence of concomitant ST intake **Secondary Efficacy Estimands** • Difference between UCB0599 and placebo in target population mean **MDS-UPDRS Part I/II subscales** at 12 months in the absence of concomitant ST intake • Difference between UCB0599 and placebo in target population mean **MDS-UPDRS Part I/II/III subscales** at 18 months in the absence of concomitant ST intake • Difference between UCB0599 and placebo in target population mean in **MDS-UPDRS Part III ePD subscore** at 18 months in the absence of concomitant ST intake • Ratio between UCB0599 and placebo based on population annualized rate of emerging symptoms assessed by **MDS-UPDRS Part II subscale** over the 18-month period • Difference between UCB0599 and placebo in target population mean **MDS-UPDRS Part I subscale** at 12 months regardless of concomitant ST intake • Difference between UCB0599 and placebo in target population mean **MDS-UPDRS Part I subscale** at 18 months regardless of concomitant ST intake • Difference between UCB0599 and placebo in target population mean **MoCA**

Table 9-1: Overview of planned efficacy analyses

	at 18 months, regardless of concomitant ST intake **Exploratory Efficacy Endpoints** • Time to worsening on MDS-UPDRS Part I subscale • Modified Hoehn and Yahr staging • CGII • CGIS • Fatigue-PRO • Early PD Function Slowness PRO • Early PD Mobility PRO • Composite endpoint (based on MDS-UPDRS and/or Early PD PROs) • PGIS, overall and fatigue-specific • PGIC, overall and fatigue-specific • SE-ADL • HADS • MDS-NMS • Starkstein Apathy Scale • EQ-5D-5L • Wearable sensor

Table 9-1: Overview of planned efficacy analyses

Secondary Efficacy Objectives	Target population: Entire study population
To demonstrate the superiority of UCB0599 over placebo with regard to **neurodegeneration of dopaminergic neurons** over 12 and 18 months in participants diagnosed with early-stage PD	**Secondary Efficacy Estimand** • Difference between UCB0599 and placebo in target population mean change from Baseline (Screening) in **DaT-SPECT mean Striatum SBR** at 18 months regardless of concomitant ST intake • Difference between UCB0599 and placebo in target population mean change from Baseline (Screening) in **DaT-SPECT mean Striatum SBR** at 12 months regardless of concomitant ST intake **Exploratory Efficacy Endpoints** • DaT-SPECT mean SBR in striatal subregions • CSF total ASYN • CSF ASYN oligomers/seeding capacity
To assess the effect of UCB0599 vs placebo with regard to **intake of ST** over 18 months in participants diagnosed with early-stage PD	**Secondary Efficacy Estimands** • Difference between UCB0599 and placebo in target population RMET, in this case, time to start of ST, within the 18-month period, regardless of adherence to assigned study medication • Target population odds ratio between UCB0599 and placebo in ST intake at 18 months, regardless of adherence to assigned study medication **Other Secondary Efficacy Estimand** • Target population odds ratio between UCB0599 and placebo in **ST intake** at 12 months, regardless of adherence to assigned study medication **Exploratory Efficacy Endpoints** • Levodopa cumulative daily dose

ASYN=alpha-synuclein; CGII=Clinical Global Impression of Improvement; CGIS=Clinical Global Impression of Severity; CSF=cerebrospinal fluid; DaT-SPECT=Dopamine Transporter Imaging with Single Photon Emission Computerized Tomography; ePD=early-stage PD; EQ-5D-5L=EuroQol-5-dimension-5-level; HADS=Hospital Anxiety and Depression Scale; MDS-NMS=Movement Disorder Society-Non-motor Scale; MDS-UPDRS=Movement Disorder Society-Unified Parkinson's Disease Rating Scale; MoCA=Montreal Cognitive Assessment; PD=Parkinson's Disease; PGIC=Patient Global Impression of Change; PGIS=Patient Global Impression of Severity; PRO=Patient-Reported Outcome; RMET=restricted (t-year) mean event time; SBR=specific binding ratio; SE-ADL=Schwab and England Activities of Daily Living; ST=symptomatic treatment

Note: "In the absence of concomitant ST intake" means that all data recorded after a participant initiates ST will be censored. "Regardless of concomitant ST intake" means that participant data will be included in the analyses even after they have initiated ST. If a participant does not comply with the 12-hour ST washout prior to any visit, the data from that particular visit will be censored.

Efficacy data analysis at 12 and 18 months will take place once all participants have completed their 18-month Visit. All efficacy analyses will be carried out for the FAS and adjusted for the randomization stratification factor (ie, gender) and age at Baseline.

Treatment will be coded as a categorical variable with 3 levels (placebo, UCB0599 high dose, and UCB0599 low dose) with placebo as the reference category.

For change from Baseline analysis, treatment will be fitted as a fixed (main) effect. For longitudinal analyses of covariance and repeated measures modeling in which Baseline value is used as outcome, a treatment by time interaction will be included in this model as implicitly, the Baseline values for all groups are assumed to be equal and are reflected in the intercept of the models (Twisk, 2013).

Where applicable, explanatory continuous covariates will be mean-centered so that the intercept term can be interpreted as the expected value of the response when the dependent variables are set to their means.

Where reported alongside estimates and corresponding confidence intervals (CIs), p-values will always be presented as continuous values.

Estimands will be described as a function of their attributes: (1) the population of interest, (2) the treatment effect of interest, (3) the participant-level variable (or endpoint) of interest, (4) the specification of how ICEs are reflected in the scientific question of interest, and (5) the population-level summary for the variable/endpoint.

9.3.1 Analysis of the Primary Efficacy Objective: "Clinical symptoms at 12 and 18 months"

9.3.1.1 Analysis of "Clinical symptoms at 12 months"

To demonstrate the superiority of UCB0599 over placebo with regard to clinical symptoms of disease progression **over 12 months** in participants diagnosed with early-stage PD.

9.3.1.1.1 Primary Efficacy Estimand: MDS-UPDRS Parts I-III sum score at 12 months ("De Jure" Estimand)

Participant-level endpoint

Slope of progression in MDS-UPDRS Parts I-III sum score measured bimonthly over 12 months or up to the initiation of ST, including Baseline score, and scores at 2, 4, 6, 8, 10, and 12 months.

ICEs and handling strategies

ST initiation will be handled using a 'hypothetical' strategy, where post-ICE data will be censored.

Handling strategies for other ICEs are given in Table 9-2.

Population-level summary

Difference in population mean slope of progression in MDS-UPDRS Parts I-III sum score over 12 months in the absence of concomitant ST intake between:

- UCB0599 high dose (360mg/day) and placebo
- UCB0599 low dose (180mg/day) and placebo

Estimator

A Linear Mixed Effect Model (LMEM) for longitudinal data/repeated measures will be applied to the data up to the initiation of ST.

Baseline MDS-UPDRS data will be fitted as part of the dependent variable. Time as a continuous variable, ie, assuming linear development over 12 months, and treatment by time interaction (fixed slope) will be fitted as fixed effects (Twisk et al, 2018). To adjust for the dependency of the repeated observations within the individual, a participant-specific random intercept and a participant-specific random effect on time (ie, participant by time interaction or random slope) will be fitted as random effects (Twisk, 2013). The random effects will induce the correlation structure in the marginal model (ie, the model not conditional on random effects following integrating them out).

A fixed effect for treatment is not included in this model: implicitly, the Baseline values for all groups are assumed to be equal and are reflected in the intercept of the model. The treatment effects can therefore be directly obtained from the regression coefficients for the treatment by time interactions.

Estimates

Estimates for the treatment effects of interest (see above) over 12 months (MDS-UPDRS units increase per month) adjusted for gender and age at Baseline, with corresponding 95% CIs.

Supporting statistics

To support clinical interpretation, the following descriptive statistics will be reported separately for each treatment groups:

1. Number of participants who have initiated ST by 2, 4, 6, 8, 10, and 12 months.
2. Mean change from Baseline at 2, 4, 6, 8, 10, and 12 months for participants who have not initiated ST.
3. Mean change from Baseline at 2, 4, 6, 8, 10, and 12 months for participants who have initiated ST.
4. Plots of individual progression of MDS-UPDRS Parts I-III sum score grouped according to when each participant initiated ST; further details on these plots will be given in the SAP.

9.3.1.1.1.1 Supplementary Efficacy Estimand to MDS-UPDRS Parts I-III sum score at 12 months ("De Facto" Estimand)

Participant-level endpoint

MDS-UPDRS Parts I-III sum score measured bimonthly over 12 months, regardless of concomitant ST intake, including Baseline score, and scores at 2, 4, 6, 8, 10, and 12 months.

ICEs and handling strategies

ST initiation will be handled using a 'treatment policy' strategy, where post-ICE data are kept as part of the analysis.

If a participant does not comply with the 12-hour ST washout prior to any visit, the data from that particular visit will be censored.

Population-level summary

Difference in population mean MDS-UPDRS Parts I-III sum score at 8, 10, and 12 months, regardless of concomitant ST intake between:

- UCB0599 high dose (360mg/day) and placebo
- UCB0599 low dose (180mg/day) and placebo

Estimator

See Section 9.3.1.2.1.1 (LMEM estimator based on Baseline to Month 18 data).

Estimates

Estimates for the treatment effects of interest (see above) at 8, 10, and 12 months (MDS-UPDRS units difference at month specified) adjusted for gender and age at Baseline, with corresponding 95% CIs.

9.3.1.1.2 Key Secondary Efficacy Estimand: MDS-UPDRS Part III subscale at 12 months ("De Jure" Estimand)

Participant-level endpoint

Slope of progression in MDS-UPDRS Part III measured bimonthly over 12 months or up to the initiation of ST, including Baseline score, and scores at 2, 4, 6, 8, 10, and 12 months.

These definitions and analyses are further detailed in the SAP.

Other attributes: As per Primary Efficacy Estimand (Section 9.3.1.1.1)

Estimator and estimates: As per Primary Efficacy Estimand (Section 9.3.1.1.1)

Supporting statistics: As per Primary Efficacy Estimand (Section 9.3.1.1.1)

Supplementary analyses: As per Primary Efficacy Estimand (Section 9.3.1.1.1)

9.3.1.1.3 Key Secondary Efficacy Estimand: MDS-UPDRS Part III subscale and Part III early-stage PD subscore at 12 months

In collaboration with the Critical Path for Parkinson's (CPP) consortium, UCB is developing a subscore more specifically targeted at the early-stage PD population based on items from the

MDS-UPDRS Part III subscale. A new estimand is proposed based on this early-stage PD (ePD) subscore measured up to Month 12.

Participant-level endpoint

MDS-UPDRS Part III subscale or ePD subscore measured bimonthly over 12 months or up to the initiation of ST, including Baseline score, and scores at 2, 4, 6, 8, 10, and 12 months.

ICEs and handling strategies

A different 'hypothetical' handling strategy of ST initiation will be implemented, where Month 12 data recorded after a participant initiates ST will be corrected using a de-mediation approach.

Prior to the de-mediation approach, intermittent missing data will be imputed using multiple imputation (MI) according to randomized treatment and ST intake status.

Population-level summary

The population-level summary of interest will be the difference in target population mean observed MDS-UPDRS Part III subscale/ePD subscore at Month 12 as if the participants had not initiated ST between the following treatment arms:

- UCB0599 high dose (360mg/day) and placebo
- UCB0599 low dose (180mg/day) and placebo

Estimator

Monotone missing data from participants who dropped out of the study will be imputed using reference-based imputation (RBI) and according to ST intake status.

Imputed datasets for those dropouts will be summarized into a single dataset to obtain Month 12 estimates, which will then be combined with the de-mediated Month 12 estimates.

An analysis of covariance (ANCOVA) will be applied to the complete Month 12 data. Treatment will be included in the model as a categorical fixed effect, gender, age at Baseline, and Baseline MDS-UPDRS Part III subscale (ePD subscore) data will be fitted as covariates.

Estimates

Estimates for the treatment effects of interest (see above) at Month 12 (MDS-UPDRS units difference) adjusted for gender and age at Baseline, with corresponding 95% CIs.

9.3.1.1.4 Secondary Efficacy Estimands: MDS-UPDRS Part I/II subscales at 12 months ("De Jure" Estimands)

Participant-level endpoint

MDS-UPDRS Part I/Part II measured bimonthly over 12 months or up to the initiation of ST, including Baseline score, and scores at 2, 4, 6, 8, 10, and 12 months.

ICEs and handling strategies

For MDS-UPDRS Part I/II subscales, ST will be handled using a 'hypothetical' strategy, where post-ICE data will be censored.

Population-level summary

Difference in population mean MDS-UPDRS Part I/II subscales over 12 months (in the absence of concomitant ST intake) between:

- UCB0599 high dose (360mg/day) and placebo
- UCB0599 low dose (180mg/day) and placebo

Estimator

See Section 9.3.1.2.3 (LMEM estimator based on Baseline to Month 18 data).

Estimates

Estimates for the treatment effects of interest (see above) at 8, 10, and 12 months (MDS-UPDRS units difference at month specified) adjusted for gender and age at Baseline, with corresponding 95% CIs.

9.3.1.1.4.1 Supplementary Efficacy Estimand to MDS-UPDRS Part I/II subscales at 12 months ("De Facto" Estimand)

Participant-level endpoint

MDS-UPDRS Part I/Part II subscale measured bimonthly over 12 months regardless of concomitant initiation of ST, including Baseline score, and scores at 2, 4, 6, 8, 10, and 12 months.

ICEs and handling strategies: As per the Supplementary Efficacy Estimand (Section 9.3.1.1.1.1).

Population-level summary

Difference in population mean MDS-UPDRS Part II subscale at 12 months, regardless of concomitant ST intake, between:

- UCB0599 high dose (360mg/day) and placebo
- UCB0599 low dose (180mg/day) and placebo

Estimator, estimates, and sensitivity analyses:

See Section 9.3.1.2.0.1 (LMEM estimator based on Baseline to Month 18 data).

9.3.1.1.5 Exploratory Efficacy Endpoints at 12 months

- Time to worsening in MDS-UPDRS Part I subscale
- Modified Hoehn and Yahr staging
- SE-ADL
- CGII
- CGIS
- Fatigue-PRO
- Early PD Function Slowness PRO
- Early PD Mobility PRO

- Composite endpoint (based on MDS-UPDRS and/or Early PD PROs)
- PGIS, overall and fatigue-specific
- PGIC, overall and fatigue-specific
- HADS
- Starkstein Apathy Scale
- MDS-NMS
- EQ-5D-5L
- Wearable sensor

Details of these analyses are provided in the SAP.

9.3.1.2 Analysis of "Clinical symptoms at 18 months"

To demonstrate the superiority of UCB0599 over placebo with regard to clinical symptoms of disease progression **over 18 months** in participants diagnosed with early-stage PD.

9.3.1.2.1 Key Secondary Efficacy Estimand: MDS-UPDRS Parts I-III sum score at 18 months ("De Jure" Estimand)

Participant-level endpoint

MDS-UPDRS Parts I-III sum score measured bimonthly over 18 months in the absence of concomitant ST intake, including Baseline score, and scores at 2, 4, 6, 8, 10, 12, 14, 16, and 18 months.

ICEs and handling strategies

As per Primary Efficacy Estimand (Section 9.3.1.1.1).

Population-level summary

Difference in population mean MDS-UPDRS Parts I-III sum score at 18 months in the absence of concomitant ST intake between:

- UCB0599 high dose (360mg/day) and placebo
- UCB0599 low dose (180mg/day) and placebo

Estimator

A LMEM for longitudinal data/repeated measures, similar to the one described for the Primary Efficacy Estimand Estimator (Section 9.3.1.1.1) but with time set as a categorical variable, will be applied to the data up to the initiation of ST.

Estimates

Estimates for the treatment effects of interest (see above) at 18 months (MDS-UPDRS units difference) adjusted for gender and age at Baseline, with corresponding 95% CIs.

9.3.1.2.1.1 Supplementary Efficacy Estimand: MDS-UPDRS Parts I-III sum score at 18 months ("De Facto" Estimand)

Participant-level endpoint

MDS-UPDRS Parts I-III sum score measured bimonthly over 18 months, regardless of concomitant ST intake, including Baseline score, and scores at 2, 4, 6, 8, 10, 12, 14, 16, and 18 months.

ICEs and handling strategies

As per the Supplementary Efficacy Estimand (Section 9.3.1.1.1.1)

Population-level summary

Difference in population mean MDS-UPDRS Parts I-III sum score at 18 months, regardless of concomitant ST intake between:

- UCB0599 high dose (360mg/day) and placebo
- UCB0599 low dose (180mg/day) and placebo

Estimator

A LMEM for longitudinal data/repeated measures, similar to the one described for the Supplementary Efficacy Estimand to the Primary Estimand (Section 9.3.1.1.1.1), with time set as a categorical variable, will be applied to all observed data, up to the end of the intended follow-up period, including ST data.

Estimates

Estimates for the treatment effects of interest (see above) at 18 months (MDS-UPDRS units difference) adjusted for gender and age at Baseline, with corresponding 95% CIs.

9.3.1.2.2 Key Secondary Efficacy Estimand: Worsening on MDS-UPDRS Part III subscale at 18-month ("De Jure" Estimand)

Participant-level endpoint

Time from Baseline to the participant's *first* 5-point increase in MDS-UPDRS Part III subscale (or to last censored time observation due to initiation of ST) within the 18-month period.

ICEs and handling strategies

The main ICE will be initiation of ST, and will be handled using a 'composite' strategy where initiation of ST is part of the endpoint definition. Study termination and loss to follow up will be handled using a 'hypothetical' strategy where post-ICE data is set to missing. For all other ICEs, see Table 9-2.

Population-level summary

Difference in target population RMET, in this case, time to 5-point increase in MDS-UPDRS Part III subscale, within the 18-month period in the absence of concomitant ST intake between:

- UCB0599 high dose (360mg/day) and placebo
- UCB0599 low dose (180mg/day) and placebo

An RMET analysis has been chosen as (i) it has been shown to be a robust method under no-PH, (ii) it can be estimated even under heavy censoring, and (iii) it has an easy clinical interpretation as the average time until an event occurs during a defined time period ranging from time 0 to a specific follow-up time point (Royston and Parmar, 2013).

Estimator

The RMET will be estimated as the area under the Kaplan-Meier 'survival' curve up to a prespecified point in time (Royston & Parmar, 2013) or in other words, the integral of the survival function over the study period. However, a modeling approach will need to be used here in order to adjust for gender. As the main analysis for time to the *first* 5-point increase in MDS-UPDRS Part III subscale, RMET from Baseline to the last observed event time will be estimated. This will be done by fitting a generalized linear model with a linear link function for the RMET, with gender and age at Baseline as covariates and treatment group as the effect of interest. Further details on this analysis will be given in the SAP.

Estimates

Estimates for the treatment effects of interest (see above) within the 18-month period assessed (time difference in months) adjusted for gender and age at Baseline, with corresponding 95% CI.

Sensitivity analyses

The RMET will be estimated for each combination of treatment group and gender as the area under the Kaplan-Meier "survival" curve up to the last observed event time (ie, without using a modeling approach). A plot of these Kaplan-Meier curves will also be produced.

9.3.1.2.3 Secondary Efficacy Estimand: MDS-UPDRS Part I/Part II/Part III subscales at 18 months ("De Jure" Estimand)

Participant-level endpoint

MDS-UPDRS Part I/Part II/Part III measured bimonthly over 18 months or up to the initiation of ST, including Baseline score, and scores at 2, 4, 6, 8, 10, 12, 14, 16, and 18 months.

ICEs and handling strategies

For MDS-UPDRS Part II and Part III, ST initiation will be handled using a 'hypothetical' strategy, where post-ICE data will be censored.

For MDS-UPDRS Part I, ST initiation will be handled using a 'treatment policy' strategy, where post-ICE data are kept as part of the analysis.

Population-level summary

Difference in population mean MDS-UPDRS Parts I/II/III subscale at 18 months, in the absence of concomitant ST intake for Part II/III, or regardless of concomitant ST initiation for Part I between:

- UCB0599 high dose (360mg/day) and placebo
- UCB0599 low dose (180mg/day) and placebo

Estimator

A LMEM for longitudinal data/repeated measures, similar to the one described for the Primary Efficacy Estimand Estimator (Section 9.3.1.1.1) but with time set as a categorical variable, will be applied to the data.

Estimates

Estimates for the treatment effects of interest (see above) at 18 months (MDS-UPDRS units, difference) adjusted for gender and age at Baseline, with corresponding 95% CIs.

Sensitivity analyses

For MDS-UPDRS Part I and II, the main models will be refit using log-transformed data, as the normality assumption for the residuals does not appear to hold for this subscale when analyzing the PPMI data (UCB internal observation).

The main model for Part II and Part III will be refit, adjusting for Baseline predictors of early initiation of ST. For MDS-UPDRS Part II this analysis will be performed on log-transformed data. This sensitivity analysis will not be performed for Part I.

9.3.1.2.3.1 Key Secondary Efficacy Estimand: MDS-UPDRS Part III subscale and Part III ePD subscore at 18 months

A new estimand based on the MDS-UPDRS Part III ePD subscore targeted at the early-stage PD population is proposed based on the data measured up to Month 18.

Participant-level endpoint

MDS-UPDRS Part III subscale or ePD subscore measured bimonthly over 18 months or up to the initiation of ST, including Baseline score, and scores at 2, 4, 6, 8, 10, 12, 14, 16, and 18 months.

ICEs and handling strategies

A different 'hypothetical' handling strategy of ST initiation will be implemented, where Month 18 data recorded after a participant initiates ST will be corrected using a de-mediation approach.

Prior to the de-mediation approach, intermittent missing data will be imputed using MI according to randomized treatment and ST intake status.

Population-level summary

The population-level summary of interest will be the difference in target population mean observed MDS-UPDRS Part III subscale/ePD subscore at Month 18 as if the participants had not initiated ST between the following treatment arms:

- UCB0599 high dose (360mg/day) and placebo
- UCB0599 low dose (180mg/day) and placebo

Estimator

Monotone missing data from participants who dropped out of the study will be imputed using RBI and according to ST intake status.

Imputed datasets for those dropouts will be summarized into a single dataset to obtain Month 18 estimates, which will then be combined with the de-mediated Month 18 estimates.

An ANCOVA will be applied to the complete Month 18 data. Treatment will be included in the model as a categorical fixed effect, gender, age at Baseline, and Baseline MDS-UPDRS Part III subscale (ePD subscore) data will be fitted as covariates.

Estimates

Estimates for the treatment effects of interest (see above) at Month 18 (MDS-UPDRS units difference) adjusted for gender and age at Baseline, with corresponding 95% CIs.

9.3.1.2.3.2 Supplementary Efficacy Estimand: MDS-UPDRS Part II/Part III subscales at 18 months ("De Facto" Estimand)

Participant-level endpoint

MDS-UPDRS Part II/III subscales measured bimonthly over 18 months, regardless of concomitant ST intake, including Baseline score, and scores at 2, 4, 6, 8, 10, 12, 14, 16, and 18 months.

ICEs and handling strategies: As per the Supplementary Efficacy Estimand (Section 9.3.1.1.4.1).

Population-level summary

Difference in population mean MDS-UPDRS Parts II/III at 18 months, regardless of concomitant ST intake between:

- UCB0599 high dose (360mg/day) and placebo
- UCB0599 low dose (180mg/day) and placebo

Estimator, estimates, and sensitivity analyses

As per Supplementary Efficacy Estimand (Section 9.3.1.2.1.1). For MDS-UPDRS Part II, this supplementary analysis will be carried out on log-transformed data.

9.3.1.2.4 Secondary Efficacy Estimand: MDS-UPDRS Part II emerging symptoms over 18 months

Participant-level endpoint

The emerging symptoms based on MDS-UPDRS Part II (Tosin et al, 2022) for individual participants are derived using the following steps:

Identify the symptoms not present at Baseline, ie, MDS-UPDRS Part II items with score '0' at Baseline.

For the items identified in step 1, calculate change from Baseline at each visit. The participant is considered to have an emerging symptom for the item, if the change from Baseline for the item is greater than 0 for 2 consecutive visits. The magnitude of change from Baseline will not be considered to determine the emerging symptom.

The sum of emerging symptoms for all items identified in step 1 is used as participant-level endpoint.

The annualized rate of events is calculated as total number of emerging symptoms divided by total duration of follow-up.

ICEs and handling strategies

ST will be handled using a 'treatment policy' strategy, where post-ICE data are kept as part of the analysis. Study termination and loss to follow up will be handled using a 'hypothetical' strategy (ie, rate of occurrence of the events is calculated only for observed duration).

Population-level summary

Ratio of annualized rate of emerging symptoms based on MDS-UPDRS Part II over 18 months period between:

- UCB0599 high dose (360mg/day) and placebo
- UCB0599 low dose (180mg/day) and placebo

Estimator

The annualized rate will be estimated using negative binomial regression. The model will include gender and age as covariates and log of observed duration as off-set. Further details on this analysis will be given in the SAP.

Estimates

Estimates for the treatment effects of interest (see above) over the 18-month period adjusted for gender and age at Baseline with corresponding 95% CI.

9.3.1.2.5 Secondary Efficacy Estimand: MoCA over 18 months

Participant-level estimand

MoCA at 18 months, regardless of concomitant ST intake.

ICEs and handling strategies

It will be assumed that the symptoms measured by the MoCA questionnaire are not affected by the recommended rescue medications, ie, levodopa, and as such ST initiation will be handled using a 'treatment policy' strategy, where post-ICE data are kept as part of the analysis.

Population-level summary

Difference in target population mean MoCA at 18 months, regardless of concomitant ST intake between:

- UCB0599 high dose (360mg/day) and placebo
- UCB0599 low dose (180mg/day) and placebo

Estimator

An ANCOVA on data observed at 18 months will be applied to all observed MoCA data pairs (Baseline and 18-month data), ie, completers analysis.

Treatment (placebo as reference) will be fitted as a categorical Fixed effect. Baseline MoCA data, gender and age at Baseline will be fitted as covariates.

Estimates

Estimates for the treatment effects of interest (see above) at 18 months (MoCA units difference), adjusted for gender and age at Baseline, with corresponding 95% CIs.

Supporting statistics

To support clinical interpretation, the following descriptive statistics will be reported separately for each treatment group:

1. Observed MoCA and change from Baseline (mean, median, SD, IQR, range) for participants who have not initiated ST.
2. Observed MoCA and change from Baseline (mean, median, SD, IQR, range) for participants who have initiated ST.

9.3.1.2.6 Exploratory Efficacy Endpoints at 18 months

- Time to worsening in MDS-UPDRS Part I subscale
- Modified Hoehn and Yahr staging
- CGII
- CGIS
- Fatigue-PRO
- Function Slowness PRO
- Mobility PRO
- Composite endpoint (based on MDS-UPDRS and/or Early PD PROs)
- PGIS, overall and fatigue-specific
- PGIC, overall and fatigue-specific
- SE-ADL
- HADS
- MDS-NMS
- Starkstein Apathy Scale
- EQ-5D-5L

9.3.2 Analysis of the Secondary Efficacy Objective: "Neurodegeneration at 12 and 18 months"

To demonstrate the superiority of UCB0599 over placebo with regard to neurodegeneration of dopaminergic neurons **over 12 and 18 months** in participants diagnosed with early-stage PD.

9.3.2.1 Secondary Efficacy Estimand: DaT-SPECT mean Striatum SBR at Month 12 and Month 18

Participants who do not have a Month 12 DaT-SPECT scan will only have their Baseline and 18 months' data included in these analyses.

Participant-level endpoint

Change from Baseline (Screening) in DaT-SPECT mean Striatum SBR measured at Month 12 and Month 18, regardless of concomitant ST intake.

ICEs and handling strategies

It will be assumed that the DaT-SPECT signal will not be affected by the recommended rescue medication (levodopa).

ST initiation will be handled using a 'treatment policy' strategy, where post-ICE data are kept as part of the analysis.

Population-level summary

Difference in population mean change from Baseline (Screening) in DaT-SPECT mean Striatum SBR at Month 12 and Month 18 regardless of concomitant ST intake between:

- UCB0599 high dose (360mg/day) and placebo
- UCB0599 low dose (180mg/day) and placebo

Estimator

A LMEM for longitudinal data ANCOVA on change from Baseline (Screening) data will be applied to all observed data.

Time (visit), treatment (placebo as reference) and treatment by time (visit) will be fitted as categorical fixed effects. Participant will be fitted as a random intercept.

Baseline (Screening) DaT-SPECT mean Striatum SBR, gender, and age at Baseline will be fitted as covariates.

Estimates

Estimates for the treatment effects of interest (see above) at Month 12 and Month 18 (DaT-SPECT SBR units difference), adjusted for gender and age at Baseline, with corresponding 95% CIs.

Sensitivity analyses

The model described in the previous section will be run on the original data (as opposed to the change from Baseline data).

An additional LMEM will be fitted to the original data, with Baseline data included as part of the response/dependent variable, rather than as a covariate, and time as continuous (instead of categorical) so as to estimate the slope between Baseline and Month 18).

Supporting statistics

To support clinical interpretation, the following descriptive statistics will be reported separately for each treatment group:

1. Observed DaT-SPECT mean striatum SBR and change from Baseline (Screening) (mean, median, SD, IQR, range) for participants who have not initiated ST.
2. Observed DaT-SPECT mean striatum SBR and change from Baseline (Screening) (mean, median, SD, IQR, range) for participants who have initiated ST.
3. Number of participants who discontinued treatment due to lack of efficacy.
4. Number of participants who discontinued treatment due to AEs.

9.3.2.2 Exploratory Efficacy Endpoints at Month 12 and Month 18

- DaT-SPECT mean SBR in striatal subregions
- CSF total ASYN
- CSF ASYN oligomers/seeding capacity

Further details will be given in the SAP.

9.3.3 Analysis of the Secondary Efficacy Objective: "Intake of ST at 12 and 18 months"

To assess the effect of UCB0599 vs placebo with regard to intake of ST over 18 months in participants diagnosed with early-stage PD.

9.3.3.1 Secondary Efficacy Estimand: Time to ST initiation over 18 months

Participant-level endpoint

Time from Baseline to initiation of ST or to last censored time observation within the 18-month period.

ICEs and handling strategies

Observations for some participants will end prior to occurrence of the event of interest, ie, start of ST. This is known as "right-censoring" adjusted in the time-to-event analysis by using actual observed times.

The main ICEs will be study termination and lost to follow up: both will be handled using a 'hypothetical' strategy where the post-ICE data will be set to missing.

Population-level summary

An RMET was chosen as it has been shown to be a robust method when the proportional hazards assumption does not hold, it can be estimated even under heavy censoring and it has an easy clinical interpretation (Royston and Parmar, 2013).

The RMET can be interpreted as the average time until an event occurs during a defined time period ranging from time 0 to a specific follow-up time point.

The difference in target population RMET (here, time to initiation of ST) up to the last observed event time within the 18-month period will be estimated between:

- UCB0599 high dose (360mg/day) and placebo
- UCB0599 low dose (180mg/day) and placebo

Estimator

The RMET from Baseline to the last observed event time will be estimated. This analysis will use the same modeling approach as described for the MDS-UPDRS Part III subscale time to worsening analysis (see Section 9.3.1.1.3 for further details). By default, this approach makes the assumption that the right-censoring mechanism is homogeneous among all participants, which may not be a valid assumption in this study; right-censoring in the context of this analysis will come from study termination and it is possible that termination may be higher or lower in the UCB0599 arms compared to placebo. To counter this potential bias, treatment group-specific weights will be obtained by applying the Kaplan-Meier estimation method separately to each group (ie, using treatment group as a stratification variable in the RMET model).

Estimates

Estimates for the treatment effects of interest (see above) within the 18-month period assessed (time difference in months) adjusted for gender and age at Baseline, with corresponding 95% CI.

Sensitivity analyses

1. The RMET will be estimated for each combination of treatment group and gender as the area under the Kaplan-Meier "survival" curve up to the last observed event time (ie, without using a modeling approach). A plot of these Kaplan-Meier curves will also be produced.

Supporting statistics

To support clinical interpretation, the following descriptive statistics will be presented for each treatment group: proportion of participants who initiated ST at 12 and 18 months, overall.

9.3.3.1.1 Supplementary Efficacy Estimand: Time to ST initiation over 18 months

As a supplementary analysis, a Cox regression model will be fitted to all observed data since this is the traditional way of modeling time-to-event data. This approach assumes proportional hazards for all individuals. Further details on this analysis will be given in the SAP.

9.3.3.2 Secondary Efficacy Estimand: Intake of ST at 18 months

Participant-level endpoint

Number of participants taking ST at 18 months, regardless of adherence to assigned study medication.

ICEs and handling strategies

The main ICEs will be study termination and lost to follow up: both will be handled using a 'hypothetical' strategy where the post-ICE data will be set to missing.

Population-level summary

Population ratio of odds of ST intake in the presence of UCB0599 over odds of ST intake in the absence of UCB0599 (ie, on placebo). In other words, population odds ratio in ST intake at 18 months between:

- UCB0599 high dose (360mg/day) and placebo
- UCB0599 low dose (180mg/day) and placebo

Estimator

Logistic regression of the effect of exposure to UCB0599 (high and low dose) on intake of ST at 18 months will be performed. Further details on this analysis will be given in the SAP.

Estimates

Estimates (odds ratios) for the treatment effects of interest (see above) at 18 months adjusted for gender and age at Baseline, with corresponding 95% CIs.

Sensitivity analyses

A relative risk regression will be carried out, and further details on this analysis will be given in the SAP.

Supporting statistics

To support clinical interpretation, the following descriptive statistic will be reported separately for each treatment group: proportion of participants on ST by 18 months.

9.3.3.3 Other Secondary Efficacy Estimand: Intake of ST at 12 months

Participant-level endpoint

Number of participants taking ST at 12 months, regardless of adherence to assigned study medication.

ICEs and handling strategies

The main ICE will be study termination and lost to follow up: both will be handled using a 'hypothetical' strategy where the post-ICE data will be set to missing.

Population-level summary

Population ratio of odds of ST intake in the presence of UCB0599 over odds of ST intake in the absence of UCB0599 (ie, on placebo). In other words, population odds ratio in ST intake at 12 months between:

- UCB0599 high dose (360mg/day) and placebo
- UCB0599 low dose (180mg/day) and placebo

Estimator

Logistic regression of the effect of exposure to UCB0599 (high and low dose) on intake of ST at 12 months will be performed. Further details on this analysis will be given in the SAP.

Estimates

Estimates (odds ratios) for the treatment effects of interest (see above) at 12 months adjusted for gender and age at Baseline, with corresponding 95% CIs.

Sensitivity analyses

A relative risk regression will be carried out, and further details on this analysis will be given in the SAP.

Supporting statistics

To support clinical interpretation, the following descriptive statistics will be reported separately for each treatment group: proportion of participants on ST by 8, 10, and 12 months.

9.3.3.4 Exploratory Efficacy Endpoint at 18 months

- Levodopa cumulative daily dose

9.3.4 Subgroup analyses

Analyses by subgroup will be performed as part of exploratory analyses.

9.3.5 Center effects

Since treatment assignment will not necessarily be balanced across countries or sites, no statistical analyses will be carried out to investigate center effects. However, for the primary endpoint and for some prespecified secondary endpoints, summary statistics will be produced by country and region (Europe and North America). Further details on which endpoints will be summarized and which summary statistics will be presented will be given in the SAP.

If the inspection of the summary statistics tables (taking into account the number of study participants recruited at each center) leads to concerns with regards to a potential differential effect from specific centers on the overall study outcome, sensitivity analyses may be performed excluding the concerning centers. These sensitivity analyses will be performed as part of an exploratory SAP and will not be reported in the clinical study report.

In addition, in response to the current pandemic situation, COVID-19 and COVID-19 vaccination summaries will be presented by country and region; additional details will be presented in the SAP.

9.4 Planned safety and PK analyses

9.4.1 Safety analyses

Safety will be assessed by analyzing incidence of any TEAE, 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 PK analyses

Predose (trough, maximum of 15 minutes prior to next dose intake) and between 1 to 6 hours postdose (first dose on that day) blood samples will be collected to measure UCB0599 and

N-oxide-metabolite plasma concentrations at the specified visits in the Schedule of Activities (Section 1.3).

The plasma concentrations will serve to collect further PK properties of UCB0599 and its N-oxide-metabolite, and these properties will be reported descriptively in the clinical study report. Detailed information on sample analysis will be provided in a bioanalysis report. The relationship between UCB0599 concentration and efficacy, pharmacodynamic or biomarker, and other (safety) endpoints may also be assessed. All collected concentration-time data will further be used to derive population approach PK parameters, and such models will be developed and reported separately.

In addition, CSF samples will be collected as described in the Schedule of Activities (Section 1.3) to measure concentrations of UCB0599 and its N-oxide metabolite.

9.5 Handling of ICEs, protocol deviations, and resulting missing data

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

- 'Treatment policy': all data will be included in the analysis regardless of whether the participant remains on the assigned investigational treatment or discontinued. This 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 occurred completely at random. In this case, all post-ICE data are set as missing (removed) and imputed under the assumption of missing at random (MAR). This strategy can be applied to ICEs which are considered uninformative with respect to the definition of the intervention effect of interest, ie, treatment efficacy. As a default approach, this strategy will be applied to any occurrence of an ICE affecting the existence of measurements and maximum likelihood (ML) imputation will be used. Alternative imputation approaches will also be considered for ICEs which are considered informative with respect to the effect of interest, ie, treatment-related study termination, such as RBI approaches. 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 be used for the MDS-UPDRS Part III time to worsening analyses; a composite endpoint of time to worsening or time to ST initiation will be used as ST initiation is considered representative of a negative outcome.

An overview of handling strategies for MDS-UPDRS ICEs and study termination is presented in Table 9-2. For details on the handling strategies for all estimands (including approaches to imputation and de-mediation), please see the SAP.

Table 9-2: Overview of handling strategies for MDS-UPDRS ICEs and study termination

	MDS-UPDRS Part I-III sum score and Part I/II/III subscales		
Estimand	**Primary, key secondary and secondary**	**Key secondary**	**Secondary and supplementary**
	In the absence of ST	Initiation of ST as part of the response	Regardless of ST
Population summary measure	**For Part I-III sum score**: Difference in slope of progression at 12 months (primary) and difference in mean at 18 months (key secondary) **For Part III subscale:** Difference in slope of progression at 12 months (key secondary) **For Part III subscale and Part III ePD subscore:** Difference in mean at 18 months (key secondary) **For Part I/II subscale:** Difference in mean at 12 and 18 months (secondary)	**For Part III subscale:** Difference in RMET (time to *first* 5-point increase) within 18 months (key secondary)	**For Part I-III sum score**: Difference in mean at 12 and 18 months (supplementary) **For Part II/III subscales:** Difference in mean at 12 and 18 months (supplementary) **For Part II subscale:** Ratio of annualized rates in emerging symptoms within 18 months (secondary) **For Part I subscale:** Difference in mean at 12 and 18 months (secondary)
ICE			
Symptomatic treatment[a]	Hypothetical (set post-ICE data to missing)	Composite (ICE is part of the endpoint)	Treatment policy (include post-ICE data)
AE-related treatment discontinuation	Treatment policy (include post-ICE data)	id	id
Treatment discontinuation	Treatment policy (include post-ICE data)	id	id

Table 9-2: Overview of handling strategies for MDS-UPDRS ICEs and study termination

	MDS-UPDRS Part I-III sum score and Part I/II/III subscales		
Estimand	**Primary, key secondary and secondary**	**Key secondary**	**Secondary and supplementary**
(all other causes)			
Other protocol deviations - important	Hypothetical (set post-ICE data to missing)	id	id
Other protocol deviations – minor[b]	Treatment policy (include post-ICE data)	id	id
Death or serious injury (all causes)	Hypothetical (set post-ICE data as missing)	id	id
Confirmed or suspected cases of COVID-19 without other ICE or study termination	Treatment policy (include post-ICE data)	id	id
COVID-19 Vaccination	Treatment policy (include post-ICE data)	id	id
Study termination and loss to follow-up			
Treatment-related	Hypothetical (set post-termination data as missing)	id	id
Other/unknown causes	Hypothetical (set post-termination data as missing)	id	id

AE=Adverse effects, COVID-19=Coronavirus Disease-2019; ICE=intercurrent event, id=idem, "the same", MDS-UPDRS=Movement Disorder Society Unified Parkinson's Disease Rating Scale, RMET=Restricted (t-year) mean event time, SAP=Statistical analysis plan, ST=Symptomatic treatment

Note: The handling strategies are defined as follows: 'treatment policy' – include post-ICE data; 'hypothetical' – set post-ICE data as missing; 'composite' - ICE data is part of the endpoint.

[a] Where the participant did not respect the Washout Period for the ST, the visit data will be censored from the analysis.

[b] In case of an event preventing a participant from attending a particular scheduled clinic visit with a MDS-UPDRS assessment (for example, due to COVID-19), this will be considered a minor protocol deviation and MDS-UPDRS data collected for this participant in clinic at future visits will be included in the analyses. When MDS-UPDRS is collected at home rather than in clinic not all MDS-UPDRS data will be collected (rigidity assessments will be missing) and the Part III and total scores cannot be calculated.

9.5.1 ICEs potentially affecting the interpretation of measurements

Symptomatic Treatment Initiation

Initiation of ST will be the main ICE affecting the interpretation of measurements. Handling of ST initiation as an ICE may vary depending on the exact type of ST prescribed; further details will be given in the SAP.

MDS-UPDRS

Initiation of ST will be considered to impact the definition of the intervention effect of interest when measured using MDS-UPDRS Part I-III sum score as well as using MDS-UPDRS Part II and Part III subscales.

In the primary estimand analysis, the post-ICE data will be censored/set to missing ('hypothetical' strategy –assuming data is missing at random) and the data will be analyzed using a likelihood-based method of analysis, ie, an LMEM for longitudinal data/repeated measures with its implicit imputation approach (White et al, 2012) applied to all participants in the target population. This type of analysis will be referred to as 'in the absence of early ST initiation'.

An alternative 'hypothetical' strategy handling of ST initiation will also be implemented where Month 18 data (or Month 12 data, as applicable) recorded after a participant initiates ST will be corrected using a de-medication approach.

In the supplementary analysis to the primary estimand, the post-ICE data will be included in the analysis ('treatment policy' strategy) provided the participant has complied with the 12-hour washout period (see Section 6.5.3) required prior to the MDS-UPDRS Part III of the MDS-UPDRS assessment. Where the participant did not respect the washout period for the ST, the visit data will be censored from the analysis. This type of analysis will be referred to as 'regardless of early ST initiation'.

DaT-SPECT

A secondary endpoint will be the mean striatal dopamine receptor SBR as measured by DaT-SPECT. In this study, it will be assumed that DaT-SPECT signal is not affected by initiation of ST although there have been some reports of marginal impact (reviewed in Ikeda et al, 2019). Initiation of ST will be considered not to impact the definition of the intervention effect of interest for DaT-SPECT, and the post-ICE data will be included in this secondary estimand analysis 'regardless of early ST initiation' ('treatment policy' strategy). Missing data due to scan

not having taken place at the participant's or Investigator's discretion will be treated as missing at random.

Treatment discontinuation/nonadherence

Treatment discontinuation (see Section 7.1) will not be considered to impact the definition of the intervention effect of interest, and the post-ICE data will be included in the analyses ('treatment policy' 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 definition of the intervention effect of interest, and the post-ICE data will be included in the analyses ('treatment policy' strategy – see SAP for details).

Major treatment nonadherence or drug administration error will be considered uninformative with respect to the definition of the intervention effect of interest, and the post-ICE data will be censored in the analyses ('hypothetical' strategy – see SAP for details).

9.5.2 ICEs potentially affecting the existence of measurements

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). Where the cause for study termination is known to be unrelated to the assigned study medication, study termination will be considered uninformative with respect to the definition of the intervention effect of interest, and the post-ICE data will be set to missing ('hypothetical' strategy - see SAP for details).

As a default approach, this strategy, accompanied with the implicit imputation of likelihood-based models, will be applied to any occurrence of study termination and the event will be ignored. Alternative approaches such as imputation (eg, control-based mean imputation) as sensitivity analyses, will also be considered.

In well-designed clinical studies, it is reasonable to assume that dropout patterns follow the MAR mechanism, although missing not at random data cannot be ruled out (Liu-Seifert et al, 2015).

Local injuries (ie, to arms/hands or legs/feet for MDS-UPDRS and to head for DaT-SPECT), or systemic acute conditions such as a stroke or an accident-related coma may prevent the taking of measurements. Treatment-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 PD, although an accident may be the consequence of PD symptoms.

Parkinson's disease-related and non PD-related serious injury or death will be considered uninformative with respect the definition of the effect of the intervention of interest, and the post-ICE data will be set to missing in the analyses ('hypothetical' strategy – see SAP for details).

Loss to follow up will be considered uninformative with respect to the definition of the effect of the intervention of interest, and the post-ICE data will be set to missing in the analyses ('hypothetical' strategy – see SAP for details).

9.5.3 Other protocol deviations

Other protocol deviations which were not pre-defined as ICEs (Section 9.5.1 and Section 9.5.2) could also affect the conduct of the study and/or impact study participant safety as well as key efficacy or PK endpoints measurement.

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 pre-defined as ICEs) will be considered uninformative with respect to the definition of the effect of the intervention of interest, and the post-ICE data will be censored in the analyses ('hypothetical' strategy – see details in Section 9.5.1).

Minor protocol deviations (not pre-defined as ICEs) will be considered not to impact the definition of the effect of the intervention of interest, and the post-ICE data will be included in the analyses ('treatment policy' strategy – see details in Section 9.5.1).

The strategies for handling ICEs will be as follows:

'Treatment policy' will refer to an approach where all data will be included in the analysis, regardless of whether the participant remains on the assigned study medication or discontinued.

'Hypothetical' will refer to an approach where data will be modified to mirror its value shall an ICE had not happened (under some hypothetical conditions). One such hypothetical condition is that the ICE occurred completely at random. In this case, all post-ICE data are set as missing under the assumption of missing completely at random. This strategy can be applied to ICEs which are considered to be uninformative with respect to the definition of the intervention effect of interest (ie, treatment efficacy). As a default approach, this strategy will be applied to any occurrence of study termination and the event will be ignored. Alternative approaches such as imputation (eg, control-based mean imputation) as sensitivity analyses, will also be considered.

9.6 Planned analysis at 12 months and data monitoring

The primary analysis for the primary efficacy estimand (MDS-UPDRS Part I-III sum score) uses data from the first 12 months of the study; this analysis as well as the analyses for the secondary estimands at 12 months (where applicable) will be carried out at study end (see details in Section 9.3).

A limited team of independent pharmacometricians and statistical programmers with access to the 12-month data will be unblinded to prepare for the exposure-response analysis to be finalized following completion of the study. Details of unblinding will be described in the unblinding charter, and care will be taken to ensure that the blinded study team remains blinded until database lock. Details of the exposure-response analysis will be provided in a separate analysis plan. The results of the final exposure-response evaluation will be provided outside of the clinical study report at study finalization.

Data Monitoring Committee and SMC:

An independent DMC will conduct safety interim reviews of all available unblinded safety and PK data at the following time points:

- When safety data for 3 months of treatment (ie, until Visit 7) are available for 100 participants.
- When safety data for 3 months of treatment (ie, until Visit 7) are available for at least 50 participants per arm
- After at least 50% of the participants have been treated for 8 months (ie, approximately 75 participants per arm)
- After at least 50% of the participants have been treated for 14 months (ie, approximately 75 participants per arm), the DMC will review the available unblinded safety and PK data.
- Ad hoc as required.

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

An SMC will review (approximately every 3 months, with the option to adapt the frequency based on recruitment rates) the available blinded safety data at the following time points:

- After 5 participants/arm have been treated for 2 weeks
- After 25 participants/arm have been treated for 1 month
- After 50 participants/arm have been treated for 1 month
- After 75 participants/arm have been treated for 1 month
- After 100 participants/arm have been treated for 1 month
- Subsequent SMC meetings will occur every 3 months

Details will be described in a separate charter.

9.7 Determination of sample size

The sample size for this study was determined based on the primary efficacy estimand as detailed in the sections below. Approximately 645 participants will be screened to achieve 450 participants randomly assigned to study medication and 429 evaluable participants, for an estimated total of 143 evaluable participants per treatment group. Participants who terminate the study (withdraw consent) or are lost to follow-up will not be replaced.

The primary comparison of interest is UCB0599 high dose (360mg/day) vs placebo. Given the limitations in our understanding of the PK/PD properties of the compound, the calculations below apply to both comparisons (UCB0599 high dose [360mg/day] and placebo and UCB0599 low dose [180mg/day] and placebo) as similar assumptions for both doses are made with respect to variability and impact on progression.

9.7.1 Primary efficacy estimand

The first efficacy objective of PD0053 is to show superiority of UCB0599 over placebo with regard to clinical symptoms of disease progression over 12 months in participants diagnosed

with early-stage PD. To measure clinical symptoms of disease progression, the MDS-UPDRS Part I-III sum score was selected as the variable of interest for the Primary Estimand and the population-level summary was chosen as the difference in the population mean slope of progression between UCB0599 and placebo up to 12 months or up to the initiation of ST, whichever comes first.

Even though the duration of the study is 18 months, the sample size was estimated to ensure 90% power at 12 months, where the proportion of participants on ST is still limited. Beyond 18 months, the number of participants under ST is expected to increase with significant potential for bias between UCB0599 groups and the placebo groups (should the compound be active), and power decrease due to data loss. The primary analysis of MDS-UPDRS is therefore planned at 12 months, and additional analyses will be performed at 18 months including post-ST data in the analysis.

In order to derive the parameters of interest for sample size estimation, an Estimator similar to the one planned for the Primary Estimand (a LMEM for longitudinal data/repeated measures, with Time as a continuous fixed effect, ie, assuming linear development over 12 months, and identical random effects to account for within-participant correlation between repeated observations was applied to a subset of the PPMI 1.0 de novo cohort, an observational study of early-stage PD participants (Parkinson's Progression Markers Initiative, 2018). Further details on how participants were selected for inclusion in this analysis and how this analysis was carried out will be included in the SAP. This participant sample was assumed to be representative of the POC study placebo arm up to 12 months.

For the purpose of sample size estimation, a closed-form sample size formula for longitudinal data was used (Ahn et al, 2014). Further details on the use of this formula will be provided in the SAP.

A 5% data loss due to study termination by 3 months (all causes) will be assumed in this study, based on expert knowledge. The sample size will be inflated accordingly (see details below). Loss to follow up and loss to ST initiation by 3 months will be considered minimal in the study setting and ignored.

Based on observations from the PPMI cohort data (further details in the SAP), 35% data loss was assumed in the study at 12 months:

- 20% due to participants initiating ST, as they will be in a controlled setting and encouraged to delay start of ST intake for as long as it is deemed medically acceptable;
- 5% due to participants lost to follow up as well as to death and serious injury;
- 10% due to participants terminating the study (all causes).

Based on the parameters obtained from the analysis performed on the restricted PPMI dataset for the placebo arm, a sample size of 143 participants per arm (N=429 total), randomized at a 1:1:1 ratio to UCB0599 high dose, low dose or placebo would provide 90% power to detect a minimum of expected 30% decrease in population mean slope of PD disease progression (eq. to 0.27 MDS-UPDRS points/month or 3.2 points/year) in the active treatment groups compared with placebo over 12 months of treatment, with 10% type I error. The sample size will be inflated by 5% (N=14) to account for participants terminating the study by 3 months, leading to a final sample size of 450 participants (N=150/arm).

Since it is assumed that between 12 and 18 months another 10% data loss (at a minimum) will be lost due to initiation of ST and another 10% due to study termination/loss to follow up, analyses at 18 months will be carried out regardless of ST intake (all data included).

9.7.2 Power for key secondary efficacy estimand (MDS-UPDRS Part III)

A key secondary estimand to the primary efficacy objective of PD0053 is the difference in population mean slope of progression between UCB0599 and placebo at 12 months in the absence of concomitant ST intake for the MDS-UPDRS Part III subscale.

Using the same approach as described in Section 9.7.1, the sample size estimated to achieve 90% power on the Primary Efficacy Estimand, MDS-UPDRS Part I-III sum score, ie, 143 participants per arm, would provide 90% power to detect a minimum of expected 35% relative decrease in population mean slope of progression on the MDS-UPDRS Part III subscale (eq. to 0.19 points/month or 2.3 points/year) in the UCB0599 treatment groups compared with the placebo group over 12 months of treatment, with 10% type I error.

9.7.3 Power for secondary efficacy estimand (DaT-SPECT mean Striatum SBR)

A Secondary Efficacy Objective of PD0053 is to show superiority of UCB0599 over placebo with regards to neurodegeneration over 18 months in participants diagnosed with early-stage PD.

To assess neurodegeneration, the DaT-SPECT mean Striatum SBR was selected as a participant-level variable and the population-level summary chosen as the difference between UCB0599 and placebo in the population mean change from Baseline (Screening) at 18 months.

Change from Baseline (Screening) data was derived from the PPMI 1.0 de novo cohort DaT-SPECT mean Striatum SBR data. Further details on data selection for this analysis will be given in the SAP.

Using a 2-sample t-test based sample size formula and the parameters for the placebo arm obtained from the PPMI 1.0 de novo DaT-SPECT data analysis, the sample size estimated to achieve 90% power on the Primary Efficacy Estimand, MDS-UPDRS Part I-III sum score, ie, 143 participants per arm, would provide 90% power to detect a minimum of expected 37.5% relative increase in population mean change from Baseline in DaT-SPECT signal (equal to 0.067 SBR unit) in the UCB0599 groups vs the placebo group at 18 months, with 10% type I error, and assuming 25% data loss (ie, an extra 10% loss to occur between 12 and 18 months due to study termination and loss to follow up at 18 months with effective N=107/arm). Data loss due to initiation of ST does not apply for the assessment of the DaT-SPECT signal as the assumption is being made that levodopa and dopamine agonists do not affect the neurodegeneration of dopamine neurons in the midbrain.

To increase information regarding DaT-SPECT SBR signal, participants intending to terminate the study (assumed to be 10% by 12 months) should have a scan before study termination (as part of the EOT visit). Participants who choose to withdraw from the study at or after 6 months and accept to have a scan at time of study termination will have their scans analyzed as if it was taken at 12 months.

Residual data attrition due to study termination and loss to follow up may be imbalanced between treatment arms by the time participants reach the 18-month timepoint, creating selection

bias (further details are provided in the SAP). This residual bias will be addressed at the analysis stage.

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 an 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 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 IRB/IEC for its review and approval.

Before initiating a study, the Investigator will have written and dated full approval from the responsible 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 Investigator will not make any changes in the study or study conduct without 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 Investigator to obtain an expedited review by the IRB/IEC as allowed.

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

UCB (or its representative) will communicate safety information to the appropriate regulatory authorities 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. In France, participants will be given at least 3 days of reflection time before signing the ICF. For France-specific requirements, please refer to Section 10.9, Appendix 9.

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. A secure link to the eConsent web portal will be sent via email, along with unique login credentials. The participant will receive a prompt to change the temporary assigned password upon first login. The informed consent materials will be presented in the eConsent portal through an electronic rendition of the IRB/IEC-approved consent documents. The study Investigator and/or designated staff will complete the informed consent process with the participant by telephone. Participants who agree to take part in the study will provide their handwritten signature using a computer mouse, touchscreen, or stylus on a computer or tablet in the designated signature block; and the consenter will countersign.

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 United States 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. Throughout this study, all data forwarded to UCB (or designee) will be identified only by the participant number assigned at Screening.

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

The participant must 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.

10.1.5 Committees structure

An independent DMC will conduct safety interim reviews of all available unblinded safety and PK data and an SMC will regularly review the available blinded safety data as described in Section 9.6.

10.1.6 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.

10.1.6.1 Case Report form 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.

10.1.6.2 Apps

Not applicable.

10.1.7 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, quality of life 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).

10.1.8 Study and site closure

The Sponsor 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 study medication development

10.1.9 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 study medication 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 medication 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, respectively.
- 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 Indices: MCV MCH %Reticulocytes	WBC Count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
	RBC Count			
	Hemoglobin			
	Hematocrit			
Clinical Chemistry	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, leukocytes 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 alcohol test • Serum and urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[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. The results of each test must be entered into the eCRF.
Other Laboratory Tests	• RBC count and/or hemoglobin in CSF for quality control purposes

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 an SAE.

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

Investigators must document their review of each laboratory safety report.

Laboratory results 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: AEs – 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 Meeting 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.

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 an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A 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 an 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 (NCI-CTCAE) 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 Investigator's Brochure (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 an 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 an 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

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

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 one of the non-estrogen 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 woman of childbearing potential 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
Implantable progestogen only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • 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, PI should consider the correct timing of starting/applying such methods in relation to the menstrual cycle and the manufacturing instruction as 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

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test.
- Additional pregnancy testing should be performed at each visit during the Treatment Period and at the SFU visit and as required locally. In France, pregnancy testing should be performed monthly. For France-specific requirements, please refer to Section 10.9, Appendix 9.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.
- Pregnancy testing, with a sensitivity of 25 mIU/mL will be performed.

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. If the study participant is later found to be on placebo, then pregnancy data collection can stop.
- 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 one 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 an SAE and will be reported as such. Any post-study 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 an SAE through spontaneous reporting.

10.5 Appendix 5: Genetics

Use and Analysis of DNA

- Genetic variation may impact a participant's response to study medication, susceptibility to, and severity and progression of disease. Variable response to study medication may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated.
- DNA samples will be used for research related to UCB0599 or PD and related diseases. They may also be used to develop tests/assays including diagnostic tests related to UCB0599 and PD. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome.
- RNA samples will be analyzed for nonhereditary pharmacogenomics biomarkers. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to UCB0599 or study medications of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on UCB0599 continues but no longer than 20 years or other period as per local requirements.

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 >5 ULN. 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 (Table 10-1).

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 • Obtain blood sample for pharmacokinetic (PK) analysis as soon as possible after the most recent dose [e]

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.	• Serum creatine phosphokinase (CPK), lactate dehydrogenase (LDH), and (optional) gamma-glutamyl transferase (GGT) • 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 CRF • Record alcohol use on the liver event alcohol intake CRF • 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

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.

- 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] PK sample may not be required for participants known to be receiving placebo or non-comparator interventions. 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 CRF. 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: Wearable sensor AEs, adverse sensor effects, SAEs, and sensor deficiencies: definition and procedures for recording, evaluating, follow-up, and reporting

ADVERSE EVENTS

Physiological and environmental data obtained from the wearable sensor will not be used for safety monitoring and reporting of UCB0599 because the sensor is unvalidated for this purpose and will only be used for exploratory endpoints in this study.

The Investigator is expected to record any sensor-related AEs in the eCRF and assess causality as it might relate to the wearable sensor. The eCRF page will allow the Investigator to assess causality in relation to the wearable sensor.

Serious adverse events should be reported in the eCRF and expedited to the Sponsor according to the protocol.

The Sponsor will send reports of SAEs relating to the Wearable sensor to Verily so that the manufacturer can comply with its reporting obligations.

SENSOR DEFICIENCIES

Sensor deficiencies, also referred to as sensor performance issues, are defined as inadequacies of a wearable sensor with respect to its identity, quality, durability, reliability, safety, or performance. Upon identification of sensor deficiencies, participants will be provided with replacement sensor(s), and the sensor(s) will be returned when possible to Verily using a Return Materials Authorization number for failure analysis investigation. All sensor deficiencies will be reported in the appropriate eCRF.

SENSOR ACCOUNTABILITY

Sensors must be kept in a locked, secure location and may only be handled by trained clinical site staff. The Principal Investigator or an authorized designee shall keep records documenting the receipt, use, and return of wearable sensors, which shall include: The date of receipt, identification of each wearable sensor (batch number/serial number or unique code), the expiration date (if applicable), the date(s) of use, participant identification and date on which the wearable sensor was returned (if applicable). At the end of the clinical investigation, the sensor inventory records will be returned to the Verily and copies will be kept in the Study Binder at the investigational sites.

DATA HANDLING

Verily will receive and securely store the raw data from the wearable sensor throughout the course of the study, providing reports of daily wearable sensor Compliance Data for each study participant on an ongoing basis. Following completion of the double-blind Treatment Period, Verily will receive from UCB the Verily Licensed Data for use in analyses to be conducted based on a mutually agreed upon data analysis plan.

PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM USE OF THE WEARABLE SENSOR

Participants are free to withdraw from using the wearable sensor at any time, without affecting their participation in the main study, and without prejudice to their continued care. A participant may withdraw at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.

If the study participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

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

10.8 Appendix 8: Rapid Alert Procedures

Not applicable

10.9 Appendix 9: Country-specific requirements

10.9.1 Specific requirements for Germany

The review of the protocol by the German Ethics Committee and Federal Office for Radiation Protection (Bundesamt für Strahlenschutz) led to the following specificity for Germany only which was implemented into the global protocol with Protocol Amendment 3, dated 04 Oct 2021:

Section 1.3 Schedule of Activities

The DaT-SPECT assessment at 12 months was removed, ie, no scan will be performed at M12 for German participants.

10.9.2 Specific requirements for France

The French National Agency for Medicines and Health Products Safety (Agence Nationale de Sécurité du Médicament et des Produits de Santé [ANSM]) and the French ethics committee (Comités de Protection des Personnes) made recommendations specific for France which were implemented into the global protocol with Protocol Amendment 3, dated 04 Oct 2021, and are reflected in the following sections:

Section 1.2 Schema

A note has been added to clarify that all visits are in-clinic visits in France.

Section 1.3 Schedule of Activities

- Footnote “b” was added to reflect that telemedicine is not implemented in the study in France and all visits are in-clinic only.
- Footnote “p”: The following country-specific requirement applies in France: Additional pregnancy testing will be performed monthly during the Treatment Period and at the SFU visit.

Section 4.1.1 Decentralized model

The following clarification (in bold) was added to clarify that the decentralized model is not applicable in France:

- The study will be conducted utilizing a partly decentralized model, ie, study visits may be composed of a combination of onsite visits and remote visits **(except in France; for France-specific requirements, please refer to Section 10.9, Appendix 9)**.

Section 5.2 Exclusion criteria

The following addition (in **bold**) applies in France for exclusion criterion 43:

- Vulnerable participants (eg, participants kept in detention, soldiers, adults with legally authorized representative, **participants who do not benefit from social security schemes such as health insurance)**, employees of the Sponsor or the CRO with direct involvement in the proposed study or other studies under the direction of the Investigator or the CRO, as well as family members of the employees or the Investigator.

Section 10.1.3 Informed consent process

The following clarification (in **bold**) regarding the reflection time during the informed consent process applies in France:

- Each participant will have the opportunity to discuss the study and its alternatives with the Investigator **and will be given at least 3 days of reflection time before signing the ICF.**

Section 10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

The following change applies in France in the second bullet under "Pregnancy testing":

- Additional pregnancy testing should be performed **monthly** during the Treatment Period and at the SFU visit and as required locally.

10.10 Appendix 10: Abbreviations and Trademarks

AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ASYN	alpha-synuclein
BP	blood pressure
BID	twice per day
BMI	body mass index
CGII	Clinical Global Impression of Improvement
CGIS	Clinical Global Impression of Severity
CI	confidence interval
CNS	central nervous system
COMT	catechol-O-methyltransferase
COVID-19	Coronavirus Disease-2019
CPP	Critical Path for Parkinson's
CRO	Contract Research Organization
CSF	cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A4	cytochrome P450 3A4
DaT-SPECT	Dopamine Transporter Imaging with Single Photon Emission Computed Tomography
DBP	diastolic blood pressure
DM	disease modification
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic Case Report form
EOT	End of Treatment

ePD	early-stage PD
EQ-5D-5L	Euro Quality of life 5-Dimensions 5-Level
EQ-VAS	EQ visual analogue scale
FAS	Full Analysis Set
FIH	first-in-human
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
IQR	interquartile range
HR	Hazard Ratio
HRT	hormone 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
LMEM	Linear Mixed Effect Model
MAO-B	Monoamine oxidase-B
MAR	missing at random
MDS-UPDRS	Movement Disorder Society Unified Parkinson's Disease Rating Scale
MDS-NMS	Movement Disorder Society Non-motor symptom scale
MI	multiple imputation
MoCA	Montreal Cognitive Assessments
MRI	magnetic resonance imaging
NDD	neurodegenerative disease
NOAEL	No observed adverse effect level
PD	Parkinson's disease
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity

PH	proportional hazard(s)
PK	pharmacokinetic(s)
POC	proof-of-concept
PPMI	Parkinson’s Progression Markers Initiative
PRO	patient-reported outcomes
PKS	Pharmacokinetic Set
QTcF	QT corrected for heart rate using Fridericia's formula
RBI	reference-based imputation
RMET	restricted (t-year) mean event time
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
SBP	systolic blood pressure
SBR	specific binding ratio
SD	standard deviation
SE-ADL	Schwab and England Activities of Daily Living
SFU	Safety Follow-up
SMC	Safety Monitoring Committee
SNCA	synuclein alpha
SS	Safety Set
ST	symptomatic treatment
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
VME	Virtual Motor Exam
WOCBP	women of childbearing potential

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 5 (30 Jun 2023)

Overall Rationale for the Amendment

PD0053 Protocol Amendment 5 was enacted to incorporate additional laboratory tests at 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 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The following changes were implemented:

Section # and Name	Description of Change	Brief Rationale
Section 1.2 Schema Section 1.3 Schedule of Activities	An in-clinic visit at Day 150 (Month 5) (Visit 8a) was added.	To increase the monitoring of liver function test parameters.
Section 2.3 Benefit/Risk assessment	Text was updated to delete hematological, gastrointestinal, and musculoskeletal effects from the list of potential risks, to clarify that the potential risk of hepatotoxicity is based on clinical data, to clarify 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 8 Study assessments and procedures	The maximum blood volume collected from each participant during the study was updated to 510mL.	To account for the blood sampling at the added study visit.
Section 8.3 Adverse events and serious adverse events	Text was updated to add that for results disclosure on public registries, TEAEs and treatment-emergent SAEs will be published.	To clarify the disclosure of TEAEs and treatment-emergent SAEs.
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.

10.11.2 Amendment 4 (24 Feb 2022)

Overall Rationale for the Amendment

Based upon a review of data from completed studies and available blinded data to date from PD0053, Protocol Amendment 4 was completed to amend exclusion and discontinuation criteria regarding renal function, diabetes, and ECG abnormalities. Clarifications were added throughout the protocol. The amended eligibility criteria are intended to better reflect the parameters in the targeted study population. The following changes were implemented:

Section # and Name	Description of Change	Brief Rationale
Global	Updates were made to the nomenclature and potential clinical presentations for hypersensitivity reaction, including updates to the role of the Investigator, SMC, and DMC in the assessment of hypersensitivity reactions and decisions on withholding dosing and restart, as well as updates to the activities for assessment and management of hypersensitivity reactions.	To increase clarity and consistency in the communication and actions required for the Important Identified Risk of Drug Hypersensitivity.
Global	Descriptions of the estimand for MoCA have been changed throughout to remove "change from Baseline."	To clarify that the analysis of the MoCA estimand is no longer a change from Baseline analysis due to different versions of the form being used at Screening and at 18 months.
Section 1.3 Schedule of Activities	Investigator assessment of ST benefit was removed.	To remove an assessment that is not captured in the study.
Section 1.3 Schedule of Activities	MoCA assessment at 12 months was removed.	To prevent bias on the MoCA assessment at 18 months since practice effects have been observed on repeating MoCA assessments (Wong et al, 2018). In addition, a different version of the MoCA will be used at 18 months compared to the Screening version. The MoCA assessment at 18 months (EOT) is considered the primary timepoint for MoCA.
Section 1.3 Schedule of Activities	CSF sampling timepoint in footnote "l" was updated from BL to V2 to match the Schedule of Activities table.	To correct an error.

Section # and Name	Description of Change	Brief Rationale
Section 3 Objectives and endpoints	CSF ASYN oligomers/seeding capacity was added as an Exploratory Efficacy Endpoint.	To further clarify the exploratory ASYN endpoints.
Section 4.2 Scientific rationale for study design	Text was added to support the use of the DaT-SPECT at Screening as an EMA-qualified tool and to provide additional information on the MoCA.	To further clarify the use of the DaT-SPECT at Screening and the MoCA throughout the study.
Section 5.1 Inclusion criteria	Inclusion criterion #4b (formerly #4a) on the DaT-SPECT reading was updated.	To further clarify the role of DaT-SPECT at Screening.
Section 5.2 Exclusion criteria	Exclusion criterion #22a (formerly #22) on diabetes was updated to remove the HbA1c value and specify that inclusion of participants with well controlled type 2 diabetes in line with local clinical practice is acceptable.	To allow investigators the discretion to decide what constitutes stable type 2 diabetes.
Section 5.2 Exclusion criteria	Exclusion criterion #23a (formerly #23), subcriterion "a" on QTcF was updated: the QTcF values for males and females that would lead to exclusion were specified.	To further clarify normal QTcF ranges in adult males and females in line with current ECG guidance.
Section 5.2 Exclusion criteria	Exclusion criterion #31a (formerly #31) on prohibited medication was split into drugs that may affect Parkinson's disease, and drugs that may affect the DaT-SPECT scan. The time frame of the prohibition was amended based on drug metabolism.	To clarify the exclusion criterion on co-medication.
Section 5.2 Exclusion criteria	Exclusion criterion #35a (formerly #35) on positive drug screen was updated to clarify that concomitant use of a medication would not lead to exclusion.	To allow enrollment of participants taking medications that may lead to a positive drug screen.

Section # and Name	Description of Change	Brief Rationale
Section 5.2 Exclusion criteria	Exclusion criterion #40b (formerly #40a) related to renal function was updated to revise subcriteria b, c, d, and e: further clarification was provided on Screening laboratory results considered acceptable.	To expand the enrolled population to those with mild and moderate renal impairment (KDIGO 2012 Clinical Practice Guideline) as representative of the target PD population.
Section 6.1 Treatments administered	Footnote "a" below the table was updated.	To correct an error.
Section 6.5.2 Prohibited concomitant treatments (medications and therapies)	The time frame for prohibited concomitant medications taken before DaT-SPECT imaging was amended based on drug metabolism.	To further specify the prohibition period for co-medication.
Section 7.1.4 Temporary Discontinuation	Text was updated to clarify that Investigator, SMC, or DMC (rather than the Sponsor in consultation with the DMC) may consider temporary discontinuation of dosing.	To clarify roles and responsibilities.
Section 7.1.5 Rechallenge	Text was updated to clarify that Investigator and SMC (rather than the Sponsor in consultation with the DMC) may consider rechallenge. Endorsement by the DMC may be obtained if the SMC requests this.	To clarify roles and responsibilities.
Section 7.2 Participant Discontinuation/Withdrawal from the study	Text was updated to clarify the role of SMC and DMC (in addition to the Investigator) in participant withdrawals.	To clarify roles and responsibilities.
Section 7.2 Participant Discontinuation/Withdrawal from the study	Discontinuation criterion #6 was updated to revise renal toxicity criteria.	To permit participants with clinically insignificant fluctuations in mild and moderate renal impairment (KDIGO 2012 Clinical Practice Guideline) to remain in the study.
Section 8.1.1.3 Dopamine Transporter Imaging with Single Photon Emission Computed Tomography	The time frame for prohibitied concomitant medications taken before DaT-SPECT imaging was updated.	To align with Section 6.5.2.

Section # and Name	Description of Change	Brief Rationale
Section 8.2.3 Vital signs	Text was updated to clarify that all pulse and BP readings (not only the average) will be recorded in the eCRF, and the average will be derived for analyses.	To specify what will be recorded in the eCRF.
Section 8.2.6 Suicidal risk monitoring	C-SSRS version and timepoint of assessment at study start were updated to align with the Schedule of Activities.	To correct an error.
Table 9-1 Overview of planned efficacy analyses	Terminology was updated from RMST to RMET; MDS-UPDRS Parts I/II/III subscales were separated out as individual endpoints; DaT-SPECT and ST intake at 12 months were added.	To further clarify the planned analyses.
Table 9-1 Overview of planned efficacy analyses	CSF ASYN oligomers/seeding capacity was added as an Exploratory Efficacy Endpoint.	To further clarify the exploratory ASYN endpoints.
Section 9.3 Planned efficacy/outcome analyses	The planned list of predictors of early initiation of ST was removed.	To move details into the SAP where the exact predictors used will be provided.
Section 9.3.1.1.1 Primary Efficacy Estimand: MDS-UPDRS Parts I-III sum score at 12 months ("De Jure" Estimand)	Sensitivity analysis #6 regarding exclusion of data collected from home visits was removed since home visits were rescheduled to be clinic visits to ensure the full range of MDS-UPDRS Part III items to be measured by a MDS-trained physician (ie, rigidity items cannot be measured by a visiting nurse).	To remove a sensitivity analysis that excludes home visit data; this analysis is no longer needed since there will be no MDS-UPDRS Part III data from home visits.
Section 9.3.1.1.5 Other Secondary Efficacy Estimand: MoCA at 12 months	Section was removed following removal of the MoCA assessment at 12 months.	To remove an analysis that is no longer needed.
Section 9.3.1.2.3 Secondary Efficacy Estimand: MDS-UPDRS Part I/Part II/Part III subscales at 18 months ("De Jure" Estimand)	The description of sensitivity analyses for MDS-UPDRS Part I/Part II/Part III was updated.	To further clarify the planned analyses.

Section # and Name	Description of Change	Brief Rationale
Section 9.3.1.2.5 Secondary Efficacy Estimand: MoCA over 18 months	The MoCA assessment originally planned at 12 months was removed, and therefore the analysis at 18 months was simplified to a post-Baseline analysis adjusted for Baseline (Screening) as a covariate because versions to be used at Screening and 18 months will differ.	To align with the change in the Schedule of Activities for the MoCA assessment due to possible practice effects.
Section 9.3.2.1.1 Supplementary Efficacy Estimand: DaT-SPECT mean Striatum SBR at 12 months	The planned analysis at 12 months was updated to be a change from Baseline analysis (instead of a post-Baseline analysis), with adjustment for Baseline as a covariate.	To improve the reporting of the analysis results.
Section 9.3.2.2 Exploratory Efficacy Endpoints at 12 and 18 months	CSF endpoints were updated to include CSF ASYN oligomers/seeding capacity in addition to CSF total ASYN.	To further clarify the exploratory ASYN endpoints.
Table 9-2 Overview of handling strategies for MDS-UPDRS ICEs and study termination	Footnotes "b" and "c" were added in order to clarify what should happen when (i) a participant did not respect the Washout Period for the ST, (ii) in case of an event preventing a participant from attending a particular scheduled clinic visit with a MDS-UPDRS assessment, and (iii) in case of MDS-UPDRS being collected at home rather than in clinic.	To further clarify the planned analyses with regard to handling of ICEs.
Section 9.5.1 ICEs potentially affecting the interpretation of measurements	A sentence was added to further clarify the handling of ST initiation as an ICE.	To make sure ST initiation is handled correctly when the presribed ST is not the medication recommended in the protocol (ie, levodopa).
Section 9.7 Determination of sample size	The number of participants planned to be screened, randomized, and evaluated was added.	To further clarify the sample size determination.
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.

Section # and Name	Description of Change	Brief Rationale
Throughout	Minor editorial and document formatting revisions.	Minor, therefore have not been summarized.

10.11.3 Amendment 3 (04 Oct 2021)

Overall Rationale for the Amendment

PD0053 Protocol Amendment 3, dated 04 Oct 2021, was completed to add a treatment arm with a lower dose of UCB0599 180mg/day (which will come into effect with the availability of the IMP for the low dose), allow the use of historical symptomatic treatments, and to harmonize feedback from regulatory authories and ethic review boards received during the initial Clinical Trial Applications (CTA). The following changes were implemented:

Section # and Name	Description of Change	Brief Rationale
Global	Where applicable, the wording "Study Watch" was renamed to "wearable sensor."	To emphasize that the watch is not investigated in the clinical study. The generic term "wearable sensor" is used throughout.
Global	"Study Hub" was renamed to "Wearable Sensor Hub."	To reflect the updates of the reference to the wearable sensor.
Global	"Device deficiencies" was replaced with "sensor deficiencies."	To reflect the updates of the reference to the wearable sensor.
Section 1.1 Synopsis (Overall study design)	Clarification on low and high doses of UCB0599 (180mg/day and 360mg/day) was added.	To provide justification for the selected new dose arm.
	Clarification on the wearable sensor familiarization period.	To allow start of use of the sensor in the first months of the treatment period.
Section 1.1 Synopsis (Treatment Groups and Duration)	Duration of Screening period was added.	Added for clarity.
Section 1.1 Synopsis (Number of participants)	The number of participants screened was increased.	To reflect that more participants are to be enrolled due to the additional treatment arm.

Section # and Name	Description of Change	Brief Rationale
Section 1.2 Schema	An additional dosage level was implemented to include 180mg/day (90mg BID).	To add a new lower dose treatment arm in support of dose selection for the pivotal studies.
	Change to the frequency of the DMC reviews.	To account for the increase in number of participants and to ensure regular independent review.
	Visits 9 (Month 6), 11 (Month 10), and 14 (Month 16) have been changed to in-clinic visits. Visits 4 (Day 10), 7 (Month 3), and 16 (Month 19) have been modified to include option of in-clinic visit or telemedicine video call supported by a research nurse.	Visits were changed to reduce potential rater variability. Remote visits were made optional in order to take into account the site's and participant's preference.
	For France only (refer to Section 10.9, Appendix 9): A note has been added that all visits in France are in-clinic visits only.	To exclude remote visits in France based on feedback from France.
Section 1.3 Schedule of Activities	"Participant experience survey" was renamed to "Optional participant experience survey."	To clarify that the survey is not mandatory.
	Not applicable to France: Addition of symbols to represent in-clinic visits or telemedicine video calls supported by a research nurse.	Remote visits were made optional in order to take into account the site's and participant's preference.
	For France only (refer to Section 10.9, Appendix 9): Footnote "b" included to clarify a country-specific requirement.	To reflect the request from France that telemedicine is not implemented in the study.
	Footnote "j" included to clarify that the DaT-SPECT scan at Screening Visit 2 is only applicable to participants without an adequate historical DaT-SPECT scan within the previous 3 months before Screening Visit 1, as determined by the central reader.	To allow participants with a previous DaT-SPECT that fulfills the quality criteria of the central reader.

Section # and Name	Description of Change	Brief Rationale
	Footnote “k” included to add that in case of early termination of study medication, the DaT-SPECT will occur at EOT (End of Treatment), provided that the previous DaT-SPECT occurred more than 6 months prior to the EOT. **For Germany only:** A note was added to clarify country-specific requirements.	To clarify the process for DaT-SPECT assessment in case of early termination of study participation.
	Footnote “l” was modified to add that participants have the opportunity to opt out of CSF sampling; however, the aim is to collect samples from at least 50 participants/arm.	To further clarify CSF sampling requirements.
	Footnote “o” was modified to clarify that study participants will be asked to take their study medication during the site visit after the blood sample is collected should the visit be scheduled before 11:00am.	Rephrased for clarity.
	For France only: A note has been added to footnote "p" to clarify country-specific requirements.	To implement a requirement from France for monthly pregnancy testing.
	Footnote “t” was modified to clarify that clinical tagging of Virtual Motor Exam (VME) on the wearable sensor is only applicable to the participants wearing the sensor.	To provide clarification on the use of the wearable sensor.
Section 2.3.1 Coronavirus Disease-2019 benefit/risk assessment	Addition of text on the benefit/risk of Covid-19 vaccinations in the study.	To provide clarification on the benefit/risk of Covid-19 vaccinations.
Section 2.3.2 Wearable Sensor Regulatory Classification	New section with details on the wearable sensor were added.	To provide clarification on the regulatory classification of the wearable sensor across regions.
Section 2.3.3 Wearable sensor benefit/risk assessment Section 2.3.3.1 Potential benefits	New sections with details on the potential benefit of the wearable sensor were added.	To provide clarification on the benefit/risk of the wearable sensor.

Section # and Name	Description of Change	Brief Rationale
Section 2.3.3.3 Wearable sensor benefit/risk conclusion	Language from the study risk determination was added.	To provide clarification on the benefit/risk of the wearable sensor
Section 4.1 Overall design	Clarification on low and high doses of UCB0599 (180mg/day and 360mg/day) was added.	To provide justification for the selected new dose arm.
Section 4.1.1 Decentralized model	Details on telemedicine visits were added.	To provide further clarification on telemedicine visits.
	For France only: Text was added to clarify that this is not applicable to France.	For clarification.
Section 4.2 Scientific rationale for study design	Clarification on 12-hour ST washout.	For clarification.
Section 4.3 Jusification for dose	Updated to include new dosage level 180mg/day (90mg BID).	To provide justification for the selected new dose arm.
Section 4.3.1 Safety-based dose levels	Table 4-1 was updated to include observed human exposures for new dosage level 180mg/day (90mg BID).	To provide justification for the selected new dose arm.
Section 4.3.2 Pharmacology based dose levels	Text below Table 4-2 was updated to include observed human exposures for new dosage level 180mg/day (90mg BID).	To provide justification for the selected new dose arm.
Section 5.1 Inclusion criteria	**For Canada only** (already implemented in other countries): The age-related inclusion criterion #1 was updated: "Study participant must be 40 to 75 years of age inclusive."	Increase the upper age limit for inclusion in the study which reflects the early PD population. This population does not present additional risk compared to the population initially included in the study.
	Inclusion criterion #2a (previously criterion #2) was updated to add in parenthesis "(including diagnosis during Screening)."	To clarify that the PD diagnosis can be established at the time of screening for the study.

Section # and Name	Description of Change	Brief Rationale
	Inclusion criterion #4a (previously criterion #4) was revised: "A Screening DaT-SPECT, or a historical DaT-SPECT within 3 months of the Screening Visit (V1) that has been qualified by the central reader, shows evidence of dopamine transporter deficit consistent with PD as determined by a central reader."	To allow participants with a previous DaT-SPECT that fulfills the quality criteria of the central reader and to further clarify the outcome of the readout by the central reader.
	Inclusion criterion #5a (previously criterion #5) was removed.	The inclusion criterion was deleted since genetic forms of PD are of minor incidence in the selected study population of age 40 and above.
	Inclusion criterion #6a (previously criterion #6) updated ≤2 to ≤2.5 modified Hoehn and Yahr staging.	To extend the study population to participants with a subtle balance issue.
	Inclusion criterion #7a (previously criterion #7) updated to include exceptions to medications for the treatment of motor symptoms of PD.	To reflect the update that participants that received short historical symptomatic treatment with an appropriate washout before trials start are allowed in the study.
Section 5.2 Exclusion criteria	Text about contacting the Medical Monitor to discuss enrollment for participants with allergies was removed from exclusion criterion #4a (previously criterion #4).	To clarify that the medical monitor is not involved in the participant selection based on feedback from the UK.
	Text about the participant being excluded from lumbar puncture but not from study participation was added to exclusion criterions #14a to #18a (previously criterions #14 to #18).	Rephrased for clarity.

Section # and Name	Description of Change	Brief Rationale
	Exclusion criterion #25a (previously criterion 25) was updated: "Study participant has had significant blood loss or has donated or received 1 or more units (450mL) of blood within 30 days prior to first drug administration Baseline Visit, or has donated plasma or platelets within 14 days prior to Baseline Visit."	Rephrased for clarity.
	Exclusion criterion #26a (previously criterion #26) updated to add "Short (up to 4 weeks) past use of medications for the treatment of motor symptoms is permitted following a sufficient washout period. Medications included are levodopa, MAO-B inhibitors, COMT inhibitors, anticholinergics, or amantadine. A sufficient washout period is at least 3 months prior to the first screening visit".	To reflect the update that participants that received short historical symptomatic treatment with an appropriate washout before trials start are allowed in the study.
	Exclusion criterion #30a (previously criterion #30) was removed, covered by exclusion criterion #26a.	To simplify the protocol.
	Renal exclusion criterion #40a (previously criterion #40) for serum creatinine > upper limit of normal was removed.	Serum creatinine is included in the calculation of the estimated glomerular filtration rate and is already considered in renal exclusion criterion 40 part "e".
	Exclusion criterion #43a (previously criterion #43) was updated to add "adults with legally authorized representative." A note has also been added for requirements specific for France.	To further specify vulnerable groups.
	Exclusion criterion #45 was added to exclude participants with serum potassium level below the lower limit of the laboratory reference range.	To add an exclusion criterion for participants with hypokalemia.

Section # and Name	Description of Change	Brief Rationale
Section 5.4 Screen failures	Text was updated to clarify that if Visit 2 was completed during screening, only Visit 1 needs to be completed for rescreening.	To clarify that MRI, CSF sampling, and DaT-SPECT should not be repeated for rescreening.
Section 6.1 Treatments administered	Inclusion of new dosage level "180mg/day (90mg BID)."	To add a new dose arm in support of dose selection for the pivotal study.
Section 6.3 Measures to minimize bias: randomization and blinding	Addition of text clarifying time bias due to additional dose arm.	Clarifying the potential bias of introducing a new dose arm in a running study.
Section 6.3.1.2 Breaking the treatment blind in an emergency situation	Removal of text "The Medical Monitor or equivalent should be consulted prior to unblinding, whenever possible."	To clarify procedures for breaking the treatment blind based on feedback from the UK.
Section 6.5.1 Permitted concomitant treatments (medications and therapies)	Text updated to add clarification on COVID-19 vaccinations in the study.	For clarification.
Section 6.5.3 Rescue medication	Text was updated to clarify the considerations for initiating ST as rescue medication.	Clarification regarding the use of rescue medication.
	Text was updated to clarify compliance of 12-hour ST washout.	To highlight the importance of the washout period.
Section 7.2 Participant Discontinuation/Withdrawal from the study	Text updated to specify that the DaT-SPECT will occur at EOT (End of Treatment), provided that the previous DaT-SPECT occurred more than 6 months prior to the EOT.	To clarify the process for DaT-SPECT assessment in case of early termination of study participation.
	Withdrawal criterion #6 was updated to add criteria for renal toxicity.	Added laboratory tests suggestive of renal toxicity to address a request from the UK.
Section 8 Study assessments and procedures	Bullet was added: "PROs (at home prior to a clinic visit or first assessments at the clinic)."	To clarify the sequence of assessments for PROs.
	Text was updated to specify the maximum blood volumes collected at every visit (50mL) and during the study (500mL).	To specify the maximum blood volumes collected based on feedback from France.
Section 8.1.1.1 MDS-UPDRS	Clarification on 12-hour ST washout.	To highlight the importance of the washout period.

Section # and Name	Description of Change	Brief Rationale
Section 8.1.1.3 Dopamine Transporter Imaging	A note has been added to clarify that no scan will be performed at Month 12 for German participants.	To clarify a country-specific requirement.
	Clarification that a historical DaT-SPECT scan within the previous 3 months before Screening Visit 1 is acceptable.	To allow participants with a previous DaT-SPECT that fulfills quality criteria of the central reader.
	Details on the DaTSCAN tracer were added.	For clarification.
Section 8.1.3 Wearable sensor	Text was added to clarify that where it is not possible to access the sensor during the Baseline period, participants may start wearing it until Visit 8 (M4).	To allow start of use of the sensor in the first months of the treatment period.
Section 8.2.1 Physical examination	Details on any abnormal findings from the focused body examinations found by the research nurse was added.	To clarify the responsiblities of the research nurse.
	For telemedicine visits, auscultation was deleted from the assessments performed by the research nurse.	Other assessments will be used for the identification of AEs and to discuss with the Investigator via video communication if an AE is suspected.
Section 8.2.1 Physical examination Section 8.2.3 Vital signs Section 8.2.4 Electrocardiograms Section 8.2.5 Clinical safety laboratory assessments Section 8.2.6 Suicidal risk monitoring	Details for remote visit were added.	To clarify the procedures during telemedicine visits based on feedback the from France.
Section 8.3 Adverse events and serious adverse events	Details on AEs related to COVID-19 vaccination was added.	To clarify the documentation and reporting process for AEs related to COVID-19 vaccination.
Section 8.3.6.2 Renal function safety monitoring and management	Text was added that an increase in serum creatinine of >25% from the previous value will trigger repeat testing within 48 hours.	Clarification based on feedback from the Canadian health authority.

Section # and Name	Description of Change	Brief Rationale
Section 8.5 Treatment of overdose	Text was added that a participant's dosing will be stopped in the event of an overdose while the participant is being evaluated.	Clarification based on feedback from the Canadian health authority.
Throughout Section 9 Statistical considerations	Updates were made throughout to refer to 3 treatment groups rather than 2.	To implement the addition of a low dose arm.
	Population-level summaries were updated throughout to show the comparison of low dose vs placebo and high dose vs placebo.	To implement the addition of a low dose arm.
	Symptomatic Treatment language was improved throughout. Reduced use of the term rescue medication and refer to "ST initiation" or "predictors of early ST initiation" rather ST intake or start of ST.	Improved language and description.
	Adjust for age at baseline (as well as gender) in main models rather than as part of a sensitivity analysis throughout.	Seen as standard adjustment.
	Sensitivity and Supplementary analysis sections were updated; some analyses removed and some added.	To refine the overall analysis.
	Restricted Mean Survival Time (RMST) was changed to be Restricted Mean Event Time (RMET) throughout.	To more accurately reflect the analyses being conducted.
Section 9.1 Definition of analysis sets	Definition of FAS was changed to refer to "1 post-baseline assessment" rather than "1 valid post-baseline assessment."	To add clarity to how this analysis set should be defined.
Section 9.2 General statistical considerations	SAS version was updated from 9.3 to 9.4.	Updated to align with current programming standards.

Section # and Name	Description of Change	Brief Rationale
Section 9.3 Planned efficacy/outcome analyses	Updates were made to the list of predictors of early ST initiation.	To reflect latest internal research.
	Text was added to explain how the three treatments will be evaluated/compared.	To implement the addition of a low dose arm.
	PPMI dataset has been updated.	To add more detail as there is now a PPMI 2.0 cohort.
	Text has been added to make the modelling approach clearer.	To clarify the description of the model.
Section 9.3.1.1.1.1 Supplementary Efficacy Estimand to MDS-UPDRS Parts I III sum score at 12 months (“De Facto” Estimand)	Text was added to make it clear that categorical linear mixed effects models (LMEMs) will use baseline data as a covariate.	To clarify the description of the model.
Section 9.3.1.1.3 Key Secondary Efficacy Estimand: Worsening on MDS-UPDRS Part III subscale at 12 months (“De Jure” Estimand) Section 9.3.1.2.2 Key Secondary Efficacy Estimand: Worsening on MDS-UPDRS Part III subscale at 18-month (“De Jure” Estimand) Section 9.3.3.1 Secondary Efficacy Estimand: Time to ST intake at 18 months	RMET modelling approach was improved.	To reflect further research on this method.
Section 9.3.5 Center effects	Updated to state that any additional analyses by country/region will be done outside of the CSR. Additional text was included about COVID-19 by country/region summaries.	Since treatment assignment will not necessarily be balanced across countries, any analyses by country will be done post-hoc. Detail added on COVID-19 summaries.
Section 9.5 Handling of ICEs, protocol deviations, and resulting missing data	Re-ordered and more detail added.	To add clarity.

Section # and Name	Description of Change	Brief Rationale
Section 9.6 Planned analysis at 12 months and data monitoring	Addition of bullet "When safety data for 3 months of treatment (ie, until Visit 7) are available for 100 participants."	To keep a DMC at the timepoint expected before the low dose arm was included.
	Bulleted list was added to specify timepoints of SMC meetings.	To clarify the SMC meeting frequency based on feedback from France.
Section 9.7 Determination of sample size	Updated to refer to 3 arms instead of 2. Text was added to explain how comparisons will be made for the 3 groups.	To implement the addition of a low dose arm
Section 9.7.1 Primary efficacy estimand Section 9.7.3 Power for secondary efficacy estimand (DaT-SPECT mean striatum SBR)	PPMI dataset has been updated.	To add more detail as there is now a PPMI 2.0 cohort.
Section 10.1.3 Informed consent process	Text was added to clarify that potential participants will have as much reflection time as needed during the informed consent process and will be under no pressure to decide on their participation in the study.	To clarify the informed consent process based on feedback from the UK.
	Text was added to clarify potential participants 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. A note has also been added for requirements specific for France (please refer to Section 10.9 Appendix 9).	To address request for clarity in the intial CTA review and to clarify a country-specific requirement.
	Text was updated to remove "legal representative."	To implement feedback from the initial CTA review.
Section 10.1.6 Data quality assurance	Addition of standard text on quality tolerance limits.	Added for clarity.

Section # and Name	Description of Change	Brief Rationale
Section 10.2: Appendix 2: Clinical laboratory tests	Text updated: RBC counts and/or Hemoglobin in CSF for quality control purposes.	To clarify that quality control of CSF sampling will be done either by RBC counts or hemoglobin analysis.
Section 10.4: Appendix 4: Contraceptive guidance and collection of pregnancy information	A note has been added to the second bullet under "Pregnancy testing" for requirements specific for France (please refer to Section 10.9 Appendix 9).	To clarify a country-specific requirement.
Section 10.9: Appendix 9: Country-specific requirements	Details added on country-specific requirements for Germany and France.	To clarify all country-specific requirements.
Section 10.11: Appendix 11 Protocol Amendment History	The Protocol Amendment Summary of Changes Table for the previous amendment has been moved to Appendix 11.	Minor administrative change.
Throughout	Minor editorial and document formatting revisions.	Minor, therefore have not been summarized.

10.11.4 Amendment 2 (21 May 2021)

Overall Rationale for the Amendment

PD0053 Protocol Amendment 2, dated 21 May 2021, was completed to increase the upper age limit for participants' inclusion in the study to 75 years, which reflects the early Parkinson's Disease population. This population does not present additional risk compared to the population initially included in the study. The following changes were implemented:

Section # and Name	Description of Change	Brief Rationale
Section 5.1 Inclusion criteria	The age-related inclusion criteria #1 was updated: "Study participant must be 40 to 70 *75* years of age inclusive"	Increase the upper age limit for inclusion in the study.
Section 2.3.1 Coronavirus Disease-2019 benefit/risk assessment	Upper age limit of the participants to be included in the study was changed from 70 to 75 years.	Increase the upper age limit for inclusion in the study.

10.11.5 Amendment 1 (29 Oct 2020)

Overall Rationale for the Amendment

PD0053 Protocol Amendment 1, dated 29 Oct 2020, was completed to remove planned video recording of study participants during the the MDS-UPDRS Part III assessment due to operational limitations at this time (eg, procedures for de-identification, video processing, video data handling, access, and storage). Video recording may be re-introduced at a later time via an amendment. The following changes were implemented:

Section # and Name	Description of Change	Brief Rationale
Section 1.2 Schedule of Activities	Video recording Informed Consent Form was removed.	Removal of planned video recording during MDS-UPDRS Part III assessment due to operational limitations at this time
Section 8.1.1.1 MDS-UPDRS	MDS-UPDRS Part III motor test recording via video using the telemedicine technology was removed.	Removal of planned video recording during MDS-UPDRS Part III assessment due to operational limitations at this time
Section 10.11 Appendix 11 Protocol Amendment History	"Not applicable" was replaced by a note that the Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.	Minor administrative change

10.12 Appendix 12: In-clinic VME Investigator rating scale

Investigators are to rate participant performance with each VME using the following rating scale.

Skill Check Task #1: Tap wearable sensor (sensor tapping)

0: Normal: No problems

1: Slight: Any of the following:

a) the regular rhythm is broken with one or two interruptions or hesitations of the movement

b) slight slowing

c) the amplitude decrements near the end of the task

2: Mild: Any of the following:

a) 3 to 5 interruptions during the movements

b) mild slowing

c) the amplitude decrements midway in the task

3: Moderate: Any of the following:

a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement

b) moderate slowing

c) the amplitude decrements starting after the first open-and-close sequence

4: Severe: Cannot or can only barely perform the task because of slowing, interruptions, or decrements.

Skill Check Task #2: Seated Rest (Rest Tremor)

0: Normal: No tremor

1: Slight: ≤1cm in maximal amplitude

2: Mild: >1 cm but <3 cm in maximal amplitude

3: Moderate: 3-10 cm in maximal amplitude

4: Severe: >10 cm in maximal amplitude

Skill Check Task#3: Arm Raise (Postural Tremor)

0: Normal: No tremor

1: Slight: Tremor is present but less than 1 cm in amplitude

2: Mild: Tremor is at least 1 but less than 3 cm in amplitude

3: Moderate: Tremor is at least 3 but less than 10 cm in amplitude

4: Severe: Tremor is at least 10 cm in amplitude

Skill Check Task #4: Hand Open and Close

0: Normal: No problems

1: Slight: Any of the following:

a) the regular rhythm is broken with one or two interruptions or hesitations of the movement

b) slight slowing

c) the amplitude decrements near the end of the task

2: Mild: Any of the following:

a) 3 to 5 interruptions during the movements

b) mild slowing

c) the amplitude decrements midway in the task

3: Moderate: Any of the following:

a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement

b) moderate slowing

c) the amplitude decrements starting after the first open-and-close sequence

4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrement.

Skill Check Task #5: Arm Twist (Pronation/Supination)

0: Normal: No problems

1: Slight: Any of the following:

a) the regular rhythm is broken with one or two interruptions or hesitations of the movement

b) slight slowing

c) the amplitude decrements near the end of the sequence

2: Mild: Any of the following:

a) 3 to 5 interruptions during the movements

b) mild slowing

c) the amplitude decrements midway in the sequence

3: Moderate: Any of the following:

a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement

b) moderate slowing

c) the amplitude decrements starting after the first supination-pronation sequence

4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.

Skill Check Task #6: Foot Stomp

0: Normal: No problems

1: Slight: Any of the following:

a) the regular rhythm is broken with one or two interruptions or hesitations of the movement

b) slight slowing

c) amplitude decrements near the end of the task

2: Mild: Any of the following:

a) 3 to 5 interruptions during the movements

b) mild slowness;

c) amplitude decrements midway in the task

3: Moderate: Any of the following:

a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement

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b) moderate slowing in speed

c) amplitude decrements after the first tap

4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements

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Skill Check Task #7: Up and Go

Rising from chair:

0: Normal: No problems. Able to arise quickly without hesitation.

1: Slight: Arising is slower than normal; or may need more than one attempt; or may need to move forward in the chair to arise. No need to use the arms of the chair.

2: Mild: Pushes self up from arms of chair without difficulty.

3: Moderate: Needs to push off, but tends to fall back; or may have to try more than one time using arms of chair, but can get up without help.

4: Severe: Unable to arise without help.

Gait:

0: Normal: No problems.

1: Slight: Independent walking with minor gait impairment.

2: Mild: Independent walking but with substantial gait impairment.

3: Moderate: Requires an assistance device for safe walking (walking stick, walker) but not a person.

4: Severe: Cannot walk at all or only with another person's assistance.

Skill Check Task #8: Stand Still (Postural Stability)

0: Normal: No postural sway.

1: Slight postural sway that is almost imperceptible.

2: Mild postural sway that is noticeable but does not disrupt balance at all.

3: Moderate postural sway that disrupts maintenance of balance in some way.

4: Severe postural sway that causes the patient to be unstable at some point.

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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 and according to current Good Clinical Practice.

Approval Signatures

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