Protocol I7S-MC-HBEH(b)

Effect of LY3154207 on Cognition in Mild-to-Moderate Dementia Due to Lewy Body Dementia (LBD) Associated with Idiopathic Parkinson's Disease (PD) or Dementia with Lewy Bodies (DLB) (The PRESENCE Study)

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(The PRESENCE Study)

LY3154207

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1. Synopsis

Title of Study:
Effect of LY3154207 on cognition in mild-to-moderate dementia due to Lewy Body Dementia (LBD) associated with idiopathic Parkinson's disease (PD) or dementia with Lewy bodies (DLB).

Rationale:
Eli Lilly and Company (Lilly) is developing LY3154207, an orally available, selective positive allosteric modulator (PAM, also called "potentiator") of the dopamine D1 receptor subtype (D1PAM). By increasing the affinity of dopamine for the D1 receptor, a D1PAM is hypothesized to amplify response to endogenous dopamine, thereby increasing D1 tone at the site of dopamine release, and represents a novel mechanism of action. By potentiating the response to the remaining brain dopamine (or administered levodopa) in subjects with insufficient physiologic dopamine such as those with LBD (PDD or DLB), a D1PAM should improve cognitive performance. In addition, a D1PAM should have a positive impact on other domains affected by LBD (PDD or DLB) including motor deficits, mood, apathy, and daytime sleepiness.

LY3154207 has been investigated in healthy subjects and subjects with Parkinson's disease. CCI [redacted]

Study I7S-MC-HBEH (HBEH) is a multicenter, randomized, double-blind, parallel-group, placebo-controlled, fixed-dosage, Phase 2 study comparing 3 dosages of LY3154207 (10, 30, or 75 mg administered orally [or 50 mg based on interim analysis] once a day) with placebo over 12 weeks in subjects with mild-to-moderate dementia associated with LBD (PDD or DLB). Study HBEH will test the hypothesis that LY3154207 administered at 10 mg, 30 mg, and/or 75 mg daily (or 50 mg based on interim analysis) (QD) oral dosing for 12 weeks will result in a significant improvement in cognition in subjects with mild-to-moderate LBD (PDD or DLB) compared with placebo. Important secondary outcomes will assess the effect of LY3154207 on function, parkinsonism, sleep and mood/behavior.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary To test the hypothesis that LY3154207 administered at 10 mg, 30 mg, and/or 75 mg daily (or 50 mg based on interim analysis) (QD) oral dosing for 12 weeks will result in a significant improvement in cognition in subjects with mild-to-moderate LBD (PDD or DLB) compared with placebo.	Change in the CoA composite score of the CDR-CCB from baseline to Week 12.
Secondary **Efficacy:**	
To evaluate the global efficacy of LY3154207	ADCS-CGIC score from baseline to Week 12
To evaluate the efficacy of LY3154207 on cognitive outcomes	Change in the CDR-CCB PoA composite score from baseline to Week 12
To evaluate the efficacy of LY3154207 on cognitive outcomes	Change in the ADAS-Cog_{13} score from baseline to Week 12
To evaluate the efficacy of LY3154207 on cognitive outcomes	Change in the MoCA score from screening to Week 12
To evaluate the efficacy of LY3154207 on neuropsychiatric symptoms	Change in the NPI total and individual item scores from baseline to Week 12
To evaluate the effect of LY3154207 on daytime sleepiness	Change in the ESS score from baseline to Week 12
To evaluate the effect of LY3154207 on PD severity	Change in the MDS-UPDRS total score (sum of Parts I-III) from baseline to Week 12
To evaluate the effect of LY3154207 on PD motor signs	Change in the MDS-UPDRS Part III from baseline to Week 12
To evaluate the efficacy of LY3154207 on functional outcome	Change in the PDAQ-15 total score from baseline to Week 12
To evaluate the effect of LY3154207 on verbal fluency	Change in D-KEFS Verbal Fluency test score from baseline to Week 12
Safety:	
To evaluate the effect of LY3154207 on acute changes of vital signs on the first day of dosing	Number of subjects who met the potentially clinically significant vital signs criteria at 3 consecutive time points at Visit 3 (Day 1 stopping rules).
To evaluate the effect of LY3154207 on SBP on the first day of dosing	Change in in-clinic SBP from 0 up to 8 hours post dose on the first day of study drug dosing
To evaluate the effect of LY3154207 on pulse rate on the first day of dosing	Change in in-clinic pulse rate from 0 up to 8 hours post dose on the first day of study drug dosing
To evaluate the effect of LY3154207 on SBP from baseline to Week 12	Change in in-clinic mean SBP at baseline to mean SBP at Week 12
To evaluate the effect of LY3154207 on pulse rate from baseline to Week 12	Change in in-clinic mean pulse rate at baseline to mean pulse rate at Week 12

Objectives	Endpoints
To evaluate the effect of LY3154207 on physical withdrawal symptoms	Change in the PWC-20 total score from Week 12 to in-clinic follow-up visit
Pharmacokinetics: To assess the PK of LY3154207 in a population of subjects with mild-to-moderate dementia due to PD	Steady-state trough plasma concentrations of LY3154207 at Week 12

Abbreviations: ADAS-Cog_{13} = 13-item Alzheimer's Disease Assessment Scale – Cognitive subscale; ADCS-CGIC = Alzheimer's Disease Cooperative Study – Clinician Global Impression of Change; CDR-CCB = Cognitive Drug Research – Computerized Cognition Battery; CoA = Continuity of Attention; D-KEFS = Delis–Kaplan Executive Function System; DLB = dementia with Lewy bodies; ESS = Epworth Sleepiness Scale; LBD = Lewy Body Dementia; MDS-UPDRS = Movement Disorder Society's Unified Parkinson's Disease Rating Scale; MoCA = Montreal Cognitive Assessment; NPI = Neuropsychiatric Inventory; PD = Parkinson's disease; PDD = Parkinson's disease dementia; PDAQ-15 = Penn Parkinson's Daily Activities Questionnaire-15; PK = pharmacokinetics; PoA = Power of Attention; PWC-20 = physician withdrawal checklist-20; QD = once a day; SBP = systolic blood pressure.

Summary of Study Design: Study I7S-MC-HBEH (HBEH) is a multicenter, randomized, double-blind, parallel-group, placebo-controlled, fixed-dosage, Phase 2 study comparing 3 dosages of LY3154207 (10, or 30, or 75 mg administered orally [or 50 mg based on interim analysis] once a day [QD]) with placebo over 12 weeks in subjects with mild-to-moderate LBD (PDD or DLB). The study includes a Screening Period (Visits 1 to 2) of a minimum of 7 days and up to 14 days, a Pretreatment Period of a minimum of 11 days and up to 17 days (Visits 2 to 3), a 12-week Treatment Period (Visits 3 to 11), and a 14-day Safety Follow-Up Period (Visits 11 to 801 or early termination [ET]/discontinuation [DC] visit to Visit 801) that includes one telephone visit (Visit 111). Subjects who meet entry criteria will be randomized in a 1:1:1:1 ratio to LY3154207 (10 or 30 or 75 mg QD) or placebo.

Treatment Arms and Duration:

Study HBEH involves a comparison of LY3154207 10 mg, 30 mg, and 75 mg (or 50 mg based on interim analysis) administered orally QD with placebo over 12 weeks.

Number of subjects: Approximately 750 subjects will be screened to achieve 340 randomized and an estimated total of 85 evaluable subjects per treatment group.

Statistical Analysis:

Efficacy Analysis:

All subjects in the evaluable patient population (EPP) will be considered for the efficacy analysis. The primary analysis on CoA will occur when all subjects complete 12 weeks of treatment. The analysis of CoA will utilize a Bayesian MMRM model. The Bayesian analysis may use uninformative priors for all terms in the model. These will be diffuse Normal distributions centered on zero. Priors for variance will follow an inverse gamma distribution. Further details of the Bayesian analysis will be provided in the SAP. The MMRM model will account for longitudinal data assessed throughout the study, after 1, 2, 4, 6, 8, 10, and 12 weeks of dosing. The change of CoA from the baseline to Week 12 will be the dependent variable.

The model will comprise fixed (baseline value, treatment, visit) and random effects (subject) and the interaction terms (treatment by visit, baseline value by visit). Unstructured variance structure will be applied in the model, but if it fails to converge, other suitable structures will be investigated. The primary comparison will be the contrast (difference in least squares mean) between treatments and placebo for the Week 12 change from baseline.

The secondary efficacy outcomes: the change from baseline at 12-week time point of total scores (or composite values) of Alzheimer's Disease Cooperative Study – Clinician Global Impression of Change (ADCS-CGIC), CDR-CCB Power of Attention (PoA), 13-item Alzheimer's Disease Assessment Scale – Cognitive subscale (ADAS-Cog_{13}), Montreal Cognitive Assessment (MoCA), Neuropsychiatric Inventory (NPI), Epworth Sleepiness Scale (ESS), Movement Disorder Society's Unified Parkinson's Disease Rating Scale (MDS-UPDRS), Penn Parkinson's Daily Activities Questionnaire 15 (PDAQ-15), and Delis–Kaplan Executive Function System (D-KEFS) will follow the same analysis method as above.

Missing records in some scales (e.g., ADAS-Cog) will be imputed as detailed in the statistical analysis plan. For the scales where the imputation is not done, if any item is missing, any total or sum involving that item will be considered missing. No adjustment for multiple comparisons will be made.

Safety Analysis: Safety analyses are based on the safety population and analysis will include listings and/or summaries of the following: adverse events (AEs), serious adverse events (SAEs), treatment-emergent adverse events (TEAEs), laboratory measures, vital signs, electrocardiogram readings and number of subjects who met the potentially clinically significant vital signs criteria at 3 consecutive time points at Visit 3 (Day 1 stopping rules).

Mixed-model repeated measures analysis will be used to compare the change in in-clinic blood pressure (BP) and pulse rate from pretreatment up to 8 hours post dose measured on the first day of study drug dosing (V3). Two baselines will be considered in the change from baseline analyses: the V3 pretreatment value and the time-matched baselines from Visit 2 (hourly value 0 to 6 hours). For the second baseline, the V3, 7- and 8-hour time points will use the V2 6-hour time point as their baseline value. A separate change from baseline analysis will be completed for each baseline approach. Mixed-model repeated measures analyses will also be used to compare change in in-clinic BP and pulse rate from V2 (daily average 0 to 6 hours) to Week 6/Visit 8 and Week 12/Visit 11 (daily average 0 to 6 hours), to evaluate the change in BP and pulse rate over 12 weeks of dosing.

Withdrawal: Withdrawal symptom analyses will be conducted on subjects who completed at least one pre-withdrawal and one post-withdrawal PWC-20 checklist. Week 12/Visit 11 will be considered baseline in the change from baseline analyses; Visit 801 will be considered the post baseline assessment. This will be examined using an analysis of covariance (ANCOVA) model with treatment arm as an independent factor and baseline value as a covariate in the model. This will allow us to assess the withdrawal symptoms between treatments and groups.

Pharmacokinetics (PK): Pharmacokinetic analyses will be conducted on subjects who receive at least 1 dose of the study drug and have 1 measurable concentration. A model-based approach

may be implemented using nonlinear mixed effects modeling (NONMEM) or other appropriate software to estimate PK parameters.

Additional endpoints and biomarker data collected during the study will be evaluated in an exploratory manner.

Interim Analysis: Safety interim analyses will be conducted on the number of subjects on each treatment who met the potentially clinically significant vital signs criteria (Table HBEH.3) at 3 ***consecutive*** time points at Visit 3 (Day 1 stopping rules). This will be done after 50, 100, and 150 subjects have completed Visit 3. CCI [redacted] Those already on 75-mg dose and passed the Day 1 stopping rules will remain on 75 mg. In the event of an unacceptable rate of subjects meeting Day 1 stopping rules at other doses, adjustments to doses may be made for subsequently randomized subjects at the discretion of the Internal Assessment Committee (IAC). Additional efficacy analyses may be conducted at the time of these safety interim analyses. A safety and efficacy interim analysis will be conducted when 170 randomized subjects have completed Visit 11 (Week 12) assessments and may also be conducted at other timepoints prior to study completion. All potential efficacy analyses may be used for internal decision making, but are not planned to stop the study.

2. Schedule of Activities

Table HBEH.1. Schedule of Activities for Protocol I7S-MC-HBEH

Procedure[a]	Screening	Pretreatment	Double-Blind Treatment									Follow-up		Unscheduled Visit	ET/DC Visit[d,t]
Study Day	Min 7 days; max 14 days prior to V2	Min 11 days; max 17 days prior to V3		7 days	14 days	21 days	28 days	42 days	56 days	70 days	84 days	2 days after V11[u]	14 days from V11 or ET/DC		
Tolerance Interval for Visit (Days)		Baseline Visit	Randomization	±1	±1	±1	±1	±3	±3	±3	±3	+1	±3		
eCRF Visit No.:	V1[b,d]	V2[b,d]	V3[b]	V4[d]	V5	V6	V7	V8[b,d]	V9	V10	V11[b,d]	V111[d]	V801	V997[c]	
Informed Consent(s) Signed (before procedures/tests)	X														
Register subject in IWRS - Subject number assigned	X														
Complete IWRS	X	X	X	X	X	X	X	X	X	X	X		X	X	X
Demographics	X														
Prior/concomitant treatment	X	X	X	X	X	X	X	X	X	X	X		X	X	X
Inclusion/exclusion criteria	X	X	X												
Modified Hoehn and Yahr Scale	X														
Medical History	X														
Physical Examination[e]	X							X			X		X		X
Height		X													
Weight		X						X			X				X
Orthostatic BP/pulse rate[f]	X	X	X	X	X	X	X	X	X	X	X		X	X	X
In-clinic BP/Pulse rate monitoring[g]		X	X					X			X		X		

Procedure[a]	Screening	Pretreatment	Double-Blind Treatment									Follow-up		Unscheduled Visit	ET/DC Visit[d,t]
Study Day	Min 7 days; max 14 days prior to V2	Min 11 days; max 17 days prior to V3		7 days	14 days	21 days	28 days	42 days	56 days	70 days	84 days	2 days after V11[u]	14 days from V11 or ET/DC		
Tolerance Interval for Visit (Days)		Baseline Visit	Randomization	±1	±1	±1	±1	±3	±3	±3	±3	+1	±3		
eCRF Visit No.:	V1[b,d]	V2[b,d]	V3[b]	V4[d]	V5	V6	V7	V8[b,d]	V9	V10	V11[b,d]	V111[d]	V801	V997[c]	
Temperature	X							X			X		X		X
12-Lead ECG	X	X		X				X			X		X	X[c]	X
Review HBPM instructions[h]		X	X	X	X					X	X				
HBPM device returned to site													X		X
Hematology	X	X			X			X			X		X	X[c]	X
Urinalysis	X	X			X			X			X		X	X[c]	X
Clinical Chemistry	X	X			X			X			X		X	X[c]	X
Serum FSH[i]	X														
PGx sampling		X													
Collection of dose administration timing (date and time)			X	X	X	X	X	X	X	X	X				X
PK Sampling[j]			X[j]	X[j]	X[j]			X[j]			X[j]				X[j]
Randomization			X												
Study drug dosing at site			X					X[k]			X[k]				
Dispense Investigational Product			X	X	X	X	X	X	X	X					
Return Investigational Product				X	X	X	X	X	X	X	X				X
Adverse Events		X	X	X	X	X	X	X	X	X	X		X	X	X

Procedure[a]	Screening	Pretreatment	Double-Blind Treatment									Follow-up		Unscheduled Visit	ET/DC Visit[d,t]
Study Day	Min 7 days; max 14 days prior to V2	Min 11 days; max 17 days prior to V3		7 days	14 days	21 days	28 days	42 days	56 days	70 days	84 days	2 days after V11[u]	14 days from V11 or ET/DC		
Tolerance Interval for Visit (Days)		Baseline Visit	Randomization	±1	±1	±1	±1	±3	±3	±3	±3	+1	±3		
eCRF Visit No.:	V1[b,d]	V2[b,d]	V3[b]	V4[d]	V5	V6	V7	V8[b,d]	V9	V10	V11[b,d]	V111[d]	V801	V997[c]	
Review Lilly Trial app (if available) instructions[l]		X	X	X	X	X	X	X	X	X	X				
Actigraphy watch provided to subjects (if available)[m]		X						X			X				
Return of Actigraphy watch (if available)[n]			X						X				X		
CDR-CCB[o,p]	X	X	X	X	X	X	X	X	X	X	X		X		X
Alzheimer's Disease Cooperative Study – Structured Clinical Global Impression interview[d]		X						X			X				X
ADCS-CGIC[d]								X			X				X
ADAS-Cog_{13}[p]		X						X			X				X
D-KEFS[p]		X						X			X				X
MoCA[p]	X							X			X				X
PDAQ-15[d]		X						X			X				X
MDS-UPDRS[d,p]		X						X			X		X		X
NPI[d]		X						X			X				X
ESS[d]		X		X				X			X		X		X
QUIP[d]		X						X			X				X
GDS-S[d]	X										X				X

Procedure[a]	Screening	Pretreatment	Double-Blind Treatment									Follow-up		Unscheduled Visit	ET/DC Visit[d,t]
Study Day	Min 7 days; max 14 days prior to V2	Min 11 days; max 17 days prior to V3		7 days	14 days	21 days	28 days	42 days	56 days	70 days	84 days	2 days after V11[u]	14 days from V11 or ET/DC		
Tolerance Interval for Visit (Days)		Baseline Visit	Randomization	±1	±1	±1	±1	±3	±3	±3	±3	+1	±3		
eCRF Visit No.:	V1[b,d]	V2[b,d]	V3[b]	V4[d]	V5	V6	V7	V8[b,d]	V9	V10	V11[b,d]	V111[d]	V801	V997[c]	
PWC-20 (Subject)											X	X	X		X
PWC-20[d] (Caregiver)											X	X	X		X
C-SSRS – Children's Version and Self-Harm Supplement Form[s]	X[q]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]		X[r]	X[r]	X[r]

Abbreviations: ADAS-Cog$_{13}$ = Alzheimer's Disease Assessment Scale – 13-Item Cognitive Subscale; ADCS-CGIC = Alzheimer's Disease Cooperative Study - Clinician Global Impression of Change; BP = blood pressure; CDR-CCB = Cognitive Drug Research Computerized Cognition Battery; C-SSRS = Columbia-Suicide Severity Rating Scale; DC = discontinuation; D-KEFS= Delis–Kaplan Executive Function System; ECG = electrocardiogram; eCOA = electronic Clinical Outcome Assessment; eCRF = electronic case report form; ED = early discontinuation; ESS = Epworth Sleepiness Scale; ET = early termination; FSH = follicle-stimulating hormone; GDS-S = Geriatric Depression Scale – Short Form; HBPM = home blood pressure monitoring; HCG = human chorionic gonadotropin; HEENT = head, ear, eye, nose, and throat; IWRS = interactive web-response system; MDS-UPDRS = Movement Disorder Society's Unified Parkinson's Disease Rating Scale; MoCA = Montreal Cognitive Assessment; NPI = Neuropsychiatric Inventory; PDAQ-15= Penn Parkinson Daily Activities Questionnaire-15; PGx = pharmacogenomic(s); PK = pharmacokinetic(s); PWC-20 = physician withdrawal checklist-20; QUIP = Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease; V = visit.

Note: Be sure that the visit allowance period takes into account the required washout duration needed for medications that are not allowed by the protocol.

a Every effort should be made for visits to occur on designated study days. The overall treatment period in the protocol should be maintained (visits should be scheduled based on the randomization visit). Procedures and assessments should be done in the order described in the Operations Manual.

b Visit 1 may be split over 2 days. In exceptional circumstances, if the clinical assessments cannot be completed within 1 day at V2, V3, V8, and/or V11, those clinical assessments may be completed the next day. The orthostatic blood pressure measurements, in-clinic blood pressure measurements, the CDR-CCB, and the laboratory procedures including PK must be completed on Day 1 of that visit. The visit interval will start from Day 1.

c ECGs or samples for clinical laboratory tests (hematology, clinical chemistry, and urinalysis) will only be collected if a retest is needed. All other procedures are required for each unscheduled visit.

[d] The caregiver is required to attend Visit 1 at the clinic to sign the informed consent and be informed about the study details. Caregiver's attendance will also be required at Visit 2, Visit 4, Visit 8, Visit 11, Visit 801, and the ET/DC visit to provide inputs for the PDAQ-15, ADCS-CGIC, GDS-S, MDS-UPDRS, NPI, ESS, and QUIP scales. The caregiver is required at Visit 11, Visit 111 and Visit 801 to provide input for the PWC-20.

[e] The physical examination should include HEENT, cardiac, lung, abdomen, extremity, skin, and neurological examinations.

[f] Orthostatic BP/pulse rate will be measured as part of the vital sign assessments at every visit. At Visit 2, Visit 3, Visit 8, Visit 11, and Visit 801, these measurements will be collected at time 0 of the in-clinic BP/pulse rate monitoring. Subjects will have 3 BP/pulse rate measurements taken in the seated position approximately 1 minute apart followed by 1 BP/pulse rate measurement taken in the standing position. Subjects should be seated for at least 5 minutes and stand for at least 3 minutes prior to taking the respective measurements. If the subject feels unable to stand, vital signs only in the seated position will be recorded.

[g] In-clinic BP and pulse rate monitoring will be done at Visit 2, Visit 3, Visit 8, Visit 11, and Visit 801. The BP and pulse rate measurements will occur at time 0 and approximately every 60 minutes thereafter at Visit 2, Visit 8, and Visit 11, in-clinic BP and pulse rate will be monitored for up to 6 hours; at Visit 3, for up to 8 hours and at Visit 801 for up to 2 hours.. The initial measurement, time 0 of the in-clinic BP and pulse rate monitoring, will be done as an orthostatic BP/pulse rate (refer to footnote f above), and subsequent BP and pulse rate measurements will be done in the seated position only. Time 0 for Visit 3, Visit 8, and Visit 11 will occur just prior to study drug dosing. At Visit 3, drug dosing should be initiated immediately following confirmation that subject meets inclusion criteria [6].

[h] The subject should be given the HBPM device at Visit 2. Home BP will be measured twice daily in the seated position using the HBPM equipment provided by Eli Lilly and Company (Lilly). Home BP measurements should be conducted for a minimum of 7 days between Visit 2 and Visit 3, for 3 weeks between Visit 3 and Visit 6, and for a minimum of 7 days between Visit 10 and Visit 11, and Visit 11 and Visit 801. Home BP should be measured twice in the morning (approximately 1 minute apart) (e.g., 8 AM) immediately following study medication dosing and twice in the evening, approximately 12 hours later (approximately 1 minute apart) (e.g., 8 PM).

[i] Refer to inclusion criterion [12e] in Section 6.1.

[j] PK sampling. At Visit 3, a PK sample is to be collected within 1 to 3 hours after the drug is administered at the site. At Visit 4, Visit 5, Visit 8, and ET/DC visit, the PK sample can be collected at any time during the visit. At Visit 11, the PK sample should be collected prior to the drug being administered at the site. The date and time of the PK sample collection as well as the date and time of the dose administration immediately preceding the PK sampling should be entered in the eCRF.

[k] Study drug dose to be administered at the clinic on the morning of Visit 8 and Visit 11 following the Time 0 in-clinic BP/pulse rate measurements.

[l] An iPad® configured with the Lilly Trial application (Lilly Trial app) will be provided to the subjects at Visit 2 (if available). Subjects should complete assessments from 2 weeks prior to dosing (starting the day following Visit 2), throughout the dosing period, and for 2 weeks after the conclusion of the treatment period (until Visit 801). This assessment should be done up to twice daily. Subjects will self-select for this optional component of the protocol at Visit 1. Subjects can decide to opt out at any time during the study. In case of opt-out or ET, the subject should return the iPad to the site at the visit following the subject opt-out or at the ET/DC visit. For subjects who complete the Lilly trial application assessments throughout the study, the iPad should be returned at Visit 801. Refer to the Operations Manual for details about Opt-in and Opt-out process.

[m] The actigraphy device (if available) should be worn on the wrist, similar to a watch, beginning at Visit 2, for 3 separate 2-week periods of time: Visit 2 to Visit 3, Visit 8 to Visit 9, and Visit 11 to Visit 801. The site will provide the device to the subjects at Visits 2, 8, and 11.

[n] Following 14 days of wearing the device, the subject should bring the device back to the site at the next scheduled visit (Visit 3, Visit 9, or Visit 801).

o CDR-CCB: At least 2 training sessions are required at Visit 1. At each visit, the CDR-CCB should be assessed after the study drug has been dosed. At Visit 4, Visit 5, Visit 6, Visit 7, Visit 9, and Visit 10, if a subject has not taken the study drug prior to the study visit, the subject must take study drug at the site prior to the CDR-CCB.

p The CDR-CCB, MoCA, ADAS-Cog_{13}, MDS-UPDRS (Part III), and D-KEFS scales should be conducted in the practically defined medication "on" state at all visits. The "on" state is defined as the individual best motor function as determined by the investigator, or at approximately 1 hour after the dose of dopaminergic therapy. Every attempt should be made to conduct these assessments in the "on" state. In the exceptional circumstance that this is not possible, the assessments could be done in the "off" state. The "on/off" state should be confirmed prior to completion of the respective scales listed above. This information will be collected in the eCOA or the eCRF. If any portion of an assessment is done in the "off" state, then that subject should be rated as in the "off" state for the whole assessment. If the subject is not on dopaminergic therapy the assessment should be documented as "on".

q The C-SSRS "Baseline" version will be used at the Screening visit (Visit 1).

r The C-SSRS "Since Last Visit" scale will be administered at each subsequent visit.

s If, based on administration of the C-SSRS, it is determined that suicide-related behaviors have occurred, then the Lilly Self-Harm Follow-Up form will be used to collect additional information to allow for a more complete assessment of these behaviors.

t All subjects who discontinue study treatment prior to a scheduled visit should have an ET/DC visit and procedures/assessments performed as soon as possible.

u If the visit window falls on a weekend/holiday then the visit should be conducted at the next possible day.

3. Introduction

3.1. Study Rationale

LY3154207 is an orally available, selective positive allosteric modulator (PAM, also called "potentiator") of the dopamine D1 receptor subtype (D1PAM). By increasing the affinity of the dopamine for the D1 receptor, a D1PAM should amplify the response to endogenous dopamine, increasing D1 tone when and where dopamine is released, and represents a novel mechanism of action. This mode of activity is in contrast to a D1 agonist, which should activate all D1 receptors to which it has access for as long as it is present (Svensson et al. 2017). In animal models of cognition and locomotor activity, D1 agonists often show bell-shaped, dose–response relationships, which are probably due to overstimulation at higher doses (Arnsten et al. 2017). Some D1 agonists also show rapid development of tolerance due to constant activation of the D1 receptor (Gulwadi et al. 2001). In contrast, because a D1PAM would be dependent on endogenous tone and thus subject to normal feedback control, it should have a much lower propensity for overstimulation. Furthermore, since endogenous tone is intermittent, there should be less potential for development of tolerance.

3.2. Background

Lewy Body Dementia (LBD), including Parkinson's disease dementia (PDD) and DLB, is a progressive neurodegenerative disorder associated with alpha-synuclein deposition, Lewy body pathology, and degeneration of nigro-striatal dopaminergic neurons. According to the Parkinson's Disease Foundation, Parkinson's disease (PD) affects approximately 1 million people in the United States (U.S.) and 7 to 10 million people worldwide (Statistics on Parkinson's). It is estimated that up to 78% of of patients with PD will develop dementia (PDD) in their lifetime (Aarsland et al.2005). DLB is the second most common dementia after Alzheimer's disease (AD) and affects 1.4 million individuals in the U.S., representing an estimated 15-20% of all dementia cases worldwide (Lewy Body Dementia Association [https://www.lbda.org/go/10-things-you-should-know-about-lbd).

LBD is pathologically characterized by intraneuronal inclusions of Lewy bodies throughout subcortical and cortical brain regions, a major component of which is misfolded aggregated α-synuclein (Beyer et al. 2009). Lewy body formation and propagation is accompanied by progressive neurodegenerative processes, particularly affecting the dopaminergic and cholinergic neurons (Harding and Halliday 2001; Klein et al. 2010; Colloby et al. 2012). These neuropathological findings are largely indistinguishable between DLB and PDD and have thus led the field to consider them the same disease.

The cognitive impairments of PDD and DLB also overlap. Progressive executive dysfunction and visual-spatial abnormalities are noted in both, but memory remains relatively intact early in the course of disease (Lippa et al. 2007). Prodromal and non-motor features are similar for both conditions and include REM sleep behavior disorder, hyposmia, prominent visual hallucinations, fluctuations in arousal, autonomic dysfunction, and depression/anxiety. They share neuroimaging characteristics with overlapping patterns of atrophy, glucose utilization, and neurotransmitter changes (cortical cholinergic deficits [Colloby et al. 2016] and striatal/cortical

dopaminergic deficits [Klein et al. 2010]). Although once considered as two separate entities, the constellation of supportive pathological, clinical, imaging, and neurochemical data suggest PDD and DLB fall within a spectrum of the same disease (Berg et al. 2014; Gomperts 2016; Friedman 2018; Jellinger 2018; Jellinger and Korczyn 2018).

Because of the dopaminergic fronto-striatal dysfunction and cholinergic deficits associated with LBD [Klein et al. 2010], LY3154207, a D1PAM, is a hypothesized mechanism to treat cognitive deficits of the disorder. LY3154207 increases the affinity of dopamine for the D1 receptor, thus amplifying the response to endogenous dopamine and increasing D1 tone when and where dopamine is released. By potentiating the response to the remaining brain dopamine (or administered L-DOPA), a D1PAM should improve cognitive performance through enhancing frontal dopaminergic neurotransmission. In addition to facilitating dopamine neurotransmission, LY3154207 may be effective in improving cognitive dysfunction through activation of cortical neurons, markers of synaptic plasticity, and D1 mediated enhanced acetylcholine neurotransmitter release. Other potential effects such as reduced daytime sleepiness, enhanced motor function, improved mood, and goal-directed behaviors leading to reduced apathy (via activation of cortical and striatal D1 receptors) would also be beneficial in LBD.

3.3. Benefit/Risk Assessment

CCI [redacted] Study HBEH is a proof-of-concept study, and no benefit for participation should be anticipated.

Subjects participating in Study HBEH may experience CCI [redacted]

CCI [redacted]

The development and reproductive risks of LY3154207 administration are unknown and therefore women of child-bearing potential (WOCBP) have been excluded from participation in Study HBEH.

More information about the known and expected benefits, risks, serious adverse events (SAEs), and reasonably anticipated adverse events (AEs) of LY3154207 are to be found in the IB.

4. Objectives and Endpoints

Table HBEH.2 shows the objectives and endpoints of the study.

Table HBEH.2. Objectives and Endpoints

Objectives	Endpoints
Primary To test the hypothesis that LY3154207 administered at 10 mg, 30 mg, and/or 75 mg daily (or 50 mg based on interim analysis) (QD) oral dosing for 12 weeks will result in a significant improvement in cognition in subjects with mild-to-moderate LBD (PDD or DLB) compared with placebo.	Change in the CoA composite score of the CDR-CCB from baseline to Week 12
Secondary **Efficacy:**	
To evaluate the global efficacy of LY3154207	ADCS-CGIC score from baseline to Week 12
To evaluate the efficacy of LY3154207 on cognitive outcomes	Change in the CDR-CCB PoA composite score from baseline to Week 12
To evaluate the efficacy of LY3154207 on cognitive outcomes	Change in the ADAS-Cog_{13} score from baseline to Week 12
To evaluate the efficacy of LY3154207 on cognitive outcomes	Change in the MoCA score from screening to Week 12
To evaluate the efficacy of LY3154207 on neuropsychiatric symptoms	Change in the NPI total and individual item scores from baseline to Week 12
To evaluate the effect of LY3154207 on daytime sleepiness	Change in the ESS score from baseline to Week 12
To evaluate the effect of LY3154207 on Parkinson's disease severity	Change in the MDS-UPDRS total score (sum of parts I-III) from baseline to Week 12
To evaluate the efficacy of LY3154207 on functional outcome	Change in the PDAQ-15 total score from baseline to Week 12
To evaluate the effect of LY3154207 on verbal fluency	Change in D-KEFS Verbal Fluency test score from baseline to Week 12
To evaluate the effect of LY3154207 on motor signs	Change in MDS- motor exam (Part III) from baseline to Week 12

Objectives	Endpoints
Safety:	
To evaluate the effect of LY3154207 on home blood pressure monitoring (HBPM) of SBP	Change in HBPM SBP from baseline to Week 12
To evaluate the effect of LY3154207 HBPM of pulse rate	Change in HBPM of pulse rate from baseline to Week 12
To evaluate the effect of LY3154207 on physical withdrawal symptoms	Change in the PWC-20 total score from Week 12 to in-clinic follow-up visit
To evaluate the effect of LY3154207 on acute changes of vital signs on the first day of dosing	Number of subjects who met the potentially clinically significant vital signs criteria at 3 consecutive time points at Visit 3 (Day 1 stopping rules)
To evaluate the effect of LY3154207 on BP on the first day of dosing	Change in in-clinic BP from 0 up to 8 hours post dose on the first day of study drug dosing
To evaluate the effect of LY3154207 on pulse rate on the first day of dosing	Change in in-clinic pulse rate from 0 up to 8 hours post dose on the first day of study drug dosing
To evaluate the effect of LY3154207 on BP from baseline to Week 12	Change in in-clinic mean BP at baseline to mean BP at Week 12
To evaluate the effect of LY3154207 on pulse rate from baseline to Week 12	Change in in-clinic mean pulse rate at baseline to mean pulse rate at Week 12
Pharmacokinetics: To assess the PK of LY3154207	Steady-state trough plasma concentrations of LY3154207 at Week 12
Tertiary/Exploratory **Efficacy**	
To evaluate the efficacy of LY3154207 on cognitive outcomes	Change in total score of the ADAS-Cog_{11} from baseline to Week 12
To evaluate the efficacy of LY3154207 on cognitive outcomes	Change in the CDR-CCB Cognitive reaction time composite score, Reaction Time Variability composite score, and Speed Score composite scores from baseline to Week 12 Change in the CDR-CCB individual task outcomes from baseline to Week 12 including simple reaction time, digit vigilance, choice reaction time, numeric working memory, spatial working memory, verbal memory, and visual memory.
To evaluate the effect of LY3154207 on depressed mood, apathy, and fatigue	Change in MDS-UPDRS Part IA score from baseline to Week 12
To evaluate the effect of LY3154207 on mood	Change in GDS-S score from screening to Week 12

Objectives	Endpoints
To evaluate the effect of LY3154207 on depressive symptoms	Change in NPI score (Part D Depression/Dysphoria) from baseline to Week 12
To evaluate the effect of LY3154207 on impulse control	Change in QUIP score from baseline to Week 12
Digital biomarkers	
To evaluate the feasibility of using the Lilly Trial application (Lilly Trial app) to evaluate the effect of LY3154207 on motor tasks or cognitive outcomes in a subset of subjects	To explore trends, utilizations, and changes in quantitative motor and cognitive outcomes as measured by the Lilly Trial App scores from predose assessments to 12 weeks
To explore the feasibility of using actigraphy to evaluate the effect of LY3154207 on various sleep parameters and day time activity including but not limited to sleep latency, duration of sleep, sleep–wake cycles, sleep architecture, and sleep disruption	Change in actigraphy measured sleep parameters as measured by an actigraphy watch from predose assessments to 12 weeks
Pharmacogenomic	
To evaluate genetic interactions with study treatment response or safety if appropriate/as warranted	Explore relationships between pharmacogenomic variations and relevant clinical outcomes.

Abbreviations: ADAS-Cog_{11} = 11-item Alzheimer's Disease Assessment Scale – Cognitive subscale; ADAS-Cog_{13} = 13-item Alzheimer's Disease Assessment Scale – Cognitive subscale; CDR-CCB = Cognitive Drug Research Computerized Cognition Battery; ADCS–-CGIC = Alzheimer's Disease Cooperative Study – Clinician Global Impression of Change; CoA = Continuity of Attention; D-KEFS = Delis–Kaplan Executive Function System ; DLB = dementia with Lewy bodies; ESS = Epworth Sleepiness Scale; LBD = Lewy Body Dementia; HBPM = home blood pressure monitoring; MDS-UPDRS = Movement Disorder Society's Unified Parkinson's Disease Rating Scale; MoCA = Montreal Cognitive Assessment; NPI = Neuropsychiatric Inventory; PDD = Parkinson's disease dementia; PDAQ-15 = Penn Parkinson's Daily Activities Questionnaire-15; PK = pharmacokinetics; PoA = Power of Attention; PWC-20 = physician withdrawal checklist-20; QD = once a day; QUIP = Questionnaire for 'Impulsive-Compulsive Disorders in Parkinson's Disease; SBP = systolic blood pressure.

5. Study Design

5.1. Overall Design

Study HBEH is a multicenter, randomized, double-blind, parallel-group, placebo-controlled, fixed-dosage, Phase 2 study comparing 3 dosages of LY3154207 (10, 30, or 75 mg administered orally [or 50 mg based on interim analysis] once a day [QD]) with placebo over 12 weeks in subjects with mild-to-moderate dementia associated with LBD (PDD and DLB). The study includes a Screening Period (Visits 1 to 2) of a minimum of 7 days and up to 14 days, a Pretreatment Period of a minimum of 11 days and up to 17 days (Visits 2 to 3), a 12-week Treatment Period (Visits 3 to 11), and a 14-day Safety Follow-Up Period including a telephone visit (Visit 11 + 2 days) and Visit 801 or early termination [ET]/discontinuation [DC]. Subjects who meet entry criteria will be randomized in a 1:1:1:1 ratio to LY3154207 (10 or 30 or 75 mg QD) or placebo. The primary objective of this study is to test the hypothesis that LY3154207 administration for 12 weeks will result in a significant improvement in cognition as measured by the change from baseline to Week 12 on the Continuity of Attention (CoA) composite score of the Cognitive Drug Research Computerized Cognition Battery (CDR-CCB), in subjects with mild-to-moderate dementia associated with LBD (PDD and DLB), compared to placebo. (Wesnes et al. 2005; Rowan et al. 2007, McKeith et al 2000).

Figure HBEH.1 illustrates the study design.

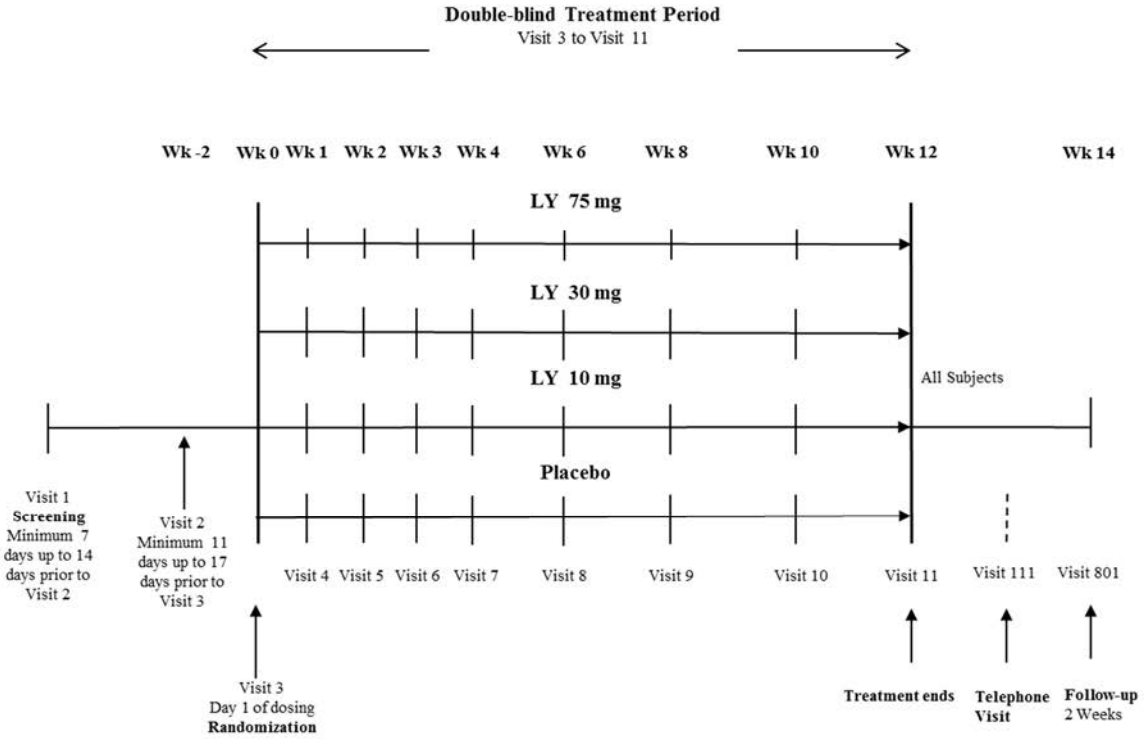

Figure HBEH.1. Illustration of study design for Clinical Protocol I7S-MC-HBEH(b).

Abbreviations and definitions are provided in Appendix 1; clinical laboratory tests are described in Appendix 2; study governance considerations are described in detail in Appendix 3; and hepatic monitoring tests for treatment-emergent abnormality are provided in Appendix 4.

5.1.1. Screening Period (Visit 1)

At or prior to Visit 1, the study will be explained to the subject (and his or her legal representative, if applicable) and caregiver. Informed consent of the subject and caregiver must be obtained prior to any study procedures conducted. The screening period length is of a minimum of 7 days to a maximum of 14 days between Visit 1 and Visit 2. See the Schedule of Activities (Section 2) for the timing of events and the measures to be assessed during the screening period.

Current or planned use of concomitant medications, the effects of vacations or absences on protocol compliance, and general compliance with the protocol should be discussed at Visit 1. Subjects must meet applicable eligibility criteria (Section 6.1 and Section 6.2) to continue to Visit 2. Refer to Section 6.4 for more information about rescreening criteria.

Visit 1 is expected to be of a duration of approximately 3 to 5 hours and may be split over 1 to 2 days.

5.1.1.1 Screening Procedures

Screening, entry and administrative procedures, cognitive and physical assessments, vitals, safety assessments, and laboratory assessments (see Schedule of Activities) are to be performed at Visit 1. For subjects treated with dopaminergic treatment for parkinsonism symptoms, the CDR-CCB and MoCA should be conducted in the practically defined medication "on" state. The "on" state is defined as the individual's best motor function as determined by the investigator or approximately 1 hour after the dose of dopaminergic therapy. Every attempt should be made to conduct these assessments in the "on" state. In the exceptional circumstance that this is not possible, the assessments could be done in the "off" state. The "on/off" state should be confirmed prior to completion of the respective scales listed above. This information will be collected in the electronic Clinical Outcome Assessment (eCOA) or the electronic case report form (eCRF). If any portion of an assessment is done in the "off" state, then that subject should be rated as in the "off" state for the whole assessment. Subjects NOT on dopaminergic therapy should be recorded as being in the "on" state for the purpose of analysis.

Medical history should include the diagnosis, whether PDD or DLB, and the timing of onset of dementia and Parkinson's symptoms and date of diagnosis if applicable. Additionally, the relationship of the onset of dementia relative to motor symptoms will be assessed. Subjects without motor symptoms should report their dementia as occurring prior to motor symptoms.

The physical examination should include head, ear, eye, nose, and throat (HEENT), cardiac, lung, abdomen, extremity, skin, and neurological examinations.

5.1.1.1.1. BP and Pulse Rate

Subjects should have a BP or pulse rate at Visit 1 and Visit 3 (time 0), as determined by 3 sequential BP/pulse rate measurements in the seated position:

- Subjects <60 years old:
  - a mean systolic blood pressure (SBP) less than or equal to 140 mmHg, a mean diastolic BP less than or equal to 90 mmHg, and a mean pulse rate less than or equal to 90 beats/min in the seated position.
  - each of the 3 SBP measurement must be less than 180 mmHg.
- Subjects ≥60 years old:
  - a mean SBP less than or equal to 150 mmHg, a mean diastolic BP less than or equal to 90 mmHg, and a mean pulse rate less than or equal to 90 beats/min in the seated position.
  - each of the 3 SBP measurement must be less than 180 mmHg.

5.1.1.1.2. CDR-CBB

At Visit 1, two training sessions of the CDR-CBB will be administered to familiarize subjects with the instrument and to minimize practice effects. Subjects must be able to complete both training sessions in order to be considered eligible for HBEH. Scores on the CDR-CCB at V1 will not be included in the analysis unless the baseline (V2) scores are incomplete or missing and then V1 scores may be used for calculation of the baseline.

5.1.1.1.3. Modified Hoehn and Yahr Scale

The Hoehn and Yahr Scale (Hoehn and Yahr 1967) is used to describe the symptom progression of PD. The scale was originally described in 1967 and included Stages 1 through 5. It has since been modified with the addition of Stages 1.5 and 2.5 to account for the intermediate course of PD. The modified Hoehn and Yahr scale is as follows:

- Stage 0: No signs of disease
- Stage 1: Unilateral disease
- Stage 1.5: Unilateral plus axial involvement
- Stage 2: Bilateral disease, without impairment of balance
- Stage 2.5: Mild bilateral disease, with recovery on pull test
- Stage 3: Mild-to-moderate bilateral disease; some postural instability; physically independent
- Stage 4: Severe disability; still able to walk or stand unassisted
- Stage 5: Wheelchair bound or bedridden unless aided

5.1.1.1.4. Clinical Diagnostic Criteria for PD and DLB

Subjects must meet diagnostic criteria for either PD or DLB.

PD Criteria: Subjects should meet MDS criteria for clinically probable PD (Postuma et al. 2015) as detailed in Appendix 5. Subjects must have parkinsonism as defined by the presence of

bradykinesia with either rest tremor and/or rigidity. Subjects must not have any absolute exclusion criteria. Subjects must not have greater than 2 red flags; if 1 red flag is present then it must be offset by 1 supportive criterion and if 2 red flags are present it must be offset by 2 supportive criteria. The MDS criteria does not have a criterion for the timing of dementia onset and therefore subjects may be considered PD whether the timing of dementia occurred prior to, concurrently or after parkinsonism. See Appendix 5 for the detailed list of absolute exclusion criteria, red flags and supportive criteria.

DLB Criteria: Subjects should meet the Fourth consensus report of the DLB Consortium diagnostic criteria for probable DLB (McKeith et al. 2017) as detailed in Appendix 6. In addition to dementia, subjects must have 2 or more of the 4 core clinical features of DLB (fluctuation in cognition, visual hallucinations, REM sleep behavior disorder and/or parkinsonism). Subjects with 1 core feature are eligible if they also have at least 1 indicative biomarker as detailed in Appendix 6. Typically, a diagnosis of DLB is made when dementia onset occurs before, concurrently, or in absence of parkinsonism. There is no minimal requirement for parkinsonism in subjects with DLB, who otherwise meet this criteria. See Appendix 6 for the detailed list of core features and indicative biomarkers.

5.1.1.1.5. Montreal Cognitive Assessment Scale

The MoCA will be administered to subjects in Visit 1 to determine if he or she meets entry criteria for dementia. Individuals must have a MoCA score of 10 to 23 at screening to be eligible for the study. The MoCA, included here as a screening cognitive assessment, is described in detail in Section 9.1.2.1.5.

5.1.1.1.6. Geriatric Depression Scale Short Form

The GDS is a site-administered questionnaire of depression in older adults (Yesavage et al. 1983). Users respond in a "Yes/No" format. Originally developed as a 30-item scale (Long Form), it has since been shortened to a 15-item scale (Short Form), which can be completed in approximately 5 to 7 minutes (Sheikh and Yesavage 1986). Of the 15 items, 10 are indicative of depression when answered "Yes" and 5 are indicative of depression when answered "No." Caregiver's input may be needed at Visit 1 for the Geriatric Depression Scale – Short form (GDS-S).

5.1.1.1.7. Columbia-Suicide Severity Rating Scale – Children's Version

The C-SSRS is a scale that captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the corresponding assessment period. The C-SSRS, included here as a screening assessment, is described in detail in Section 9.4.4. The C-SSRS "Baseline" version will be used at screening, and the findings will constitute the baseline assessment.

The C-SSRS will be administered to the patient with the study partner/study informant present or available by telephone, after the cognitive and functional assessments. Responses from both the study partner/study informant and patient will be considered when administering the scale. If a suicide-related thought or behavior is identified at any time during the study, a thorough evaluation will be performed by a study physician, and appropriate medical care will be provided.

The Lilly Self-Harm Supplement should be completed every time the C-SSRS is administered. If, based on administration of the C-SSRS, it is determined that suicide-related behaviors have occurred, then the Lilly Self-Harm Follow-Up form will be used to collect additional information to allow for a more complete assessment of these behaviors.

5.1.2. Pretreatment Period (Visit 2)

See the Schedule of Activities (Section 2) for the timing of events and the measures to be assessed at Visit 2.

Visit 2 is expected to be of a duration of approximately 6 hours. All study procedures for the visit are to be completed within 1 day. In exceptional circumstances, if the clinical assessments cannot be completed within 1 day, those clinical assessments may be completed the next day. The orthostatic blood pressure measurements, in-clinic blood pressure measurements, the CDR-CCB, and the laboratory procedures including pharmacokinetics (PK) must be completed on Day 1 of that visit. The visit interval will start from Day 1.

Subjects must continue to meet applicable eligibility criteria (Section 6.1 and Section 6.2) to continue to Visit 3. Subjects who do not meet all inclusion criteria or who meet any exclusion criteria will be discontinued from the study.

5.1.2.1 Blood Pressure and Pulse Rate Measures

Orthostatic BP/pulse rate measurements will be collected at time 0 of the in-clinic BP/pulse rate monitoring. Subjects will have 3 BP/pulse rate measurements taken in the seated position approximately 1 minute apart followed by 1 BP/pulse rate measurement taken in the standing position. Subjects should be seated for at least 5 minutes and stand for at least 3 minutes prior to taking the respective measurements. If the subject feels unable to stand, vital signs only in the seated position will be recorded.

In-clinic BP and pulse rate measurements will occur at time 0 and every 60 minutes thereafter up to 6 hours. The initial measurement, time 0 of the in-clinic BP and pulse rate monitoring, will be done as an orthostatic BP/pulse rate (refer to orthostatic BP/pulse rate above), and subsequent BP and pulse rate measurements will be done in the seated position only.

5.1.2.2 Cognitive, Motor, and Functional Assessments

For subjects treated with dopaminergic therapy for parkinsonism symptoms, CDR-CCB, Alzheimer's Disease Assessment Scale – 13-Item Cognitive Subscale [ADAS-Cog$_{13}$], Movement Disorder Society's Unified Parkinson's Disease Rating Scale [MDS-UPDRS] [Part III]) and Delis–Kaplan Executive Function System (D-KEFS) assessments should be conducted in the practically defined medication "on" state. The "on" state is defined as the individual's best motor function as determined by the investigator or approximately 1 hour after the dose of dopaminergic therapy. Every attempt should be made to conduct these assessments in the "on" state. In the exceptional circumstance that this is not possible, the assessments could be done in the "off" state. The "on/off" state should be confirmed prior to completion of the respective scales listed above. This information will be collected in the eCOA or the eCRF. If any portion of an assessment is done in the "off" state, then that subject should be rated as in the

"off" state for the whole assessment. Subjects NOT on dopaminergic therapy should be recorded as being in the "on" state for the purpose of analysis.

Caregiver's input will be needed at Visit 2 for the Penn Parkinson Daily Activities Questionnaire-15 (PDAQ-15), Alzheimer's Disease Cooperative Study – Clinician Global Impression interview, MDS-UPDRS, Neuropsychiatric Inventory (NPI), Epworth Sleepiness Scale (ESS), and Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP) scales.

The C-SSRS "Since Last Visit" scale will be assessed. If, based on assessment of the C-SSRS, it is determined that suicide-related behaviors have occurred, then the Lilly Self-Harm Follow-Up form will be used to collect additional information to allow for a more complete assessment of these behaviors.

5.1.2.3 Actigraphy and iPAD Device

The actigraphy device, similar to a watch, will be placed on the wrist of the subject at Visit 2 (if available and if consented) for the 2-week period of time until Visit 3 (see Section 9.8.1.2 and the Operations Manual).

An iPad configured with the Lilly Trial application (Lilly Trial app) will be provided to the subjects (if available and if consented) (see Section 9.8.1.1 and the Operations Manual). Subjects should complete assessments starting the day following Visit 2, throughout the dosing period, and for 2 weeks after the conclusion of the treatment period (until Visit 801). This assessment should be done up to twice daily.

5.1.2.4 Home Blood Pressure Monitoring

The subject should be given the home blood pressure monitoring (HBPM) device at Visit 2 and instructed to measure Home BP twice daily in the seated position using the HBPM equipment provided by Lilly for a minimum of 7 days between Visit 2 and Visit 3. Home BP should be measured twice in the morning (approximately 1 minute apart) (e.g., 8 AM) immediately following study medication dosing and twice in the evening, approximately 12 hours later (approximately 1 minute apart) (e.g., 8 PM).

5.1.3. Double-Blind Period (Visit 3 through Visit 11)

See the Schedule of Activities (Section 2) for the timing of events and the measures to be assessed during the double-blind period.

Estimated length of study visits:

- Visit 3: approximately 8 hours
- Visit 4, Visit 5, Visit 6, Visit 7, Visit 9, and Visit 10: approximately 2 hours
- Visit 8 and Visit 11: approximately 6 hours

All study procedures for the respective visits should be completed within 1 day. In exceptional circumstances, if the clinical assessments cannot be completed within 1 day at V3, V8, and/or V11, those clinical assessments may be completed the next day. The orthostatic blood pressure measurements, in-clinic blood pressure measurements, the CDR-CCB, and the laboratory

procedures including PK must be completed on the first day of that visit. The visit interval will start from the first day of visit.

Visit 3 (Day 1 of dosing)

5.1.3.1. Orthostatic BP/Pulse Rate Measurements

Prior to dosing, orthostatic BP/pulse rate measurements will be collected at time 0 of the in-clinic BP/pulse rate monitoring. Subjects will have 3 BP/pulse rate measurements taken in the seated position approximately 1 minute apart followed by 1 BP/pulse rate measurement taken in the standing position. Subjects should be seated for at least 5 minutes and stand for at least 3 minutes prior to taking the respective measurements. If the subject feels unable to stand, vital signs only in the seated position will be recorded.

The mean should be calculated from the 3 initial in-clinic BP/pulse rate measurements taken in the seated position, and must meet inclusion criteria [6] in order to proceed with dosing (Table HBEH.4). At Visit 3, subjects not fulfilling inclusion criteria [6] at their time 0 BP/pulse rate measurements can have their BP/pulse rate re-evaluated within 3 days. If inclusion criteria [6] is subsequently met (within 3 days of Visit 3), subject may proceed with dosing. If inclusion criteria [6] is subsequently not met (within 3 days of Visit 3), the subject must be discontinued. Subjects who continue to meet entry criteria will be randomized to LY3154207 (10, 30, or 75 mg QD) or placebo immediately following confirmation that subject meets inclusion criteria [6]. Subjects should be dosed immediately after randomization.

The time 0 mean BP and pulse rate will be used for the baseline measurement to assess the change threshold for the development of potentially clinically significant BP/pulse rate (Table HBEH.3).

After time 0, in-clinic BP and pulse rate measurements will be taken every 60 minutes in the seated position only for up to 8 hours. Subjects who meet potentially clinically significant BP/pulse rate measurement (Table HBEH.3) at 3 consecutive timepoints (Day 1 stopping rules) should be discontinued from the study.

Table HBEH.3. Potentially Clinically Significant Vital Sign Criteria

	Low[a]	High[a]
Systolic BP (mm Hg)	≤90 AND ≥20 decrease	≥180 AND ≥20 increase
Diastolic BP (mm Hg)	≤50 AND ≥15 decrease	≥105 AND ≥15 increase
Pulse Rate (bpm)	≤50 AND ≥15 decrease	≥120 AND ≥15 increase

Abbreviations: BP = blood pressure, bpm = beats per minute, mm Hg = millimeters of mercury

[a] Both conditions on absolute AND relative values are required for the measures to meet the criteria for potentially clinically significant (for example BP ≥180 AND ≥20 increase are both required for systolic blood pressure to meet the criteria for potentially clinically significant)

Table HBEH.4. Vital Sign Inclusion Criteria [6] for Subjects at Visit 1 and Visit 3 (time 0)

	Subjects <60 Years	Subjects ≥60 Years
Mean Systolic BP[a] (mm Hg)	≤140	≤150
Mean Diastolic BP (mm Hg)	≤90	≤90
Mean Pulse Rate (bpm)	≤90	≤90

[a] Each of the 3 SBP measurement must be less than 180 mmHg

5.1.3.2. PK Sample

A PK sample is to be collected within 1 to 3 hours after the drug is administered at the site. The date and time of the PK sample collection as well as the date and time of the dose administration immediately preceding the PK sampling will be recorded.

5.1.3.3. Home Blood Pressure Monitoring

Home BP measurements should be conducted for a minimum of 7 days between Visit 2 and Visit 3, for approximately 3 weeks between Visit 3 and Visit 6, and for a minimum of 7 days between Visit 10 and Visit 11, and Visit 11 and Visit 801. Home BP should be measured twice in the morning (approximately 1 minute apart) (e.g., 8 AM) immediately following study medication dosing and twice in the evening, approximately 12 hours later (approximately 1 minute apart) (e.g., 8 PM).

5.1.3.4. Visit 4 to Visit 11

Visits will occur at weekly intervals (7 days ± 1 day) for Visit 4 through Visit 7, and will occur at biweekly intervals (14 days ± 3 days) for Visit 8 through Visit 11.

Study drug is to be administered at the clinic on the morning of Visit 8 and Visit 11 following the Time 0 in-clinic BP/pulse rate measurements.

In-clinic BP/pulse rate monitoring at Visit 8 and Visit 11 will be conducted as described in Section 5.1.2.

At each visit, the CDR-CCB should be assessed after the study drug has been administered. At Visit 4, Visit 5, Visit 6, Visit 7, Visit 9, and Visit 10, if a subject has not taken study drug prior to the study visit, the subject must take study drug at the site prior to the CDR-CCB assessment.

MoCA, ADAS-Cog13, MDS-UPDRS [Part III], and D-KEFS will be performed according to the Study Schedule.

Caregiver's inputs will be needed at Visit 4, Visit 8, Visit 11, or ET/ DC for the PDAQ-15, Alzheimer's Disease Cooperative Study – Clinician Global Impression of Change (ADCS-CGIC), MDS-UPDRS, NPI, ESS, GDS-S, and/or QUIP scales. Caregiver's input, separate from the subject, will be needed at Visit 11, Visit 111 and Visit 801 for the PWC-20 early termination.

5.1.4. Telephone Visit (Visit 111)

A telephone visit will be conducted 2 days following Visit 11. The PWC-20 will be assessed with the subject and caregiver, separately, at this telephone visit.

5.1.5. Follow-Up Period (Visit 801)

A follow-up visit will be performed at Visit 801, which will occur 14 days ± 3 days following the subject's last dose of study medication.

Visit 801 is expected to be of a duration of approximately 2 hours.

Caregiver's inputs will be needed at Visit 801 for MDS-UPDRS, PWC-20, and ESS.

See the Schedule of Activities (Section 2) for the timing of events and the measures to be assessed during the follow-up period.

5.2. Number of Subjects

Approximately 750 subjects will be screened to achieve 340 randomized and evaluable subjects for an estimated total of 85 evaluable subjects per treatment group.

5.3. End of Study Definition

End of the study is the date of the last scheduled procedure shown in the Schedule of Activities (Section 2) for the last subject.

5.4. Scientific Rationale for Study Design

Study HBEH will include subjects who meet the revised MDS criteria for PD (Postuma et al. 2015) or those who meet the revised criteria for DLB, and all who have mild-to-moderate dementia as defined by a decline in cognitive function, which in the opinion of the investigator has resulted in functional impairment and a MoCA score between 10 and 23 (Trzepacz et al. 2015). The inclusion of LBD (PDD or DLB) in HBEH meets current thinking about LBD that, apart from the timing of cognitive impairment, PDD and DLB are clinically and pathologically indistinguishable and would likely respond to similar therapeutic approaches (Aarsland et al. 2004; Ballard et al. 2006).

Placebo is included as the control, in a blinded manner for investigator and site staff and subjects, to allow for an unbiased assessment of the safety data generated, which will allow for a more robust comparison between LY3154207 and placebo data. Comparison of 3 dosage levels of LY3154207 was chosen to evaluate dosage exposure response for safety and efficacy. Initial visits (Visit 3 to Visit 7) were selected to occur at a weekly interval to provide a detailed evaluation of the efficacy and safety of LY3154207 during the initial treatment. A dosing duration of 12 weeks was selected, as it is estimated to be the minimum duration in which a beneficial effect on cognition may be observed.

5.5. Justification for Dose

Three fixed dosages of LY3154207 (10, 30, or 75 mg administered orally [or 50 mg QD, see Section 10.3.7, Interim Analysis]) were selected based on current preclinical pharmacology and toxicology data, and clinical PK, pharmacodynamic and safety data.

The key considerations regarding the dose selection were to:

- ensure a broad exposure exploration around the effective concentration 25 (EC25) defined as the drug concentration at which 25% of the maximal response has been achieved. CCI [redacted]
- CCI [redacted]
- explore the possibility of an inverted U-shaped pharmacodynamic effect on cognition
- explore whether different dosages of LY3154207 have differential efficacy on domains of PD (cognition, motor, wakefulness).

In Study HBEA, CSF samples were collected in healthy subjects, and the peak mean CSF concentrations of LY3154207 following a CCI [redacted] Given that LY3154207 PK is dose linear, the proposed dosages of 10, 30, and 75 mg LY3154207 are expected to encompass CCI [redacted]

CCI [redacted]

CCI [redacted]

Evidence from D1 agonists and other activating agents working via dopamine pathways suggests an inverted U-shaped pharmacodynamics effect on cognition (Cools and D'Esposito 2011). Although there is no evidence of an inverted U-shaped response in the Phase 1 data, CCI [redacted]

CCI [redacted] in sleep-deprived healthy subjects receiving a single dose of LY3154207.

Taken together, these data suggest that a CCI [redacted] is likely to cover a broad exposure range, will allow exploration of the broad range of pharmacodynamic effects, may identify an inverted U-shaped dose–response relationship if such effect exists, minimize the risk of either under- or overdosing, and explore differential effects on relevant clinical domains (cognition, motor, wakefulness).

6. Study Population

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

6.1. Inclusion Criteria

Subjects are eligible to be included in the study only if they meet all of the following criteria (note that inclusion criteria [6] must be met at additional visits):

Type of Subject and Disease Characteristics

[1] Male and female subjects aged 40 to 85 years (inclusive).

[45] Meet diagnostic criteria for PD (Postuma et al. 2015) or DLB (McKeith et al. 2017) (See Appendix 5 and 6)

[2] Inclusion criterion 2 removed with Amendment b

[3] Have dementia as defined by a decline in cognitive function, which in the opinion of the investigator has resulted in functional impairment.

[4] Have a MoCA score of 10 to 23

[5] Are Modified Hoehn and Yahr Stages 0 to 4.

[6] Have a BP or pulse rate at Visit 1 and Visit 3 (time 0), as determined by 3 sequential BP/pulse rate measurements in the seated position:

- Subjects <60 years old:
  - a mean systolic blood pressure (SBP) less than or equal to 140 mmHg, a mean diastolic BP less than or equal to 90 mmHg, and a mean pulse rate less than or equal to 90 beats/min in the seated position.
  - each of the 3 SBP measurement must be less than 180 mmHg.
- Subjects ≥60 years old:
  - a mean SBP less than or equal to 150 mmHg, a mean diastolic BP less than or equal to 90 mmHg, and a mean pulse rate less than or equal to 90 beats/min in the seated position.
  - each of the 3 SBP measurement must be less than 180 mmHg.

[7] If on anti-parkinsonian agents, subjects must be on stable dosage for at least 3 weeks prior to Visit 1, and should remain on stable doses during the course of the study.

[8] If on medications affecting cognition (rivastigmine, galantamine, donepezil, memantine), subjects must be on stable dosage for at least 3 weeks prior to Visit 1 and should remain at a stable dosage during the course of the study.

[9] If on antidepressant medications, subjects must be on stable dosage for at least 3 weeks prior to Visit 1 and should remain at a stable dosage during the course of the study.

[10] If on clozapine, quetiapine, and pimavanserin to address drug-induced or disease-related psychosis, subjects must be on stable dosage for 3 weeks prior to Visit 1 and should remain at a stable dosage during the course of the study.

[11] If on antihypertensive medications, subjects must be on stable dosage for at least 3 weeks prior to Visit 1

Subject Characteristics

[12] Contraception.

[12a] Male subjects, regardless of their fertility status, with nonpregnant WOCBP partners must agree to either remain abstinent (if this is their preferred and usual lifestyle) or use condoms as well as 1 additional highly effective (less than 1% failure rate) method of contraception (such as combination oral contraceptives, implanted contraceptives, or intrauterine devices) or effective method of contraception (such as diaphragms with spermicide or cervical sponges) for the duration of the study and until their plasma concentrations are below the level that could result in a relevant potential exposure to a possible fetus, predicted to be 90 days following the last dose of study drug (below the no-observed-adverse-effect-level [NOAEL]/10) plus 90 days.

[12b] Men and their partners may choose to use a double–barrier method of contraception. (Barrier protection methods without concomitant use of a spermicide are not an effective or acceptable method of contraception. Thus, each barrier method must include use of a spermicide. It should be noted, however, that the use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these barrier methods are combined).

[12c] Men with pregnant partners should use condoms during intercourse for the duration of the study and until 93 days following the last dose of study drug.

[12d] Men should refrain from sperm donation for the duration of the study and until their plasma concentrations are below the level that could result in a relevant potential exposure to a possible fetus, predicted to be 93 days following the last dose of study drug.

[12e] Female subjects not of childbearing potential may participate and include those who are:

- infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as Mullerian agenesis; or

- post-menopausal – defined as:
  - A woman at least 40 years of age with an intact uterus, not on hormone therapy, who has had at least 1 year of spontaneous amenorrhea with a follicle-stimulating hormone level >40 mIU/mL; or
  - A woman 55 or older not on hormone therapy, who has had at least 6 months of spontaneous amenorrhea; or
  - A woman at least 55 years of age with a diagnosis of menopause prior to start of hormone replacement therapy.

[13] In the investigator's opinion is able to comply with all appointments for clinic visits, tests, and procedures, including venipuncture, computerized assessments and examinations required by the protocol.

[14] Are able to swallow capsules.

[15] Have a level of understanding such that the subject can communicate with the site study personnel, understand the study requirements.

[16] All subjects must have a reliable caregiver who is in frequent contact with the subject (defined as at least 10 hours per week) and will accompany the subject to Visit 1, Visit 2, Visit 4, Visit 8, Visit 11, Visit 111 (telephone only) and Visit 801.

[17] The caregiver must be able to communicate with site personnel and be willing to comply with protocol requirements, and in the investigator's opinion must have adequate literacy to complete the protocol-specified questionnaires.

[18] Agree not to post any personal medical data related to the study or information related to the study on any website or social media site (e.g., Facebook, Twitter, LinkedIn, Google+, etc.).

Informed Consent

[19] Provision of signed and dated informed consent form (ICF) from subject and caregiver prior to any study-specific procedures being performed.

6.2. Exclusion Criteria

Subjects will be excluded from study enrollment if they meet any of the following:

Medical Conditions

[20] Are WOCBP.

[21] Have significant central nervous system or psychiatric disease, other than PD or DLB, that in the investigator's opinion may affect cognition or the ability to complete the study.

[22] Have a history in the last 6 months of transient ischemic attacks or ischemic stroke.

[23] Have a history of intra-cerebral hemorrhage due to hypertension.

[24] Have a history of hypertensive encephalopathy.

[25] Have atypical or secondary parkinsonism due to drugs (e.g., antipsychotics) or disease (such as progressive supranuclear palsy, essential tremor, multiple system atrophy [e.g., striatonigral degeneration, olivopontocerebellar atrophy], or postencephalitic parkinsonism).

[26] Have a current implantable intracranial stimulator or history of intracranial ablation surgery (e.g., subthalamic, globus pallidus-internal segment).

[27] Exclusion criterion 27 removed with Amendment b

[28] Exclusion criterion 28 removed with Amendment b

[29] Exclusion criterion 29 removed with Amendment b

[30] Have a history of substance abuse within the past 1 year (drug categories defined by the Diagnostic and Statistical Manual of Mental Disorder, 5th Edition, and/or substance dependence within the past 1 year, not including caffeine and nicotine).

[31] Exclusion criterion 31 removed with Amendment b

[32] Have a serious or unstable medical illness, other than LBD (PDD or DLB), including cardiovascular, hepatic, respiratory, hematologic, endocrinologic, neurologic, or renal disease, or clinically significant laboratory or electrocardiogram (ECG) abnormality as determined by the investigator.

- have a history in the last 6 months of exertional angina, unstable angina, myocardial infarction, and acute coronary syndrome
- have a history of heart failure of either New York Heart Association Class III or IV
- have a history of additional risk factors for Torsades de Pointes (e.g., chronic hypokalemia, family history of Long QT Syndrome)

[33] Subjects with acute liver disease (e.g., acute viral hepatitis, alcoholic hepatitis); subjects with a known chronic liver disease (e.g., hepatitis B, C, alcoholic liver disease, cirrhosis); alanine aminotransferase (ALT) or aspartate aminotransferase (AST) equal to or higher than 2X upper limit of normal (ULN); total bilirubin (TBL) equal to or higher than 1.5X ULN; (except for subjects with Gilbert's syndrome); or alkaline phosphatase (ALP) equal to or higher than 2X ULN.

[34] Subjects have answered "yes" to either Question 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) or Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the "Suicidal Ideation" portion of the C-SSRS - Children's version, or answer "yes" to any of the suicide-related behaviors (actual attempt, interrupted attempt, aborted attempt, preparatory act or behavior) on the "Suicidal Behavior" portion of the C-SSRS; and the ideation or behavior occurred within the past month.

Prior/Concomitant Therapy

[35] Have used antipsychotic medications, with the exception of clozapine, quetiapine, pimavanserin in the 6 months prior to screening (Visit 1) and at any time during the course of the study.

[36] Have used anticholinergics trihexyphenidyl and benztropine in the 4 weeks prior to screening (Visit 1) and at any time during the course of the study.

[37] Have motor conditions for which the antiparkinsonian treatment is expected to change during the course of the study, as well as unpredictable motor fluctuations that in the investigator's opinion would interfere with conducting assessments.

[38] Are taking any medications or food, herbal or dietary supplements that are inhibitors (e.g., ketoconazole, grapefruit juice), or strong/moderate inducers of cytochrome P450 3A4 (CYP3A4) (e.g., rifampicin) or are unable or unwilling to discontinue usage of them 4 weeks prior to Visit 3. If subjects are willing and able to discontinue use of CYP3A4 inhibitors or strong/moderate inducers at least 4 weeks prior to Visit 3, they may proceed in the study. Refer to the Operations Manual for a list of inhibitors and inducers of CYP3A4.

Prior/Concurrent Clinical Trial Experience

[39] Are currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.

[40] Have participated, within the last 3 months, in a clinical study involving an interventional product or device.

[41] Have previously been exposed to LY3154207.

Other Exclusions

[42] Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

[43] Are Lilly employees, employees of IQVIA, or employees of a third party organization involved in the conduct of the study.

[44] Exclusion criterion 44 removed with Amendment b

6.2.1. Rationale for Exclusion of Certain Study Candidates

CCI [redacted]

Subjects with unpredictable motor fluctuations or those expected to require PD medication changes during the course of the study will be excluded, as this may affect performance on cognitive tasks and influence the interpretation of other clinically relevant outcomes.

CNS diseases and other neuropsychiatric disorders (e.g., active psychosis, substance abuse) that can affect performance on cognitive tasks and compliance with the protocol are also excluded.

Medications that negatively affect cognition (e.g., certain anticholinergics, exclusion criterion #36) and motor function (e.g., certain antipsychotics, exclusion criterion #35) will be excluded, given the potential of these medications to confound clinically relevant outcomes.

CCI [redacted]

In addition, WOCBP have been excluded because nonclinical studies of development and reproduction with LY3154207 have not been conducted.

6.3. Lifestyle Restrictions

Subjects should be instructed not to donate blood or blood products during the study or for 93 days following the last dose of LY3154207. Male subjects should be instructed to not donate sperm during the study for 93 days following the last dose of LY3154207.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. The interval between the initial screening and the rescreen should be at least 4 weeks. When the subject is rescreened, the subject must sign a new ICF, be assigned a new subject identification number, and undergo all screening procedures.

7. Treatments

7.1. Treatments Administered

This study involves a comparison of LY3154207 75 mg (or 50 mg, see Section 10.3.7, Interim Analyses), 30 mg, and 10 mg administered orally QD with placebo. Table HBEH.5. shows the treatment regimens.

Table HBEH.5. Treatment Regimens

Regimen	Dose
LY Dose Group 1	10 mg LY (2 × 5-mg caps and 1 placebo caps)
LY Dose Group 2	30 mg LY (1 × 25 -mg caps, 1 x 5 mg caps and 1 placebo caps)
LY Dose Group 3	75 mg LY (3 × 25-mg caps)
Or	50 mg LY (2 x 25-mg caps and 1 placebo caps)
Placebo	3 placebo caps

Abbreviations: caps = capsule; LY = LY3154207.

The investigator or his/her designee is responsible for the following:

- explaining the correct use of the investigational agent(s) to the subject and/or legal representative
- verifying that instructions are followed properly
- maintaining accurate records of investigational product dispensing and collection
- at the end of the study returning all unused medication to Lilly, or its designee, unless the sponsor and sites have agreed all unused medication is to be destroyed by the site, as allowed by local law.

7.1.1. Packaging and Labeling

The drug product is supplied for clinical trial use as capsules for oral administration.

Capsules: Each capsule is composed of LY3154207 with no inactive ingredients other than the hypromellose capsule shell. Each capsule contains LY3154207 4-Hydroxybenzoic acid equivalent to 5 mg or 25 mg of the LY3154207 drug substance. The drug product should be stored according to instructions on the label.

Clinical trial materials will be labeled according to the country's regulatory requirements.

7.2. Method of Treatment Assignment

Subjects who meet all criteria for enrollment will be randomized to double-blind treatment at Visit 3. Subjects will be randomized in a blinded fashion to the 4 treatment arms (Placebo; LY3154207 10 mg; LY3154207 30 mg; LY3154207 75 mg [or 50 mg based on interim analysis – refer to Section 10.3.7]) at 1:1:1:1 ratio. Randomization will use a minimization procedure in order to balance for investigator site and the current use of AChEIs (Yes, No) using an interactive web-response system (IWRS).

The IWRS will be used to assign blister packs containing double-blind investigational product to each subject. One blister pack will be dispensed for each week of dosing, for example, for 14-day study intervals, 2 blister packs will be dispensed at each visit. Site personnel will confirm that they have located the correct blister packs by entering a confirmation number found on the blister packs into the IWRS.

Selection and Timing of Doses

The doses should be administered at approximately the same time each day in the morning. At Visit 3, Visit 8, and Visit 11, the dose will be administered at the clinic. The actual date and time of the dose administrations on the day of Visit 3, Visit 4, Visit 5, Visit 8, Visit 11, and ET/DC visit will be recorded in the subject's eCRF.

7.3. Blinding

This is a double-blind study. To preserve the blinding of the study, a minimal number of Lilly personnel will see the randomization table and treatment assignments prior to study completion. The efficacy and safety interim analyses will be completed by an Independent Internal Assessment Committee (IAC) who will be unblinded. An additional group not directly involved in this study will review unblinded digital biomarker data at prespecified interim analyses.

Emergency unblinding for AEs may be performed through the IWRS, which may supplement or take the place of emergency codes generated by a computer drug-labeling system. This option may be used ONLY if the subject's well-being requires knowledge of the subject's treatment assignment. All calls resulting in an unblinding event are recorded and reported by the IWRS.

If an investigator, site personnel performing assessments, or subject is unblinded, the subject must be discontinued from the study.

In case of an emergency, the investigator has the sole responsibility of determining if unblinding of a subject's treatment assignment is warranted for medical management of the event. The subject's safety must always be the first consideration in making such a determination. Every effort should be made to notify Lilly Medical representative prior to unblinding if feasible. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

7.4. Dosage Modification

Investigator-initiated dosage modifications are not allowed in this study.

7.5. Preparation/Handling/Storage/Accountability

The investigator or his/her designee is responsible for the following:

- confirming appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved prior to use of the study treatment.
- ensuring that only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments 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 treatment accountability, reconciliation, and record maintenance (such as receipt, reconciliation, and final disposition records).

7.6. Treatment Compliance

Subject compliance with study medication will be assessed at each visit. Compliance will be assessed by counting returned capsules. Capsules dispensed and returned should be recorded in the CRF.

Compliance is defined as having taken ≥80% to <120% of the prescribed amount of medication.

7.7. Concomitant Therapy

Concomitant medications to treat the underlying PD (known as antiparkinsonian agents) are permitted, provided the subject has been on a stable dosage regimen for at least 3 weeks prior to Visit 1, and should remain on a stable dosage for the duration of the study. Routine medications taken PRN are allowed. However, if in the investigator's opinion PD medications need to be adjusted to manage motor symptoms during the course of the study, the reason for change in medication should be recorded as an AE and the concomitant medication eCRF page updated accordingly. In addition, the study sponsor should be notified as soon as feasible and a notification generated.

In addition to medications for PD, drugs for common conditions in an older population, such as hypertension, hypercholesterolemia, and ischemic heart disease, are acceptable. Specifically, antihypertensive medications should be stable for 3 weeks prior to V1. During the course of the study, antihypertensive medications may be adjusted for medical need. The concomitant medication eCRF page should be updated accordingly and if applicable the reason for change in medication should be recorded as an AE.

Drugs and supplements that are known inhibitors or inducers of CYP3A4, as well as trihexyphenidyl and benztropine, are specifically excluded.

If subjects are taking atorvastatin, they should be instructed to take atorvastatin in the evening (approximately 12 hours after study drug dosing).

Concomitant medications to treat cognition (rivastigmine, galantamine, donepezil, memantine) and depression are permitted, if subjects have been on a stable dosage regimen for at least 3 weeks prior to Visit 1 and should remain on a stable dosage for the duration of the study. Concomitant medications to treat psychosis (clozapine, quetiapine, and pimavanserin) are permitted, provided the subject has been on a stable dosage regimen for at least 3 weeks prior to Visit 1 and should remain on a stable dosage for the duration of the study. However, if in the investigators opinion cognitive and antipsychotic medications need to be adjusted during the course of the study to address a clinical change, the reason for change in medication should be recorded as an AE and the concomitant medication eCRF page updated accordingly. In addition, the Lilly CRP or designee must be contacted as soon as possible to determine whether the subject should continue in the study.

If the need for concomitant medication arises, inclusion or continuation of the subject may be at the discretion of the investigator after consultation with the Lilly CRP or designee. All concomitant medications taken during the study must be recorded on the concomitant medication eCRF page.

Subjects and their caregiver should be instructed to consult with the appropriate study personnel at the site prior to initiation of any new medications or supplements and prior to changing dose or discontinuing from concomitant medications or supplements.

Additional information about concomitant medications is provided in the Operations Manual.

7.8. Treatment after the End of the Study

7.8.1. Treatment after Study Completion

Study completion will occur following the final analysis of primary and secondary objectives, as determined by Lilly. Investigators will continue to follow Schedule of Activities (Section 2) for all subjects until notified by Lilly that study completion has occurred.

LY3154207 will not be made available after conclusion of the study to subjects.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

8.1.1. Permanent Discontinuation from Study Treatment

Possible reasons leading to permanent discontinuation of study treatment:

- Subject Decision
  - the subject or the subject's designee, for example, legal guardian, requests to discontinue the investigational product.
- Day 1 stopping rules - Discontinuation due to change in acute vital signs on Day 1 (Visit 3)
  If during Day 1 (Visit 3) and following study drug dosing, any of the potentially clinically significant vital signs criteria (Table HBEH.3) are met at 3 ***consecutive*** time points using in-clinic vital sign monitoring, then the subject should be discontinued from the study drug. The relative value of the potentially clinically significant vital sign criteria is calculated by comparing to the mean of the 3 seated blood pressure and pulse rate at Time 0 of Visit 3 (baseline).
  - For vital sign measurements that meet the criteria for potentially clinically significant vital signs (Table HBEH.3) after Visit 3, management will be left to the discretion of the investigator and may include discontinuation of study drug. The investigator should consult with the Lilly CRP or designee.
- Discontinuation due to a hepatic event or liver test abnormality
  Subjects who are discontinued from the study due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via eCRF.
  Discontinuation of the investigational product for abnormal liver tests should be considered by the investigator when a subject meets 1 of the following conditions after consultation with the Lilly-designated medical monitor:
  - ALT or AST >8X ULN
  - ALT or AST >5X ULN for more than 2 weeks
  - ALT or AST >3X ULN and TBL >2X ULN or international normalized ratio >1.5
  - ALT or AST >3X ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
  - ALP >3X ULN
  - ALP >2.5X ULN and TBL >2X ULN
  - ALP >2.5X ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

In addition, subjects will be discontinued from the investigational product in the following circumstances:

- Mean Fredericia's corrected QT interval on the ECG (QTcF) >500 milliseconds or an absolute change >60 milliseconds when compared with baseline

Subjects discontinuing from the study treatment prematurely for any reason should complete an early termination visit and safety follow-up (V801) to complete AE and other follow-up procedures per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events) and Section 9.4 (Safety).

8.1.2. Temporary Discontinuation from Study Treatment

Temporary discontinuation from study drug treatment is allowed if a short-term treatment of an excluded medication is necessary, secondary to hospitalization, personal circumstances, or to evaluate the study drug impact on an uncertain AE. Study drug may be restarted at the investigator's discretion. If temporary discontinuation is due to an AE, it should be reported to the Lilly CRP or their representative. Temporary treatment discontinuation and restarting should be documented in the eCRF. Restarting treatment after a discontinuation period that is greater than 3 consecutive days should be discussed between the investigator and Lilly CRP or their representative.

8.1.3. Discontinuation of Inadvertently Enrolled Subjects

If the sponsor or investigator identifies a subject who did not meet enrollment criteria and was inadvertently enrolled, then the subject should be discontinued from study treatment. However, if the investigator and the sponsor CRP agree that it is medically appropriate to continue in the study, the investigator must obtain documented approval from the sponsor CRP to allow the inadvertently enrolled subject to continue in the study.

If the subject is discontinued from the study, the subject should complete an early termination visit and safety follow-up (V801) to complete safety follow-up as outlined in Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety).

8.2. Discontinuation from the Study

Subjects will be discontinued in the following circumstances:

- enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- investigator decision
    - the investigator decides that the subject should be discontinued from the study

  - if the subject, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent

- subject decision
  - the subject or the subject's legal representative requests to be withdrawn from the study

Subjects discontinuing from the study prematurely for any reason should complete an early termination visit and safety follow-up (V801), to complete AE and other safety follow-up per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety).

8.3. Lost to Follow-Up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact subjects who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

Site personnel, or an independent third party, will attempt to collect the vital status of the subject within legal and ethical boundaries for all subjects randomized, including those who did not get investigational product. Public sources may be searched for vital status information. If vital status is determined, this will be documented and the subject will not be considered lost to follow-up.

Neither Lilly personnel nor Lilly Third Party vendors will be involved in any attempts to collect vital status information.

9. Study Assessments and Procedures

Study assessments and procedures and their timing (including tolerance limits for timing) are summarized in Section 2 (Schedule of Activities).

Appendix 2 lists the clinical laboratory tests that will be performed for this study.

Unless otherwise stated in the subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

9.1. Efficacy Assessments

Screening measures used for diagnosis and establishment of study eligibility are described elsewhere (Section 2 and Section 5.1.1).

To assess the efficacy of LY3154207, which targets attentional and executive function pathways, a set of cognitive tests has been selected as primary and secondary endpoints in Study HBEH.

Cognitive and functional testing for each subject should be performed in the same order as outlined in the Operations Manual to reduce potential variability. If possible, each assessment should be performed on a given subject by the same rater at each visit. The principal investigator has the responsibility of selecting who will administer the instruments at the site, as long as all training requirements (see the Operations Manual) have been met by those raters.

The following is a brief description of the assessments that will be used in this study.

9.1.1. Primary Efficacy Assessments

Continuity of Attention Composite Score from the Cognitive Drug Research Computerized Cognition Battery: The CoA component of the CDR-CCB has been selected as the primary endpoint for this study because it measures the ability to sustain concentration and has demonstrated a significant treatment effect in previous trials in subjects with LBD (PDD or DLB) within the time frame of the current study (Wesnes et al. 2005; Rowan et al. 2007). The battery is a simple "yes/no" computerized assessment that is feasible across a range of PD motor impairment, and as the CoA score is based on accuracy but not speed of response, it is resistant to confounding due to motor impairment (Wesnes et al. 2002). The CDR-CCB is not dependent on skill of a rater, and hence there is less inter-rater variability; learning effects can be minimized with training and it targets domains relevant to subjects with LBD. Treatment effects with acetylcholinesterase inhibitors in LBD subjects have been demonstrated using the CDR (Wesnes et al. 2005; Rowan et al. 2007, McKeith et al 2000). The CoA is calculated from the CDR-CCB by summing the number of correct responses in the digit vigilance and choice reaction time tasks and then subtracting the number of digit vigilance false alarms.

The CDR-CCB system includes tests of attention (simple and choice reaction time, digit vigilance), working memory (spatial and numeric) and episodic memory (word recognition, picture recognition) (Wesnes 2008), from which CoA, Power of Attention (PoA), and cognitive

reaction time can be determined. The CDR-CCB is computer controlled, with information presented on high resolution monitors and responses recorded via a response module containing 2 buttons, 1 marked "no" and the other "yes" (Wesnes et al. 2002; Rowan et al. 2007). The CDR-CCB assessment including the tasks listed below will be completed at each visit:

Word presentation: 12 words are presented on the monitor at the rate of 1 every 3 seconds for the subject to remember.

Picture presentation: A series of 14 pictures are presented on the monitor at the rate of 1 every 3 seconds.

Simple reaction time: The subject is instructed to press the "yes" response button as quickly as possible every time the word "yes" is presented on the monitor. Twenty stimuli are presented with a varying interstimulus interval.

Digit vigilance task: A target digit is randomly selected and then constantly displayed to the right of the monitor screen. A series of digits are then presented in the center of the screen at the rate of 80/min and the subject is required to press the "yes" button as quickly as possible every time the digit in the series matched the target digit. There are 15 targets. The task lasts for approximately 2 minutes in total.

Choice reaction time: *E*ither the word "no" or the word "yes" are presented on the monitor, and the subject is instructed to press the corresponding button as quickly as possible. There are 20 trials for which each stimulus word is chosen randomly with equal probability and there is a varying interstimulus interval.

Spatial working memory: A picture of a house is presented on the screen with 4 of its 9 windows lit. The subject will aim to memorize the position of the lit windows. For each of the 18 subsequent presentations of the house, the subject is required to decide whether or not the one window lit was also lit in the original presentation. The subject will record their response by pressing the "yes" or "no" response button as appropriate.

Numeric working memory: A series of 3 digits is presented for the subject to hold in memory. This is followed by a series of 18 probe digits for each of which the subject has to decide whether or not it was in the original series and press the "yes" or "no" response button as appropriate.

Word recognition: The original words plus 12 distractor words are presented one at a time in a randomized order. For each word, the subject is required to indicate whether or not they recognized it as being from the original list of words by pressing the "yes" or "no" button as appropriate.

Picture recognition: The original pictures plus 14 distractor pictures are presented one at a time in a randomized order. For each picture, the subject is required to indicate whether or not they recognized it as being from the original series by pressing the "yes" or "no" button as appropriate.

Stanford Sleepiness Scale (Hoddes et al. 1973): The subject rates his or her alertness at the present time using a scale of 1 to 7, with 1 being the most alert and 7 being almost asleep.

9.1.2. Secondary Efficacy Assessments

The following assessments should be administered in the same order at specified visits (refer to the Operations Manual for information about the procedural order). Measures should be administered by the same rater to reduce potential variability. To minimize missing data, the rater should go through each measure orally with the subject or caregiver (as designated in the instructions), recording responses appropriately. The same caregiver should be used as the informant at all visits.

9.1.2.1. Measures of Cognitive Function and Related Outcomes

The following assessments will serve as measures to assess cognitive functioning and related outcome:

9.1.2.1.1. Alzheimer's Disease Cooperative Study – Clinician Global Impression of Change Scale

The ADCS-CGIC is a 7-point, categorical scale that provides a single global rating of change from baseline (Schneider et al. 1997) and includes a baseline interview to set subject-specific probes for the follow-up assessments. A score of 1 indicates marked improvement; a score of 2, moderate improvement; a score of 3, minimal improvement; a score of 4, no change; a score of 5, minimal worsening; a score of 6, moderate worsening; and a score of 7, marked worsening. Minimal changes were predefined as clinically detectable changes that did not affect a subject's clinical status; moderate changes as definite, detectable changes that had a corresponding effect on clinical status; and marked changes as those that had a dramatic effect on clinical status.

9.1.2.1.2. Power of Attention Composite Score from the CDR-CCB

The PoA is a composite score derived from the CDR-CCB that measures the intensity of concentration (ability to focus attention): the faster the responses, the more processes are being brought to bear upon the task. The PoA composite score will be calculated by summing the mean choice reaction time, simple reaction time, and digit vigilance reaction time scores.

9.1.2.1.3. Alzheimer's Disease Assessment Scale – 13-Item Cognitive Subscale

Cognitive function will be assessed by using a 13-item version of ADAS-Cog. This version is composed of the original 11-item ADAS-Cog, which measures memory, language, and praxis (Rosen et al. 1984). In addition, it includes Delayed Recall (episodic memory) and Number Cancellation (attention) items that have been shown as reliable and sensitive measures for assessing a wide range of dementia severity (Mohs et al. 1997).

The ADAS-Cog has been designed to evaluate the cognitive impairment characteristic of mild-to-moderate AD dementia. In a placebo-controlled registration study of rivastigmine in PDD, the ADAS-Cog_{11} was used to measure a significant treatment effect over 24 weeks (Emre et al. 2004). ADAS-Cog_{11} has frequently been used in drug studies in mild-to-moderate AD and to date is the only cognition measure used as a primary endpoint in a registration trial for a product approved for PDD. The 2 additional items in the ADAS-Cog_{13}, number cancellation

and delayed recall, offer the opportunity for a more comprehensive assessment of cognition in LBD than the ADAS-Cog_{11}.

The primary cognitive functions tested include components of memory, language, praxis, and attention. Memory is evaluated by the following items: Word Recall (immediate and delayed), Orientation, Word Recognition, and Remembering Test Instructions (based on the Word Recognition task). Language is evaluated by the following items: Spoken Language Ability, Comprehension of Spoken Language, Word-finding Difficulty, Commands, and Naming Objects and Fingers. Praxis is evaluated by the items Constructional Praxis and Ideational Praxis. Attention is evaluated by the number cancellation task. The assessment is expected to take approximately 35 to 50 minutes.

The ADAS-Cog_{13} measures severity of impairment. Higher scores reflect greater cognitive impairment. The maximum score is 85. Most item scores are based on the number of words not recalled or the number of errors: Word Recall, Commands, Constructional Praxis, Delayed Word Recall, Naming, Ideational Praxis, Orientation, and Word Recognition. Remembering Test Instructions is rated based on the number of reminders during the Word Recognition task. Spoken Language Ability, Comprehension of Spoken Language, and Word-finding Difficulty are rated on a scale of severity of dysfunction ranging from 0 to 5, where 0 = no impairment, 1 = very mild, 2 = mild, 3 = moderate, 4 = moderately severe, and 5 = severe. The score for the Number Cancellation item ranges from 0 to 5, based on ranges of numbers of target items correctly crossed off by the subject within the time limit; the fewer correct responses, the higher the score.

9.1.2.1.4. Delis–Kaplan Executive Function System

The D-KEFS Verbal Fluency test requires subjects to produce as many words per minute as they can, starting with a particular letter, with higher scores indicating better performance (Delis et al. 2001).

The D-KEFS verbal fluency has shown a significant response ($p<.001$) to rivastigmine therapy in a 24-week randomized controlled trial in subjects with PDD (Emre et al. 2004). The D-KEFS verbal fluency test is preferred as a measure of executive function in PDD because it is not confounded by motor deficits. This specific measure of executive function, a domain commonly affected in LBD, will complement other measures of cognition included in Study HBEH that do not adequately assess this domain.

9.1.2.1.5. Montreal Cognitive Assessment Scale

The MoCA (available at www.mocatest.org) was developed as a brief screening instrument for mild cognitive impairment and mild AD to address limitations of the Mini-Mental State Examination (MMSE) (Nasreddine et al. 2005). The MoCA has been identified as a suitable screening instrument for the detection of cognitive impairment in PD (Hoops et al. 2009) and DLB (McKeith et al. 2017). Since development, it has been increasingly utilized to detect cognitive impairment in subjects with PD. The MoCA is divided into 7 subscores (maximum possible subscore):

- visuospatial/executive (5 points)
- naming (3 points)
- memory (5 points for delayed recall)
- attention (6 points)
- language (3 points)
- abstraction (2 points)
- orientation to time and place (6 points)

Visuospatial abilities are assessed using a clock-drawing task and a 3-dimensional cube copy. Multiple aspects of executive function are assessed using an alternation task adapted from the Trail Making B task, a phonemic fluency task, and a 2-item verbal abstraction task. The short-term memory recall task involves 2 learning trials of 5 nouns and delayed recall after approximately 5 minutes. Attention, concentration, and working memory are evaluated using a sustained attention task, a serial abstraction task, and digits forward and backward. Language is assessed using a 3-item confrontation naming task with low-familiarity animals (lion, camel, and rhinoceros), repetition of 2 syntactically complex sentences, and the aforementioned fluency task. Finally, 1 point is added if the subject has <12 years of education. The MoCA has a maximum possible total score of 30 points, with higher scores indicating better cognitive performance. A score of greater than 26 is considered normal (Nasreddine et al. 2005; Hoops et al. 2009).

Use of MoCA in the context of PD to screen for subjects with cognitive impairment is consistent with the Parkinson Study Group (PSG) Cognitive/Psychiatric Working Group and MDS recommendations; although, due to limitations of data for the MoCA on change over time or change with treatment, the PSG only reviewed the scale in the context of trials where executive functioning was not a primary outcome (Chou et al. 2010; Litvan et al. 2012). The MoCA has consistently demonstrated higher sensitivity than the MMSE for the detection of mild cognitive impairment in various subject populations including PD and DLB (Nasreddine et al. 2005; Smith et al. 2007, Zadikoff et al. 2008; Olson et al. 2011; Freitas et al. 2012; Biundo et al. 2016; Wang et al. 2013). Using a cut-off score of less than or equal to 26 as a predictor of cognitive impairment, results from the MoCA identified from 52% to 83% of subjects with PD who had already been identified as having mild cognitive impairment (Smith et al. 2007; Hoops et al. 2009; Nazem et al. 2009). A MoCA score of 26 or less has also provided excellent discrimination between subjects who had mild cognitive impairment and those who did not (receiver operating characteristic curve analyses 78% to 90%; sensitivity 90%; specificity 75% (Dalrymple-Alford et al. 2010). Satisfactory test–retest reliability and inter-rater reliability have been demonstrated (interclass correlation coefficients 0.79 and 0.81, respectively) (Gill et al. 2008). Additionally, good correlation between the MoCA and a neuropsychological battery (assessing the domains of memory and executive function) was observed (coefficient of 0.72) (Gill et al. 2008).

9.1.2.1.6. Penn Parkinson's Daily Activities Questionnaire-15

The PDAQ-15 is a 15-item measure of instrumental activities of daily living (IADL) that is impacted by cognitive impairment in subjects with PDD. The PDAQ-15 is derived from the original 50-item scale, which has demonstrated test–retest reliability, construct validity, sensitivity, and specificity to PD cognitive impairment (Brennan et al. 2016a, 2016b), and the questionnaire is completed by the caregiver. The score range is 0 to 60, with higher scores indicating better function. It is derived from a larger 50-item scale that demonstrates excellent test–retest reliability and construct validity, and is both sensitive and specific in PD cognitive impairment. The PDAQ-15 demonstrates ability to discriminate between cognitively normal, mild cognitive impairment, and dementia in PD, and correlates with global measures of cognition (dementia rating scale) and performance-based functional measures. The PDAQ-15 will provide a disease-specific assessment of the effect of LY3154207 on cognitive IADL in order to understand the relationship between change in cognition and change in IADL in PDD and DLB.

9.1.2.2. Measures of Parkinson's Disease Severity

9.1.2.2.1. Movement Disorder Society's United Parkinson's Disease Rating Scale

The MDS-UPDRS Part I (non-motor aspects of experiences of daily living) assesses a wide spectrum of non-motor symptoms of PD and will be used to assess the impact on non-motor features with special interest in apathy, fatigue, and depression. Part II (motor aspects of experience of daily living), Part III (motor examination), and Part IV (motor complications) will be used to assess Parkinson's–related motor function as well as potential impact on motor complications (dyskinesias and motor fluctuations). In general, each item of the scale is scored from 0 to 4 using the following clinical descriptors (Goetz et al. 2007):

- 0 = normal
- 1 = slight; refers to symptoms/signs with sufficiently low frequency or intensity to cause no impact on function
- 2 = mild; refers to symptoms/signs of frequency or intensity sufficient to cause a modest impact on function
- 3 = moderate; refers to symptoms/signs sufficiently frequent or intense to impact considerably, but not prevent, function
- 4 = severe; refers to symptoms/signs that prevent function.

The total MDS-UPDRS is a sum of Parts I, II, and III and ranges from 0 (no impairment) to 263 (maximum impairment).

9.1.2.3. Measures of Behavioral Symptoms

The following measures will serve as tools to assess the impact of LY3154207 on behavioral symptoms associated with LBD as well as the effects on motor functions.

9.1.2.3.1. Neuropsychiatric Inventory

The NPI is a well-validated clinical rating instrument designed specifically to assess a wide range of abnormal behaviors encountered in dementia subjects (Cummings et al. 1994; Cummings 1997). The NPI is an informant-based interview that utilizes scripted questions to

explore 12 different symptom domains: delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/lability, aberrant motor activity, night-time behavioral disturbances, and appetite and eating abnormalities. For each domain, the caregiver is asked a screening question to determine whether the abnormal behavior has been present within the previous 4 weeks and represents a change in the subject since the onset of illness. If the behavior has been present, then a series of subquestions are asked to obtain more detailed information about the specific features of the behavioral disturbance. For any behavior that has been present in the past 4 weeks, the caregiver is asked to rate the frequency of the behavior on a 4-point scale (Rarely – less than once per week; Sometimes – about once per week; Often – several times per week but less than every day; Very often – once or more per day or continuously present), and the severity of the behavior on a 3-point scale (Mild – produces little distress in the subject; Moderate – more disturbing to the subject but can be redirected by the caregiver; Severe – very disturbing to the subject and difficult to redirect).

A total score for each symptom is calculated by multiplying the frequency rating by the severity rating. The total NPI score is the sum of all symptom scores and has a possible range of 0 to 144, with higher scores indicating a greater degree of symptomatology.

The NPI also contains a Caregiver Distress Scale (NPI-D) that was designed to quantitate the distress experienced by caregivers, as it relates specifically to the individual symptoms assessed in the subject by the NPI. For each symptom deemed to be present in the past 4 weeks, the caregiver is asked to rate the distress the symptom has caused him or her on a 6-point scale (based on response to the question "How emotionally distressing do you find this behavior?"): 0 = not at all, 1 = minimally, 2 = mildly, 3 = moderately, 4 = severely, 5 = very severely or extremely. The maximum score for the Caregiver Distress Scale is 60.

9.1.2.3.2. Epworth Sleepiness Scale

The ESS is widely used in the field of sleep medicine as a subjective measure of a subject's sleepiness. It is an 8-item questionnaire that measures one's chances of "dozing off" in different daytime situations over the past week; scores range from 0 to 24, with scores ≥10 indicating excessive daytime sleepiness (Johns 1991). This scale is easily administered, widely used, and deemed "Recommended" by the MDS Sleep Scale Task Force for screening and measuring the severity of sleep problems in PD (Högl et al. 2010). For the purposes of Study HBEH, the ESS will be assessed by the caregiver. The ESS scores correlated significantly with MMSE scores and also with cognitive domain scores for attention/working memory, executive function, memory, and visuospatial function (Goldman et al. 2013). Daytime sleepiness in PD is associated with cognitive impairment in PD, especially in the setting of dementia, and attention/working memory, executive function, memory, and visuospatial deficits (Goldman et al. 2013).

9.1.2.3.3. Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease

The QUIP is a subject- and/or informant-reported screening questionnaire for impulse control disorders (ICDs) and compulsive behaviors in PD. It assesses behaviors across 3 domains:

1. ICD including gambling, sexual, buying and eating;
2. other compulsive behaviors such as punding and hobbyism, and wandering;
3. compulsive medication use.

Scores for each ICD and related disorder range from 0 to 16, with a higher score indicating greater severity (i.e. frequency) of symptoms. The total QUIP rating scale score for all ICDs and related disorders combined ranges from 0 to 112. It has demonstrated high discriminant validity compared with gold standard diagnostic criteria. It has good inter-rater and test–retest reliability and has demonstrated responsiveness to change in a treatment study of ICD in PD (Weintraub et al. 2009; Weintraub et al. 2012). As medications that enhance dopaminergic tone have been associated with the development of ICD in PD, the systematic evaluation of this potential complication is critical (Weintraub et al. 2006).

9.1.3. Appropriateness of Efficacy Assessments

Efficacy: As previously stated, the CoA has demonstrated a significant treatment effect in similar populations (Wesnes et al. 2005; Rowan et al. 2007). The CoA is a parameter calculated using the CDR-CCB, which has been widely used in dementia research for more than 25 years. Because it is a computerized assessment system, the CDR-CCB has low inter-rater variability. Two training sessions in a single day have demonstrated an ability to minimize learning effects up to 8 weeks (Wesnes, personal communication). The CDR-CCB system also has a large normative database of over 6000 healthy volunteers from 18 to 87 years of age, thereby making it possible to detect both the level of cognitive impairment present in subjects prior to treatment and the effect of treatment on cognitive changes (Wesnes 2008).

The secondary efficacy measures described in Section 9.1.2 are also established measures of cognitive function and related outcomes, as well as behavioral symptoms associated with PD dementia and DLB, and considered appropriate assessments for this population.

9.2. Adverse Events

Investigators are responsible for monitoring the safety of subjects who have entered this study and for alerting Lilly or its designee about any event that seems unusual, even if this event may be considered an unanticipated benefit to the subject.

The investigator is responsible for the appropriate medical care of subjects during the study.

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the investigational product or the study, or that caused the subjects to discontinue the investigational product prior to study completion. The subject should be followed until the event resolves, stabilizes with

appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

After the ICF is signed, study site personnel will record via eCRF the occurrence and nature of each subject's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to investigational product and/or protocol procedure via eCRF.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, study device, or a study procedure, taking into account the disease, concomitant treatment, or pathologies.

A "reasonable possibility" means that there is a cause-and-effect relationship between the investigational product, study device and/or study procedure, and the AE.

The investigator answers yes/no when making this assessment.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

If a subject's investigational product is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via eCRF, clarifying if possible the circumstances leading to any dosage modifications, or discontinuations of treatment.

9.2.1. Serious Adverse Events

An SAE is any AE from this study that results in 1 of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (i.e. immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent 1 of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All AEs occurring after signing the ICF are recorded in the eCRF and assessed for serious criteria. The submission of SAE reports to the sponsor begins after the subject has signed the

ICF and has received investigational product. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product, the SAE report should be submitted to the sponsor as per SAE reporting requirements and timelines (see Section 9.2) if it is considered reasonably possibly related to study procedure.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information. Subjects with a serious hepatic AE should have additional data collected using the eCRF.

Pregnancy (during maternal or paternal exposure to investigational product) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued and/or completed the study (the patient's final study disposition CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to investigational product or procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the identification, recording, and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.2. Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of subjects, monitor quality, and to facilitate process and product improvements.

Subjects will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product so that the situation can be assessed.

9.3. Treatment of Overdose

For this study, any dose of investigational product greater than twice participant's assigned daily dose within a 24-hour time period will be considered an overdose.

In the event of an overdose, the investigator or treating physician should use supportive therapy as necessary and contact the Clinical Research Physician (or designee) immediately.

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

9.4. Safety

9.4.1. Electrocardiograms

For each subject, 12-lead digital ECGs will be collected as triplicates according to the Schedule of Activities (Section 2). Subjects must be supine for approximately 10 minutes prior to ECG collection and remain supine but awake during ECG collection.

Consecutive replicate ECGs will be obtained at approximately 1-minute intervals. Electrocardiograms may be obtained at additional times, when deemed clinically necessary. Collection of more ECGs (more replicates) than expected at a particular time point is allowed when needed to ensure high-quality records.

Electrocardiograms will initially be interpreted by a qualified healthcare provider (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the subject is still present to determine whether the subject meets entry criteria at the relevant visit(s) and for immediate subject management, should any clinically relevant findings be identified.

Any clinically significant findings from ECGs that result in a diagnosis and that occur after the subject receives the first dose of the investigational treatment should be reported to Lilly or its designee as an AE via eCRF.

If a clinically significant quantitative or qualitative change from baseline is identified after enrollment, the investigator will assess the subject for symptoms (e.g., palpitations, near syncope, syncope) to determine whether the subject can continue in the study. The investigator or qualified designee is responsible for determining if any change in subject management is needed and must document his/her review of the ECG printed at the time of evaluation from at least 1 of the replicate ECGs from each time point.

All digital ECGs will be electronically transmitted to a designated central ECG laboratory. A cardiologist at the central ECG laboratory will then conduct a full over-read on 1 of the replicates (including all intervals). A report based on data from this over-read will be issued to the investigative site. For each set of replicates, the cardiologist will determine the RR and QT intervals, QRS duration, and pulse rate on the ECGs that were not fully over-read. These data are not routinely reported back to the investigative site. However, any clinically significant finding that was not present on the fully over-read ECG will be reported to the investigator and to Lilly. All data from the over-reads will be placed in the Lilly database for analytical and study report purposes.

When there are differences in ECG interpretation between the investigator (or qualified designee) and the cardiologist at the central ECG laboratory, the investigator's (or qualified designee's) interpretation will be used for study entry and immediate subject management.

Interpretations from the cardiologist at the central ECG laboratory will be used for data analysis and report writing purposes.

The investigator (or qualified designee) must document his/her review of 1 of the replicate ECGs printed at the time of collection, the final over-read ECG report issued by the central ECG laboratory, and any alert reports.

9.4.2. Vital Signs

Vital signs including pulse rate, orthostatic BP, temperature, and weight will be measured as detailed in the Schedule of Activities (Section 2).

Orthostatic Blood Pressure Monitoring: For orthostatic BP monitoring, subjects will have 3 BP/pulse rate measurements taken in the seated position approximately 1 minute apart followed by 1 BP/pulse rate measurement taken in the standing position. For orthostatic BP monitoring, subjects should be seated for at least 5 minutes and stand for at least 3 minutes prior to taking the respective measurements. If the subject feels unable to stand, vital signs only in the seated position will be recorded.

Orthostatic BP/pulse rate will be measured as part of the vital sign assessments at every visit. At Visit 2, Visit 3, Visit 8, Visit 11, and Visit 801, these measurements will be collected at time 0 of the in-clinic BP/pulse rate monitoring. Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. Additional vital signs may be measured during each study period if warranted and agreed upon between the sponsor and investigator. (Table HBEH.3)

In-clinic Blood Pressure and Pulse Rate Monitoring: In-clinic BP and pulse rate monitoring will be done at Visit 2, Visit 3, Visit 8, Visit 11, and Visit 801. The BP and pulse rate will be measured at time 0 and every 60 minutes thereafter. The initial measurement, at time 0 of the in-clinic BP and pulse rate monitoring, will be done as an orthostatic BP/pulse rate (refer to Orthostatic Blood Pressure Monitoring above), and subsequent BP and pulse rate measurements will be taken in the seated position only. Time 0 at Visit 3, Visit 8 and Visit 11 will occur just prior to study drug dosing. At Visit 3, drug dosing should be initiated immediately following confirmation that subject met inclusion criteria [6]. At Visit 2, Visit 8, and Visit 11, in-clinic BP and pulse rate will be monitored for up to 6 hours, At Visit 3, for up to 8 hours and at Visit 801 for up to 2 hours (Table HBEH.4).

Home Blood Pressure Monitoring: Home BP measurements will be collected in this study. Blood pressure measurements should be taken twice daily in the seated position using the HBPM equipment provided by Lilly. The subject should be given the HBPM device at Visit 2. Home BP measurements should be conducted for a minimum of 7 days between Visits 2 and 3, for 3 weeks between Visits 3 and 6, and a minimum of 7 days between Visits 10 and 11, and Visits 11 and 801. Home BP should be taken twice in the morning (approximately 1 minute apart) (e.g., 8 AM) immediately following study medication dosing and twice in the evening, approximately 12 hours later (approximately 1 minute apart) (e.g., 8 PM).

All HBPM data will be electronically transmitted to a designated HBPM data processing vendor.

9.4.3. Laboratory Tests

For each subject, laboratory tests detailed in (Appendix 2) should be conducted according to the Schedule of Activities (Section 2).

With the exception of laboratory test results that may unblind the study, Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor, if a central vendor is used for the clinical trial.

Any clinically significant findings from laboratory tests that result in a diagnosis and that occur after the subject receives the first dose of investigational product should be reported to Lilly or its designee as an AE via eCRF.

9.4.4. Columbia-Suicide Severity Rating Scale – Children's Version

Consistent with Food and Drug Administration (FDA) regulatory guidance (FDA 2012), any occurrence of suicide-related thoughts and behaviors will be assessed as indicated in the Study Schedule (Section 2). The C-SSRS is a scale that captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the corresponding assessment period. The scale includes suggested questions to elicit the type of information needed to determine if a suicide-related thought or behavior occurred.

The C-SSRS is available in an adult's and a children's version. There is no version of the C-SSRS designed for use in a cognitively impaired population such as subjects with PD dementia; therefore, the children's version will be used. Terms captured by the use of the C-SSRS children's version can be mapped to Columbia Classification Algorithm for Suicide Assessment (Posner et al. 2007), to facilitate future pooling of data.

The first time the scale is assessed in this study, the C-SSRS "Baseline" version will be used, and the findings will constitute the baseline assessment. The C-SSRS "Since Last Visit" scale will be used for all subsequent assessments.

The C-SSRS will be assessed after the cognitive and functional assessments. Responses from subject will be considered when assessing the scale. If a suicide-related thought or behavior is identified at any time during the study, a thorough evaluation will be performed by a study physician, and appropriate medical care will be provided.

If, based on assessment of the C-SSRS, it is determined that suicide-related behaviors have occurred, then the Lilly Self-Harm Follow-Up form will be used to collect additional information to allow for a more complete assessment of these behaviors.

9.4.5. Physician Withdrawal Checklist

The Penn Physician Withdrawal Checklist (PWC-20) is a 20-item checklist that will be used to assess the presence and severity of withdrawal symptoms. The PWC-20 should be assessed on the subject and caregiver, separately. The scale was originally developed to assess the severity of withdrawal symptoms in anxiolytic medication discontinuation (Rickels et al. 2008). The PWC-20 is a validated, shortened version of the original 35-item checklist, where the 20-items were selected based on their statistical ability to differentiate between placebo and active drug

plus share correlation with the 35-item checklist (Schweizer et al. 1990; Rickels et al. 1990). The 20 items assess the subject's level of symptoms on a variety of withdrawal symptoms since last visit. Each of the 20 items are scored as 0 (not present), 1 (mild), 2 (moderate), 3 (severe).

9.4.6. Safety Monitoring

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods.

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, only members of the IAC (an advisory group for this study formed to protect the integrity of data; refer to Section 10.3.7) can conduct additional analyses of the safety data.

9.4.6.1. Hepatic Safety Monitoring

If a subject experiences elevated ALT ≥3X ULN, ALP ≥2X ULN, or elevated TBL ≥2X ULN, tests for hepatic parameters (Appendix 4) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator and in consultation with the study medical monitor. Monitoring of ALT, AST, TBL, and ALP should continue until levels normalize or return to approximate baseline levels.

Hepatic Safety Data Collection

Additional safety data should be collected via the eCRF if 1 or more of the following conditions occur:

1. Elevation of serum ALT to ≥5X ULN on 2 or more consecutive blood tests.
2. Elevated serum TBL to ≥2X ULN (except for cases of known Gilbert's syndrome).
3. Elevation of serum ALP to ≥2X ULN on 2 or more consecutive blood tests.
4. Subject discontinued from treatment due to a hepatic event or abnormality of liver tests.
5. Hepatic event considered to be an SAE.

9.4.7. Appropriateness of Safety Assessments

The clinical safety measurements (AE reporting, physical examinations, vital signs, HBPM, ECGs, and clinical safety laboratory tests; Section 9.2 and Section 9.4) are well-established methods in drug development research and are standard procedures for clinical trials.

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples will be collected to determine the plasma concentrations of LY3154207. Instructions for the collection and handling of blood samples will be provided by the sponsor. At Visit 3, a PK sample is to be collected within 1 to 3 hours after the drug is administered at the site. At Visit 4, Visit 5, Visit 8, and ET/DC, the PK sample can be collected at any time during the visit. At Visit 11, the PK sample should be collected prior to the drug being administered at the site. The

date and time (24-hour clock time) of the PK sample collection as well as the date and time of the dose administration immediately preceding the PK sampling will be recorded.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Bioanalytical samples collected to measure investigational product concentration and metabolism and/or protein binding will be retained for a maximum of 2 years following last subject visit for the study.

The PK analyses will be based on validated bioanalytical assays and will use conventional PK analysis methods.

9.6. Pharmacodynamics

Not applicable.

9.7. Pharmacogenomics

9.7.1. Whole Blood Sample for Pharmacogenetic Research

A whole blood sample will be collected for pharmacogenetic analysis as specified in the Schedule of Activities (Section 2) where local regulations allow.

The collection and storage of samples for genetic studies (including samples for pharmacogenetic studies) is to continue our ongoing efforts to understand the correlation between the clinical outcome with the drug(s) under study in the clinical trial and the genetic makeup of the subject. DNA extracted from the whole blood samples collected from the subjects may be used to generate genetic data on a genome genotyping array. The genotype data may be used to perform a targeted genetic analysis of the genes of interest to understand potential safety and efficacy concerns should they arise either during this trial, future trials for this drug, or if the drug is launched and on the market. For example, genetic variations in well-known drug-metabolizing enzymes, such as cytochrome P450 (CYP), including CYP3A4, could be a potential set of genes of interest to answer any safety concerns.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples may be used to investigate variable response to LY3154207 and to investigate genetic variants thought to play a role in LBD. Assessment of variable response may include evaluation of AEs or differences in efficacy.

All samples will be coded with the subject number. These samples and any data generated can be linked back to the subject only by the investigator site personnel.

Samples will be retained at a facility selected by Lilly or its designee for a maximum of 15 years after the last subject visit for the study, or for a shorter period if local regulations and/or ethical review boards (ERBs) impose shorter time limits. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may

not be observed until later in the development of LY3154207 or after LY3154207 becomes commercially available.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing approaches include whole genome or exome sequencing, genome-wide association studies, and candidate gene studies. Regardless of technology utilized, genotyping data generated will be used only for the specific research scope described in this section.

9.8. Biomarkers

9.8.1. Digital Biomarkers

9.8.1.1. Lilly Trial Application

The Lilly Trial application (Lilly Trial app), if available, will be used to assess the feasibility of collecting clinical research domains such as cognitive and motor functioning under real world conditions using an iPad-enabled application (see Operations Manual). In addition, the ability of the Lilly Trial app to measure the effect of LY3154207 on motor and cognitive outcomes in a subset of subjects will be explored. The app uses a series of tasks that activate iPad sensors to collect and track data from the subjects. These measures include a variety of potential tests measuring motor functions and cognition (e.g., tapping and memory tests). An iPad configured with the Lilly Trial app will be provided to the subjects at Visit 2 (if available). Subjects will complete assessments from 2 weeks prior to dosing (starting day following Visit 2), throughout the dosing period, and for 2 weeks after the conclusion of the treatment period (until Visit 801). Subjects will self-select for this optional component of the protocol at Visit 1. If subject consents to participate, sites should capture this information in IWRS at Visit 1 to ensure the iPad is provisioned on time for Visit 2. Subjects can decide to opt out at any time during the study. The selected domains of the app will be completed up to twice daily.

The Lilly Trial app will be deployed for use during the pretreatment, treatment, and post-treatment phases of the study to validate findings from the Phase 1 studies using this app and to determine its utility for future studies in this population.

These data are exploratory data and will be used for exploratory purposes.

9.8.1.2. Actigraphy

As an increase in mean sleep latency in sleep-deprived subjects was identified as a drug-response indicator, a wearable device capable of detecting and characterizing changes in various sleep parameters including but not limited to sleep latency, duration of sleep, sleep–wake cycles, and sleep disruption may be employed, in a subset of subjects, if available. We will explore the feasibility of using actigraphy to evaluate the effect of LY3154207 on various sleep parameters and day time activity. If available, the actigraphy device will be worn on the wrist, similar to a watch, beginning at Visit 2, for 3 separate 2-week periods of time: Visit 2 to Visit 3, Visit 8 to Visit 9, and Visit 11 to Visit 801. The site will provide the device to the subjects at Visits 2, 8, and 11; and following 14 days of wearing the device, the subject will bring the device to the site

at the regularly scheduled visit at the end of the 14-day period (Visit 3, Visit 9, or Visit 801), whereupon the site will mail it to the vendor using previously addressed mailing materials (see Operations Manual). These data are exploratory data and will be used for exploratory purposes.

9.9. Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters will not be evaluated in this study.

10. Statistical Considerations

10.1. Sample Size Determination

Approximately 750 subjects may be screened in order that 340 subjects are randomized in the study. CCI [redacted] If the true effect size for LY3154207 relative to placebo on the CoA is 0.4 with the sample size of 340 there will be over 80% probability of passing this criterion. A 20% discontinuation rate by Week 12 has been accounted for in the sample size determination.

Sample size was estimated based on the work of Wesnes et al. (2005) where the difference in mean change from baseline for rivastigmine compared to placebo and the pooled standard deviation (SD) for CoA were estimated as 5.7 units and 18 units, respectively. The rivastigmine effect corresponding to a reduction in the deficit of subjects compared to age-matched healthy volunteers is approximately 45%. Based on this, the effect size of 0.4 in this study corresponds to a mean difference of 7.2 units (approximately 57% reduction in the deficit).

This sample size will allow for assessment of the in-clinic BP and pulse rate on the first day of dosing in order to evaluate any changes after the first dose of treatment that were observed in Phase 1. If the SD of the in-clinic SBP is assumed to be 15 mmHg, then the difference from the mean to the upper limit of a 95% confidence interval (CI) of the change from baseline of SBP relative to placebo is expected to be <4.7 mmHg. If there is any initial rise in BP or pulse rate, the in-clinic 6- and 12-week assessments along with the HBPM measure will be used to assess if the rise accommodates. The difference from the mean to the upper limit of a 95% CI of the change in average SBP measured at each of these visits relative to placebo is expected to be <3.5 mmHg. This assumes an SD of 10 mmHg and a 20% discontinuation rate.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Entered	All subjects who sign informed consent
Evaluable Patient Population (EPP)	All randomized subjects who received at least 1 dose of study treatment, who have the baseline efficacy assessment and have at least 1 post-dose efficacy assessment. Analyses will be according to the treatment the subject actually received.
Completers	All randomized subjects who have completed all study procedures, including follow-up and/or ET/DC visit.
Safety population	All randomized subjects who take at least 1 dose of study treatment. In the event of a treatment error, subjects will be analyzed according to the treatment they actually received.
Per Protocol population	Subjects who complete the study with no major protocol deviations
PK Analysis Population	PK analyses will be conducted on subjects who receive at least 1 dose of the study drug and have one measurable concentration

Abbreviations: DC = discontinuation; ET = early termination; PK = pharmacokinetic.

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

Statistical analysis for this study will be the responsibility of Lilly or its designee.

Unless otherwise specified, all efficacy analyses will be conducted on the evaluable patient population (EPP). This includes all data from all randomized subjects who received at least 1 dose of study medication and have the baseline efficacy assessment and at least 1 postdose efficacy assessment. Analyses will be according to the treatment the subject actually received. Efficacy analyses will be repeated with a per-protocol analysis set including only those subjects who completed the study with no major protocol deviations to verify robustness of the results.

No adjustments will be made for multiple comparisons. When change from baseline is assessed, subjects will be included in the analysis only if both the baseline and a postbaseline measures are available. Unless otherwise defined, a baseline measure is the last non-missing observation collected prior to the subject receiving study treatment.

Safety analyses will be conducted on the safety analysis set comprising all subjects who received at least 1 dose of study medication. Summary statistics, tabulations, and graphs will be provided, as appropriate.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report (CSR). Additional exploratory analyses of the data will be conducted, as deemed appropriate. However, these analyses may not be included in the CSR.

The statistical analyses specified in the protocol will be detailed in the statistical analysis plan (SAP). However, some of the exploratory analysis suggested by data will not be specified in SAP.

10.3.1.1. Handling of Missing Items for Scales

The total and subscale scores will be derived from individual items. If any of the individual items are missing or unknown, every effort will be made to obtain the score for the missing item or items. However, failing to gather missing information, some scales (e.g., ADAS-Cog) will be imputed as appropriate. The scales for which imputation is adopted will be detailed in the SAP.

For the scales where imputation is not done, if any item is missing, any total or sum involving that item will be considered missing.

10.3.2. Treatment Group Comparability

10.3.2.1. Time to Study Disposition/Discontinuation

The reasons for discontinuation and the time in days-to-study disposition will be summarized by treatment group for all randomized subjects. A corresponding listing will also be produced.

The reason for discontinuation will be collected when the subject's participation in the study ends and will be summarized as frequency and percentage by treatment group for all randomized subjects.

10.3.2.2. Protocol Deviations

Listings of subjects with significant protocol deviations will be provided based on the safety population. Protocol deviations will be summarized using frequencies and percentages.

10.3.2.3. Subject Characteristics

Baseline characteristics will be summarized for the EPP and per-protocol populations by treatment group and overall. Summaries will include descriptive statistics for continuous measures and frequencies and percentage for categorical measures. Comparability between treatment groups will be evaluated based on the point estimates and the associated variability.

10.3.2.4. Concomitant Therapy

Prior medications are defined as those that stop before randomization (Visit 3). Concomitant medications are defined as those being taken on or after randomization (Visit 3). A summary of concomitant medications will be presented as frequencies and percentages for each treatment group. If the start or stop dates of therapies are missing or partial to the degree that determination cannot be made as to whether the therapy is prior or concomitant, the therapy will be deemed concomitant.

Summary tables will also be provided for PD concomitant medications and cognitive enhancing medications.

Prior and concomitant medications will also be listed.

Medications will be coded using the World Health Organization drug dictionary.

10.3.2.5. Treatment Compliance

Treatment compliance information for each treatment arm will be collected through capsule counts at each visit, and the number of capsules taken relative to the number expected to be taken will be summarized.

10.3.3. Efficacy Analyses

10.3.3.1. Primary Analyses

The primary analysis on CoA will occur when all subjects complete 12 weeks of treatment. The analysis of CoA will utilize a Bayesian MMRM model. The Bayesian analysis may use uninformative priors for all terms in the model. These will be diffuse Normal distributions centered on zero. Priors for variance will follow an inverse gamma distribution. Further details of the Bayesian analysis will be provided in the SAP. The MMRM model will account for longitudinal data assessed throughout the study, after 1, 2, 4, 6, 8, 10, and 12 weeks of dosing. The change of CoA from the baseline to Week 12 will be the dependent variable. The model will comprise fixed (baseline value, treatment, visit) and random effects (subject) and the interaction terms (treatment by visit, baseline value by visit). Unstructured variance structure will be applied in the model, but if it fails to converge, other suitable structures will be

investigated. The primary comparison will be the contrast (difference in least squares mean) between treatments and placebo for the Week 12 change from baseline.

10.3.3.2. Secondary Efficacy Analyses

The secondary efficacy outcomes (ADCS-CGIC, PDAQ-15, ADAS-Cog_{13}, CDR-CCB PoA, D-KEFS, MoCA, NPI, ESS, and MDS-UPDRS [total and Part III]) will be assessed at the 12-week time point. Each of these secondary endpoints will be analyzed using an MMRM model, which will include terms for: baseline value, treatment, visit, and the relevant interaction terms. Further covariates may be included such as age, site, and the severity of PD motor function as well as severity of dementia at baseline as appropriate. The change of the score from baseline will be the dependent variable. If subscores for a particular scale are deemed clinically relevant to analysis, it will be completed as an exploratory analysis.

10.3.3.3. Tertiary/Exploratory Efficacy Analyses

The following exploratory efficacy endpoints will be analyzed using MMRM model.

- Change in the total score for the ADAS-Cog_{11} from baseline to Week 12 (as a subset of ADAS-Cog_{13})
- Change in the CDR elements (Cognitive reaction time composite score, Reaction Time Variability composite score, Speed Score composite scores, Simple Reaction Time outcomes, Choice Reaction time task outcomes, Digit Vigilance outcomes, Numeric Working Memory outcomes, Spatial Working Memory Outcomes, Verbal Memory outcomes, Visual Memory outcomes) from baseline to Week 12
- Change in MDS-UPDRS individual subscales – non-motor experiences of daily living (Part I), motor experiences of daily living (Part II), and motor complications (Part IV) subscales from baseline to Week 12
- Change in MDS-UPDRS Part IA score from baseline to Week 12
- Change in GDS-S score from screening to Week 12
- Change in NPI score (Part D Depression/Dysphoria) from baseline to Week 12
- Change in QUIP score from baseline to Week 12

Where appropriate, these results will be investigated in more depth.

Exploratory Digital Biomarker Analysis: Data from digital biomarkers (Lilly Trial app and Actigraphy watch) from baseline to Week 12 will be explored using appropriate visual, univariate, and multivariate methods to understand the relationship of the biomarker endpoints to other clinical endpoints in terms of treatment effect. The data may also be used to explore the validity and reliability of these assays in LBD subjects. If applicable, potential predictive biomarkers associated with interpretable clinical benefit may further be examined with biological evidence.

10.3.4. Safety Analyses

All subjects who receive at least 1 dose of LY3154207 will be evaluated for safety and toxicity.

Safety parameters (AEs, laboratory analytes, vital signs, ECGs) and number of subjects who meet the potentially clinically significant vital signs criteria at 3 consecutive time points at

Visit 3 (Day 1 stopping rules) will be summarized using descriptive statistics for continuous variables and frequencies along with percentages for categorical variables during the treatment period.

Comparisons between 3 doses of LY3154207 and placebo will be made using an MMRM model for the in-clinic BP, pulse rate, and HBPM measurements during the treatment period. No adjustments for multiple comparisons will be made.

The PWC-20 endpoint will be analyzed using an ANCOVA model with a covariate for baseline score. The primary analyses will be a change from baseline (Visit 11) to the in person follow up visit (Visit 801).

10.3.4.1. Adverse Events

Treatment-emergent adverse events will be defined as events that first occurred or worsened on or after randomization (Visit 3). Should there be insufficient data for AE start date, stop date, and time, the AE will be considered treatment emergent.

Treatment-emergent adverse events will be calculated based on AE identifier and coded according to established Medical Dictionary for Regulatory Activities (MedDRA) terms and summarized by MedDRA System Organ Class (SOC) and Preferred Term. Adverse event terms and severity grades will be assigned by the investigator using Common Terminology Criteria for Adverse Events, version 4.0.

An overview of AEs, including the number and percentage of subjects who died, suffered serious adverse events (SAEs), discontinued due to AEs, and who suffered TEAEs, will be provided.

Summaries of AEs by decreasing frequency of Preferred Term within SOC will be provided for the following:

- preexisting conditions
- TEAEs
- TEAEs by maximum severity
- TEAEs occurring in greater than 1% of subjects by Preferred Term
- SAEs
- AEs reported as reason for discontinuation

These summaries will include number and percentages of subjects with TEAEs

A summary of TEAEs by visit will also be provided.

Preexisting conditions, TEAEs, SAEs, and discontinuations due to AEs will be listed.

10.3.4.2. Suicidal Ideation and Behavior

Suicide-related thoughts and behaviors, based on the C-SSRS, will be listed by subject and visit. Only subjects who show suicidal ideation/behavior will be displayed (i.e. if a subject's answers are all "no" for the C-SSRS, then that subject will not be displayed). However, if a subject reported any ideation or behavior at any time point, then all their ideation and behavior will be displayed, even if not positive.

10.3.4.3. Vital Signs and Weight

Vital sign measurements and weight will be analyzed as continuous data (change from baseline to each visit) and the treatment-emergent abnormalities as categorical data.

If there are multiple records of vital sign or weight measurements at baseline or postbaseline visits, the last record will be used. The exception is for the orthostatic BP and pulse rate taken as part of the vital sign assessments at Visit 1, Visit 4, Visit 5, Visit 6, Visit 7, Visit 9, Visit 10, unscheduled visit, and ET/DC visit, and the initial measurement at time 0 of the in-clinic BP and pulse rate monitoring. At these visits, 3 BP/pulse rate measurements will be taken in the seated position and the mean of these will be utilized for analysis purposes. Orthostatic changes will be calculated by comparing the mean of the 3 BP and pulse rate measurements taken in the seated position to the value of the single BP and pulse rate measurement taken in the standing position. Summary statistics will be presented for observed values at baseline and for change from baseline results at each scheduled postbaseline visit. Systolic and diastolic BP and pulse (collected in sitting position), orthostatic SBP, orthostatic diastolic and orthostatic pulse (measurement after 5 minutes in the seated position minus that after 3 minutes in the standing position), temperature, and weight will be summarized by treatment group for all subjects in the safety population.

The incidence of treatment-emergent abnormal high or low vital signs will be presented by treatment group and visit. Treatment-emergent vital sign evaluations are defined for evaluations collected after the initiation of study medication. Any vital sign meeting the criteria will be considered abnormal. For each vital sign at each postbaseline visit, only subjects who had a baseline result and had a non-missing result at that postbaseline visit will be included in the denominator when computing the proportion of subjects with treatment-emergent high, low, or abnormal values.

Summary statistics of change from baseline in weight will be provided. Body mass index at baseline will be summarized by treatment.

A listing of treatment-emergent abnormal vital signs will also be presented.

- Day 1 (Visit 3) in-clinic BP and pulse rate change post first dose

  Change in in-clinic BP and pulse rate from 0 up to 8 hours postdose measured on the first day of study drug dosing will be analyzed using an MMRM analysis with baseline value, treatment, time postdose (hours), and the relevant interaction terms. Two baselines will be considered: the Visit 3 pretreatment value (time 0) and the time-matched baselines from Visit 2 (hourly value 0 to 6 hours). For the second of these, there is no time-matched value for the 7- and 8-hour time points of Visit 3, so the 6-hour time point of Visit 2 will be used as their baseline value. A separate change from baseline analysis will be completed for each baseline approach.

- Change in in-clinic BP and pulse rate from baseline (Visit 2, predrug) up to Week 12 (V11)

Change in in-clinic BP and pulse rate measured at Visit 2 (daily average 0 to 6 hours) to the in-clinic BP and pulse rate measured at Week 6/Visit 8 and Week 12/Visit 11 (daily average 0 to 6 hours) will be analyzed by an MMRM model with baseline value, treatment, and the relevant interaction terms. Analysis at 6 weeks will help to evaluate any significant changes (if any) in BP and pulse rate earlier than 12 weeks (end of study) and if they accommodate by 6 weeks.

- Daily average change in home BP measurements and pulse rate from baseline to Week 12.

10.3.4.4. Laboratory Analyses

Laboratory measurements will be analyzed as continuous data (change from baseline) measured as International System Units or as categorical data (proportion of treatment-emergent abnormalities).

If there are multiple records of laboratory measurements at baseline or postbaseline visits, the last record will be used.

Change from baseline to postbaseline visits at which laboratory measurements are taken will be summarized using descriptive statistics.
For all laboratory analytes, frequencies of subjects with notable changes (i.e. increases or decreases of a prespecified amount unique to each analyte) from baseline to each postbaseline visit will also be summarized for all subjects and stratified by low, normal, or high at baseline.

10.3.4.5. Electrocardiograms

The ECG measurements will be analyzed as continuous data (change from baseline) or as categorical data (proportion of treatment-emergent abnormalities).

Electrocardiogram is measured in triplicates and the average of triplicates will be used at baseline and each double-blind period visit. If there are multiple records after averaging ECG triplicates within a visit, the last record of averages will be used.

All ECG parameters change from baseline to each postbaseline visit at which ECG measurements are taken will be summarized.

Incidence of treatment-emergent abnormal ECGs will be also be summarized.

10.3.5. Pharmacokinetic/Pharmacodynamic Analyses

LY3154207 concentrations will be illustrated graphically and summarized descriptively. If warranted and based on availability of data, the exposure–response relationship of plasma LY3154207 concentrations to efficacy endpoints and/or safety endpoints may be explored. Subject and healthy subject data, including but not limited to plasma LY3154207 concentrations, from other clinical studies evaluating LY3154207 may be combined with data from this study to support additional analyses. A model-based approach may be implemented using nonlinear mixed effects modeling (NONMEM) or other appropriate software to estimate PK or pharmacodynamic parameters.

10.3.6. Other Analyses

10.3.6.1. Subgroup Analyses

The CDR-CCB CoA and its component scores will be assessed based on the following subgroups: concomitant PD therapy, concomitant AChEI therapy, PDD or DLB, and GDS (less than or equal to 6). All subgroup analyses will be considered exploratory and additional subgroup analyses may be performed as suggested by the data.

10.3.7. Interim Analyses

A limited number of pre-identified individuals may gain access to the limited unblinded data, as specified in the unblinding plan. Information that may unblind the study during the analyses will not be reported to study sites or blinded study team until the study has been unblinded.

The efficacy and safety interim analyses will be completed and reviewed by an IAC.

Study sites will receive information about interim results ONLY if they need to know for the safety of their subjects.

Safety interims will be conducted on the number of subjects on each treatment who met the potentially clinically significant vital signs criteria at 3 consecutive time points at Visit 3 (Day 1 stopping rules). This will be done after 50, 100, and 150 subjects have completed Visit 3. [redacted] Those already on 75-mg dose and passed the Day 1 stopping rules will remain on 75 mg. In the event of an unacceptable rate of subjects meeting Day 1 stopping rules at other doses, adjustments to doses may be made for subsequently randomized subjects at the discretion of the IAC. Additional efficacy analyses may be conducted at the time of these safety interim analyses or as needed to inform internal decision making.

A safety and efficacy interim analysis will be conducted when 170 randomized subjects have had the opportunity to complete Visit 11 (Week 12) assessments. The statistical analysis will include all 170 subjects in the interim analysis, which will evaluate both the efficacy and the safety. In addition, the PK data may be reviewed. An additional interim analysis of efficacy and safety may be conducted prior to study completion for internal decision making. While all potential efficacy analyses may be used for internal decision making, they are not planned to stop the study for efficacy or futility because this is an exploratory study and there are other key endpoints being assessed, not just the primary endpoint.

Unblinding details are specified in the unblinding plan section of the SAP or a separate unblinding plan document.

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADAS-Cog$_{13}$	Alzheimer's Disease Assessment Scale – 13-item Cognitive Subscale
ADAS-Cog$_{11}$	Alzheimer's Disease Assessment Scale – 11-item Cognitive Subscale
ADCS-CGIC	Alzheimer's Disease Cooperative Study - Clinician Global Impression of Change
AE	adverse event: Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
blinding/masking	A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the subject is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the subject are not. A double-blind study is one in which neither the subject nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
C_{max}	maximum observed drug concentration
C-SSRS	Columbia-Suicide Severity Rating Scale
CDR-CCB	Cognitive Drug Research Computerized Cognition Battery
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CoA	Continuity of Attention
Companion diagnostic	An in vitro diagnostic device (assay or test) that provides information that is essential for the safe and effective use of a corresponding therapeutic product

complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related requirements, good clinical practice (GCP) requirements, and applicable regulatory requirements.
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CSF	cerebrospinal fluid
CSR	clinical study report
CV	cardiovascular
CYP	cytochrome P450
CYP3A4	cytochrome P450 3A4
D1PAM	positive allosteric modulator of the dopamine D1 receptor
D-KEFS	Delis–Kaplan Executive Function System
DLB	dementia with Lewy bodies
EC25	effective concentration 25
ECG	electrocardiogram
eCOA	electronic Clinical Outcome Assessment
Enroll	The act of assigning a subject to a treatment. Subjects who are enrolled in the study are those who have been assigned to a treatment.
Enter	Subjects entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
EPP	evaluable patient population
ERB	ethical review board
ESS	Epworth Sleepiness Scale
GCP	good clinical practice
GDS-S	Geriatric Depression Scale – Short Form
HEENT	head, ear, eye, nose, and throat
HBPM	home blood pressure monitoring
IB	Investigator's Brochure

IAC	Internal Assessment Committee
IADL	instrumental activities of daily living
ICD	impulse control disorder
ICF	informed consent form
ICH	International Council for Harmonisation
Informed consent	A process by which a subject voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IWRS	interactive web-response system
LBD	Lewy Body Dementia
MDS	Movement Disorder Society
MDS-UPDRS	Movement Disorder Society's United Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-model repeated measures
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
NOAEL	no-observed-adverse-effect level
NONMEM	nonlinear mixed effects modeling
NPI	Neuropsychiatric Inventory
PD	Parkinson's disease
PDAQ-15	Penn Parkinson's Daily Activities Questionnaire-15
PDD	Parkinson's disease dementia
PK	pharmacokinetic(s)

PoA	Power of Attention
PSG	Parkinson Study Group
QD	once a day
QTcF	Fredericia's corrected QT interval on the ECG
QUIP	Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease
REM	rapid eye movement
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
Screen	The act of determining if an individual meets requirements for participation in a clinical study.
SD	standard deviation
SOC	System Organ Class
SUSAR	suspected unexpected serious adverse reaction
TBL	total bilirubin
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
ULN	upper limit of normal
WOCBP	women of child-bearing potential

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a,b]	**Clinical Chemistry**[a,b,c]
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Mean cell volume	Total bilirubin
Mean cell hemoglobin concentration	Direct bilirubin
Leukocytes (WBC)	Alkaline phosphatase
Neutrophils, segmented	Alanine aminotransferase (ALT)
Lymphocytes	Aspartate aminotransferase (AST)
Monocytes	Blood urea nitrogen (BUN)
Eosinophils	Creatinine
Basophils	Uric acid
Platelets	Calcium
	Glucose, nonfasting
Urinalysis[a,b]	Albumin
Specific gravity	Cholesterol
pH	Creatine kinase (CK)
Protein	
Glucose	
Ketones	**Serum FSH (females only)**[a,b,c,d]
Blood	
Urine leukocyte esterase	

Abbreviations: FSH = follicle-stimulating hormone; RBC = red blood cells; WBC = white blood cells.

[a] Assayed by the Lilly-designated Central Laboratory.

[b] Results will be confirmed by the Lilly-designated Central Laboratory at the time of initial testing.

[c] Refer to the Schedule of Activities.

[d] Refer to inclusion criteria [12e] in Section 6.1.

Appendix 3. Study Governance Considerations

Appendix 3.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

Appendix 3.1.1. Informed Consent

The investigator is responsible for:

- ensuring that the subject/subject's legal representative understands the nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary.
- ensuring that informed consent is given by each subject or legal representative. This includes obtaining the appropriate signatures and dates on the informed consent form (ICF) prior to the performance of any protocol procedures and prior to the administration of investigational product.
- answering any questions the subject/subject's legal representative may have throughout the study and sharing in a timely manner any new information that may be relevant to the subjects/subject's legal representative's willingness to continue his or her participation in the study.
- ensuring that a copy of the ICF is provided to the subject or the subject's legal representative and is kept on file.
- ensuring that the medical record includes a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Caregivers will also sign a separate informed consent. If it is not known that the caregiver will change, the new caregiver would need to sign the ICF when he/she takes over the care for the subject and study participation. The change in caregiver would also need to be documented on the eCRF.

As used in this protocol, the term "informed consent" includes all consent and assent given by subject or their legal representatives and by caregivers.

Appendix 3.1.2. Recruitment

Lilly or its designee is responsible for the central recruitment strategy for subjects. Individual investigators may have additional local requirements or processes.

Appendix 3.1.3. Ethical Review

The investigator or an appropriate local representative must give assurance that the ethical review board (ERB) was properly constituted and convened as required by International Council for Harmonisation (ICH) guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF, including any changes made by the ERBs, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on Good Clinical Practice (GCP).

The study site's ERB(s) should be provided with the following:

- the protocol and related amendments and addenda, current Investigator Brochure (IB) and updates during the course of the study
- informed consent form
- other relevant documents (e.g., curricula vitae, advertisements)

Appendix 3.1.4. Regulatory Considerations

This study will be conducted in accordance with the protocol and with:

- the consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- the applicable ICH GCP Guidelines
- the applicable laws and regulations

Some of the obligations of the sponsor will be assigned to a third party.

Appendix 3.1.5. Investigator Information

Physicians with a specialty in neurology, geriatric medicine, and/or psychiatry will participate as investigators in this clinical trial.

Appendix 3.1.6. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

Appendix 3.1.7. Final Report Signature

The clinical study report (CSR) coordinating investigator will sign the final CSR for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

The investigator with the most qualified subjects will serve as the CSR coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the CSR coordinating investigator.

The sponsor's responsible medical officer and statistician will approve the final CSR for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Appendix 3.2. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- sponsor investigator study site trainings to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the eCRFs, and study procedures.
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate eCRF data and use standard computer edits to detect errors in data collection
- conduct a quality review of the database

In addition, Lilly or its representatives will periodically check a sample of the subject data recorded against source documents at the study site. The study may be audited by Lilly or its representatives, and/or regulatory agencies at any time. Investigators will be given notice prior to an audit.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

Appendix 3.2.1. Data Capture System

An electronic data capture system will be used in this study. The site maintains a separate source for the data entered by the site into the sponsor-provided electronic data capture system.

Electronic Clinical Outcome Assessment (eCOA) measures (e.g., a rating scale) are entered into an eCOA instrument (at the time that the information is obtained). In these instances, where there is no prior written or electronic source data at the site, the eCOA instrument record will serve as the source.

If eCOA records are stored at a third-party site, investigator sites will have continuous access to the source documents during the study and will receive an archival copy at the end of the study for retention.

Any data for which the eCOA instrument record will serve to collect source data will be identified and documented by each site in that site's study file.

Case report form data will be encoded and stored in a clinical trial database. Data managed by a central vendor, such as laboratory test data or electrocardiogram data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

Any data for which paper documentation provided by the subject will serve as the source document will be identified and documented by each site in that site's study file.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

Appendix 3.3. Study and Site Closure

Appendix 3.3.1. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly or its designee, the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 3.3.2. Discontinuation of the Study

The study will be discontinued if Lilly or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 3.4. Publication Policy

The publication policy for Study HBEH is described in the Clinical Trial Agreement.

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required during follow-up with subjects in consultation with the Lilly, or its designee, clinical research physician.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody[a]**
AST	
GGT	**Alkaline Phosphatase Isoenzymes[a]**
CPK	
	Anti-smooth muscle antibody (or anti-actin antibody)[a]

Abbreviations: ALT = alanine aminotransferase; AST = aspirate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

[a] Assayed by Lilly-designated laboratory.

[b] Reflex/confirmation dependent on regulatory requirements and/or testing availability.

Appendix 5. MDS Diagnostic Criteria for Parkinson's Disease – Red Flags and Supportive Criteria

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ABSOLUTE EXCLUSION CRITERIA

1. unequivocal cerebellar abnormalities on exam;
2. downward vertical supranuclear gaze palsy or selective slowing of downward vertical saccades;
3. diagnosis of behavioral variant of frontotemporal dementia or primary progressive aphasia within the first 5 years of disease;
4. parkinsonian features restricted to the lower limb for greater than 3 years;
5. treatment with a dopamine receptor blocker or dopamine depleting agent that temporally suggests drug-induced parkinsonism;
6. absence of observable response to high-dose levodopa therapy;
7. unequivocal cortical sensory loss, clear limb ideomotor apraxia, or progressive aphasia;
8. normal functional imaging of the presynaptic dopaminergic system (PET or SPECT);
9. documentation of an alternative condition to account for parkinsonism or expert opinion that an alternative diagnosis is more likely than PD.

RED FLAGS

1. Rapid progression of gait impairment requiring regular use of wheelchair within 5 years of onset.
2. A complete absence of progression of motor symptoms or signs over 5 or more years unless stability is related to treatment.
   Note: This criterion is targeted at patients who may have been misdiagnosed with parkinsonism. This must be defined based on observation (i.e. historical information cannot suffice). The absence of progression must be continuous over a minimum of 5 years.
3. Early bulbar dysfunction, defined as one of severe dysphonia, dysarthria (speech unintelligible most of the time), or severe dysphagia (requiring soft food, NG tube, or gastrostomy feeding) within the first 5 y of disease.
   Note: Severity definitions are from the Movement Disorder Society's – sponsored revision of the United Parkinson's Disease Rating Scale (MDS-UPDRS) (i.e. 4 for dysarthria, ≥3 for dysphagia).
4. Inspiratory respiratory dysfunction defined as either diurnal or nocturnal inspiratory stridor or frequent inspiratory sighs.
5. Severe autonomic failure in the first 5 y of disease.
   This can include:

a. Orthostatic hypotension: orthostatic decrease of blood pressure within 3 min of standing by at least 30 mmHg systolic or 15 mmHg diastolic, in the absence of dehydration, medication, or other diseases that could plausibly explain autonomic dysfunction.
b. Severe urinary incontinence or urinary retention in the first 5 y of disease (excluding longstanding low-volume stress incontinence in women), which is not simply functional incontinence (i.e., inability to get to the bathroom in a reasonable time). In men, urinary retention must not be caused by prostate disease, and this must be associated with erectile dysfunction.
Note: Autonomic dysfunction is a common feature of PD; however, this criterion is intended to identify the severe autonomic dysfunction associated particularly with multiple system atrophy. If the patient has more than 5 years' disease duration at assessment, these features must have occurred within the first 5 years (documented either by chart review for orthostatic hypotension or by a clear onset time on history for urinary incontinence).

6. Recurrent (>1/y) falls because of impaired balance within 3 years of onset.
Note: For this criterion, falls are considered to be attributable to impaired balance, implying that falls attributable to loss of consciousness (syncope, seizure), or to situations during which persons with normal balance would also fall (athletic activities, violence, slipping on ice, and so forth) are not included. Clinical judgment is required to determine whether impaired balance played a key role in the fall.
7. The presence of disproportionate anterocollis (dystonic in nature) or contractures of hand or feet within the first 10 y.
8. Absence of any of the common non-motor features of disease despite 5 y disease duration. These include:
   - Sleep dysfunction: sleep-maintenance insomnia, excessive daytime somnolence, symptoms of rapid eye movement sleep behavior disorder
   - Autonomic dysfunction: constipation, daytime urinary urgency (i.e., not simply nocturia), symptomatic orthostasis
   - Hyposmia
   - Psychiatric dysfunction: depression, anxiety, or hallucinations

   Note: This criterion is designed primarily to detect nonparkinsonian conditions mimicking PD (e.g., subjects without evidence of dopaminergic deficit, dystonic tremor, essential tremor)
9. Otherwise unexplained pyramidal tract signs, defined as pyramidal weakness or clear pathologic hyperreflexia (excluding mild reflex asymmetry in the more affected limb, and isolated extensor plantar response).
Note: Mild reflex asymmetry is excluded because it can commonly be seen in PD. Isolated extensor plantar response is excluded because of the difficulty in differentiating this from a "striatal toe" (an occasional finding in PD), and the possibility that unrelated pathology (e.g., mild cervical myelopathy) can produce this finding.

10. Bilateral symmetric parkinsonism throughout the disease course. The patient or caregiver reports bilateral symptom onset with no side predominance, and no side predominance is observed on objective examination.

SUPPORTIVE CRITERIA

1. Clear and dramatic beneficial response to dopaminergic therapy. To meet this criterion, during initial treatment, patients should have returned to normal or near-normal level of function. In the absence of clear documentation of initial response (e.g., initial treatment with lower-efficacy agents or very low dose), a dramatic response also can be classified as:
    a. Marked improvement with dose increases or marked worsening with dose decreases. Mild changes with dose changes do not qualify. This can be documented either objectively (defined as >30% in UPDRS III with change in treatment), or subjectively with a clear history of marked changes provided by a reliable patient or caregiver.
    b. Unequivocal and marked on/off fluctuations, which must have at some point included predictable end-of-dose wearing off.

    Note: To meet this criterion, it is not sufficient to document some beneficial response to dopaminergic therapy; the response must be unequivocal and of large amplitude. If treatment response is of modest amplitude, the patient does not meet this criterion. The requirement of predictable end-of-dose wearing off is to ensure that these are true dopaminergic fluctuations (as opposed to day-to-day variability, for example). The documentation of predictable end-of-dose wearing off can be from retrospective history (i.e., patients do not have to currently be experiencing predictable fluctuations).
2. Presence of levodopa-induced dyskinesia
3. Rest tremor of a limb, documented on clinical examination (in the past, or on current examination).

    Note: This is included primarily for two reasons: (1) rest tremor is less common in alternate conditions, and (2) rest tremor may occasionally be less responsive to therapy; if so, criterion 1 may be harder to meet in tremor-predominant PD.
4. Positive results from at least one ancillary diagnostic test having a specificity greater than 80% for differential diagnosis of PD from other parkinsonian conditions. Currently available tests that meet this criterion include:
    - Olfactory loss (in the anosmic or clearly hyposmic range, adjusted for age and sex)
    - Metaiodobenzylguanidine scintigraphy clearly documenting cardiac sympathetic denervation

    Note: To meet these criteria, the marker must have been demonstrated to provide more than 80% specificity in most studies (with a minimum of three studies from different centers).

Appendix 6. DLB Diagnostic Criteria

Core Clinical Features	Indicative Biomarkers
Fluctuating cognition with pronounced variations in attention, and alertness	Reduced dopamine transporter (DaT) uptake in basal ganglia via SPECT or PET
Recurrent visual hallucinations	Abnormal 123iodine-MIBG myocardial scintigraphy
REM Sleep behavior disorder (RBD)	Polysomnographic confirmation of REM sleep without atonia (RBD)
Spontaneous Parkinsonism (at least one of bradykinesia, rest tremor, or rigidity)	

Probable DLB requires dementia (Dementia should predate, occur concurrently or within 1 year of Parkinsonism) plus 2 or more Core Clinical Features OR 1 Core Feature and 1 or more Indicative Biomarkers (McKeith et al, 2017).

Appendix 7. Protocol Amendment Summary

I7S-MC-HBEH(b) Effect of LY3154207 on Cognition in Mild-to-Moderate Dementia Due to Lewy Body Dementia (LBD) Associated with Idiopathic Parkinson's Disease (PD) or Dementia with Lewy Bodies (DLB) (The PRESENCE Study)

Overview

Protocol I7S-MC-HBEH(b) Effect of LY3154207 on Cognition in mild-to-moderate Dementia Due to Lewy Body Dementia (LBD) Associated with Idiopathic Parkinson's Disease (PD) or Dementia with Lewy Bodies (DLB) has been amended. The new protocol is indicated by amendment (b) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the specific changes made to this protocol are as follows:

- Expanded the patient population to include those individuals with DLB with insufficient motor symptoms to meet MDS criteria for PD. Previously only subjects with dementia who met MDS criteria for PD were included, this allowed for patients with DLB to enroll as long as they met the MDS criteria for PD. This is reflected in changes to the title, background and inclusion criteria to allow all patients with dementia associated with LBD (PD or DLB) to be enrolled.
- A secondary safety objective and endpoint are added to evaluate the effect of LY3154207 on physical withdrawal symptoms by adding PWC-20 checklist. Understanding the symptoms associated with study drug withdrawal will help inform drug discontinuation strategies.
- The addition of a telephone visit 111 (2 days after v11) to Schedule of activities will allow for the assessment of early withdrawal symptoms via PWC-20 (approximately 5 half-lives after last drug dose) when withdrawal symptoms may be maximum with minimal additional participant burden.
- Eliminate GDS score of ≤6 at screening, to address a common reason for screen failure. This may also allow us to better assess the impact of LY3154207 on mood and the relationship between mood and cognition.
- Changes to the duration of stability requirement for certain concomitant medications to ensure consistency across medication classes and improve protocol compliance.
- The visit 1 duration was updated to 3 to 5 hours split over 1 to 2 days to reflect feedback from sites on the actual time to conduct the visit.
- Inclusion and exclusion criteria updated to improve compliance and reduce areas of confusion.
- Editorial changes throughout document to improve clarity.

Amendment Summary for Protocol I7S-MC-HBEH Amendment (b)

Section # and Name	Description of Change	Brief Rationale
Section 1. Synopsis and Section 4. (Objective(s)/Endpoints)	A secondary safety objective and endpoint are added. Objective: To evaluate the effect of LY3154207 on physical withdrawal symptoms Endpoint: Change in the PWC-20 total score from Week 12 to in-clinic follow-up visit	PWC-20 added to evaluate the effect of LY3154207 on physical withdrawal symptoms
Section 1. Synopsis (Summary of Study Design)	A telephone visit 111 (2 days after V11) is added to the schedule of activities to assess withdrawal symptoms using the PWC-20.	The addition of a telephone visit will allow for the assessment of early withdrawal symptoms (approximately 5 half-lives after last drug dose), when withdrawal symptoms may be maximum with minimal additional participant burden.
Section 1. Synopsis (Number of subjects)	Approximate number of subjects to be screened changed from 400 to 750	Compared with a predicted screen failure rate of 15%, the observed rate is approximately 55%. The numbers have been adjusted accordingly.
Section 1. Synopsis (Withdrawal)	Assessment of withdrawal symptoms using the PWC-20 was added at visit 11	Understanding the symptoms associated with study drug withdrawal will help inform drug discontinuation strategies.
Section 1. Synopsis (Interim Analysis)	Added language to allow for additional efficacy interim analyses, as deemed necessary for internal decision making only.	Modified text to allow flexibility in the timing and number of additional efficacy interims.
Section 2 Schedule of Activities	Modified to account for additional assesments and visits	Added to provide instruction
Section 5.1.1. Screening Period (Visit 1)	Visit 1 is expected to be of a duration of approximately ~~2~~ 3 to ~~4~~ 5 hours and may be split over 1 to 2 days.	The visit duration was updated to reflect feedback from sites on the actual time for conducting the visit.
Section 5.1.1.1. Screening Procedures	Screening procedures are updated. Added CDR-CBB training and Clinical diagnostic criteria for PDD and DLB	As the primary outcome, it is critical to ensure that all subjects can complete the CDR, in addition, the training reduces practice effects.
6.1. Inclusion Criteria	[2] Meet diagnostic criteria for PD (Postuma et al. 2015) or DLB (McKeith et al. 2017) (See Appendix 5 and 6 for details)	Revised to define expanded patient population.

Section # and Name	Description of Change	Brief Rationale
6.2.1. Rationale for Exclusion of Certain Study Candidates	CNS diseases and other neuropsychiatric disorders (e.g., active psychosis, substance abuse) that can affect performance on cognitive tasks and compliance with the protocol are also excluded.	Clarification and modification based on changes to inclusion criteria (e.g. GDS >6 removed).
9.4.5. Physician Withdrawal Checklist	The Penn Physician Withdrawal Checklist (PWC-20) is a 20-item checklist originally developed to assess the severity of withdrawal symptoms in anxiolytic medication discontinuation (Rickels et al. 2008). The PWC-20 is a validated, shortened version of the original 35-item checklist, where the 20 items were selected based on their statistical ability to differentiate between placebo and active drug, plus share correlation with the 35-item checklist (Schweizer et al. 1990; Rickels et al. 1990). The 20 items assess the subject's level of symptoms on a variety of withdrawal symptoms since last visit. Each of the 20 items are scored as 0 (not present), 1 (mild), 2 (moderate), 3 (severe)	Description of PWC-20, added per previous rationale.

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~. Additions have been identified by the use of underscore.

1. Synopsis

Title of Study:
Effect of LY3154207 on cognition in mild-to-moderate dementia due to Lewy Body ~~Parkinson's Disease~~ Dementias (~~PDD~~LBD) associated with idiopathic Parkinson's disease (PD) or dementia with Lewy bodies (DLB).

Rationale:
Eli Lilly and Company (Lilly) is developing LY3154207, an orally available, selective positive allosteric modulator (PAM, also called "potentiator") of the dopamine D1 receptor subtype (D1PAM). By increasing the affinity of dopamine for the D1 receptor, a D1PAM is hypothesized to amplify response to endogenous dopamine, thereby increasing D1 tone at the site of dopamine release, and represents a novel mechanism of action. By potentiating the response to the remaining brain dopamine (or administered levodopa) in subjects with insufficient physiologic dopamine such as those with LBD (PDD or DLB)~~PDD and DLB~~, a D1PAM should improve cognitive performance. In addition, a D1PAM should have a positive impact on other domains affected by LBD (PDD or DLB)~~PDD and DLB~~ including motor deficits, mood, apathy, and daytime sleepiness.

CCI [redacted]

Study I7S-MC-HBEH (HBEH) is a multicenter, randomized, double-blind, parallel-group, placebo-controlled, fixed-dosage, Phase 2~~a~~ study comparing 3 dosages of LY3154207 (10, 30, or 75 mg administered orally [or 50 mg based on interim analysis] once a day ~~[QD]~~) with placebo over 12 weeks in subjects with mild-to-moderate dementia associated with LBD (PDD or DLB)~~PDD~~. Study HBEH will test the hypothesis that LY3154207 administered at 10 mg, 30 mg, and/or 75 mg daily (or 50 mg based on interim analysis) (QD) oral dosing for 12 weeks will result in a significant improvement in cognition in subjects with mild-to-moderate LBD (PDD or DLB)~~PDD~~ compared with placebo. Important secondary outcomes will assess the effect of LY3154207 on function, parkinsonism, sleep and mood/behavior.

CCI [redacted]

Objective(s)/Endpoints:

Objectives	Endpoints
Primary To test the hypothesis that LY3154207 administered at 10 mg, 30 mg, and/or 75 mg daily (or 50 mg based on interim analysis) (QD) oral dosing for 12 weeks will result in a significant improvement in cognition in subjects with mild-to-moderate LBD (PDD or DLB) ~~PDD~~ compared with placebo.	Change in the CoA composite score of the CDR-CCB from baseline to Week 12.
Secondary **Safety:**	
To evaluate the effect of LY3154207 on acute changes of vital signs on the first day of dosing	Number of subjects who met the potentially clinically significant vital signs criteria at 3 consecutive time points at Visit 3 (Day 1 stopping rules).
To evaluate the effect of LY3154207 on SBP on the first day of dosing	Change in in-clinic SBP from 0 up to 8 hours post dose on the first day of study drug dosing
To evaluate the effect of LY3154207 on pulse rate on the first day of dosing	Change in in-clinic pulse rate from 0 up to 8 hours post dose on the first day of study drug dosing
To evaluate the effect of LY3154207 on SBP from baseline to Week 12	Change in in-clinic mean SBP at baseline to mean SBP at Week 12
To evaluate the effect of LY3154207 on pulse rate from baseline to Week 12	Change in in-clinic mean pulse rate at baseline to mean pulse rate at Week 12
To evaluate the effect of LY3154207 on physical withdrawal symptoms	Change in the PWC-20 total score from Week 12 to in-clinic follow-up visit
To evaluate the effect of LY3154207 on motor signs ~~and behavioral function~~	Change in ~~total~~ MDS-~~UPDRS (sum of Part I-III) and individual subscales – non-motor experiences of daily living (Part I), motor experiences of daily living (Part II),~~ motor exam (Part III)~~, and motor complications (Part IV) subscales~~ from baseline to Week 12
To evaluate the effect of LY3154207 on ~~S~~BP on the first day of dosing	Change in in-clinic ~~S~~BP from 0 up to 8 hours post dose on the first day of study drug dosing
To evaluate the effect of LY3154207 on ~~S~~BP from baseline to Week 12	Change in in-clinic mean ~~S~~BP at baseline to mean ~~S~~BP at Week 12

Abbreviations: ADAS-Cog_{11} = 11-item Alzheimer's Disease Assessment Scale – Cognitive subscale; ADAS-Cog_{13} = 13-item Alzheimer's Disease Assessment Scale – Cognitive subscale; CDR-CCB = Cognitive Drug Research Computerized Cognition Battery; ADCS–-CGIC = Alzheimer's Disease Cooperative Study – Clinician Global Impression of Change; CoA = Continuity of Attention; D-KEFS = Delis–Kaplan Executive Function System ; DLB = dementia with Lewy bodies; ESS = Epworth Sleepiness Scale; LBD = Lewy Body Dementia; HBPM = home blood pressure monitoring; MDS-UPDRS = Movement Disorder Society's Unified Parkinson's Disease Rating Scale; MoCA = Montreal Cognitive Assessment; NPI = Neuropsychiatric Inventory; PDD = Parkinson's disease dementia; PDAQ-15 = Penn Parkinson's Daily Activities Questionnaire-15; PK = pharmacokinetics; PoA = Power of Attention; PWC-20 = physician withdrawal checklist-20; QD = once a day; QUIP = Questionnaire for 'Impulsive-Compulsive Disorders in Parkinson's Disease; SBP = systolic blood pressure.

Summary of Study Design: Study I7S-MC-HBEH (HBEH) is a multicenter, randomized, double-blind, parallel-group, placebo-controlled, fixed-dosage, Phase ~~2a~~ 2 study comparing 3 dosages of LY3154207 (10, or 30, or 75 mg administered orally [or 50 mg based on interim analysis] once a day [QD]) with placebo over 12 weeks in subjects with mild-to-moderate LBD (PDD or DLB)~~PDD~~. The study includes a Screening Period (Visits 1 to 2) of a minimum of 7 days and up to 14 days, a Pretreatment Period of a minimum of 11 days and up to 17 days (Visits 2 to 3), a 12-week Treatment Period (Visits 3 to 11), and a 14-day Safety Follow-Up Period (Visits 11 to 801 or early termination [ET]/discontinuation [DC] visit to Visit 801) that includes one telephone visit (Visit 111). Subjects who meet entry criteria will be randomized in a 1:1:1:1 ratio to LY3154207 (10 or 30 or 75 mg QD) or placebo. ~~The primary objective of the study is to test the hypothesis that LY3154207 administration for 12 weeks will result in a significant improvement in cognition as measured by the change from baseline to Week 12 in the Continuity of Attention (CoA) composite score of the Cognitive Drug Research Computerized Cognition Battery (CDR-CCB), in subjects with mild-to-moderate PDD, compared to placebo. The CoA has demonstrated a significant treatment effect in previous trials in subjects with PDD (Wesnes et al. 2005; Rowan et al. 2007).~~

Number of subjects: Approximately ~~400~~ 750 subjects will be screened to achieve 340 randomized and an estimated total of 85 evaluable subjects per treatment group.

Withdrawal: Withdrawal symptom analyses will be conducted on subjects who completed at least one pre-withdrawal and one post-withdrawal PWC-20 checklist. Week 12/Visit 11 will be considered baseline in the change from baseline analyses; Visit 801 will be considered the post baseline assessment. This will be examined using an analysis of covariance (ANCOVA) model with treatment arm as an independent factor and baseline value as a covariate in the model. This will allow us to assess the withdrawal symptoms between treatments and groups.

Interim Analysis: Safety interim analyses will be conducted on the number of subjects on each treatment who met the potentially clinically significant vital signs criteria (Table HBEH.3) at 3 ***consecutive*** time points at Visit 3 (Day 1 stopping rules). This will be done after 50, 100, and 150 subjects have completed Visit 3. CCI [redacted] Those

already on 75-mg dose and passed the Day 1 stopping rules will remain on 75 mg. In the event of an unacceptable rate of subjects meeting Day 1 stopping rules at other doses, adjustments to doses may be made for subsequently randomized subjects at the discretion of the Internal Assessment Committee (IAC). Additional efficacy analyses may be conducted at the time of these safety interim analyses. A safety and efficacy interim analysis will be conducted when 170 randomized subjects have completed Visit 11 (Week 12) assessments and may also be conducted at other timepoints prior to study completion. All potential efficacy analyses may be used for internal decision making, but are not planned to stop the study.

Table HBEH.1. Schedule of Activities for Protocol I7S-MC-HBEH

Procedure[a]	Screening	Pretreatment	Double-Blind Treatment									Follow-up		Unscheduled Visit	ET/DC Visit[d,t]
Study Day	Min 7 days; max 14 days prior to V2	Min 11 days; max 17 days prior to V3		7 days	14 days	21 days	28 days	42 days	56 days	70 days	84 days	2 days after V11[u]	14 days from V11 or ET/DC		
Tolerance Interval for Visit (Days)		Baseline Visit	Randomization	±1	±1	±1	±1	±3	±3	±3	±3	±1	±3		
eCRF Visit No.:	V1[b,d]	V2[b,d]	V3[b]	V4[d]	V5	V6	V7	V8[b,d]	V9	V10	V11[b,d]	V111[d]	V801	V997[c]	
Informed Consent(s) Signed (before procedures/tests)	X														
Register subject in IWRS - Subject number assigned	X														
Complete IWRS	X	X	X	X	X	X	X	X	X	X	X		X	X	X
Demographics	X														
Prior/concomitant treatment	X	X	X	X	X	X	X	X	X	X	X		X	X	X
Inclusion/exclusion criteria	X	X	X												
Modified Hoehn and Yahr Scale	X														
Medical History	X														
Physical Examinations[e]	X							X			X		X		X
Height		X													
Weight		X						X			X				X
Orthostatic BP/pulse rate[f]	X	X	X[d]	X	X	X	X	X	X	X	X		X	X	X
In-clinic BP/Pulse rate monitoring[g]		X	X					X			X		X		

Procedure[a]	Screening	Pretreatment	Double-Blind Treatment									Follow-up		Unscheduled Visit	ET/DC Visit[d,t]
Study Day	**Min 7 days; max 14 days prior to V2**	**Min 11 days; max 17 days prior to V3**		**7 days**	**14 days**	**21 days**	**28 days**	**42 days**	**56 days**	**70 days**	**84 days**	**2 days after V11[u]**	**14 days from V11 or ET/DC**		
Tolerance Interval for Visit (Days)		**Baseline Visit**	**Randomization**	**±1**	**±1**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**+1**	**±3**		
eCRF Visit No.:	**V1[b,d]**	**V2[b,d]**	**V3[b]**	**V4[d]**	**V5**	**V6**	**V7**	**V8[b,d]**	**V9**	**V10**	**V11[b,d]**	**V111[d]**	**V801**	**V997[c]**	
Temperature	X							X			X		X		X
12-Lead ECG	X	X		X				X			X		X	X[c]	X
Review HBPM instructions[h]		X	X	X	X					X	X				
HBPM device returned to site													X		X
Hematology	X	X			X			X			X		X	X[c]	X
Urinalysis	X	X			X			X			X		X	X[c]	X
Clinical Chemistry	X	X			X			X			X		X	X[c]	X
Serum FSH[i]	X														
PGx sampling		X													
Collection of dose administration timing (date and time)			X	X	X	X	X	X	X	X	X				X
PK Sampling[j]			X[j]	X[j]	X[j]			X[j]			X[j]				X[j]
Randomization			X												
Study drug dosing at site			X					X[k]			X[k]				
Dispense Investigational Product			X	X	X	X	X	X	X	X					
Return Investigational Product				X	X	X	X	X	X	X	X				X
Adverse Events		X	X	X	X	X	X	X	X	X	X		X	X	X
Review Lilly Trial app (if available) instructions[l]		X	X	X	X	X	X	X	X	X	X				

Procedure[a]	Screening	Pretreatment	Double-Blind Treatment									Follow-up		Unscheduled Visit	ET/DC Visit[d,t]
Study Day	**Min 7 days; max 14 days prior to V2**	**Min 11 days; max 17 days prior to V3**		**7 days**	**14 days**	**21 days**	**28 days**	**42 days**	**56 days**	**70 days**	**84 days**	**2 days after V11[u]**	**14 days from V11 or ET/DC**		
Tolerance Interval for Visit (Days)		**Baseline Visit**	**Randomization**	**±1**	**±1**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**+1**	**±3**		
eCRF Visit No.:	**V1[b,d]**	**V2[b,d]**	**V3[b]**	**V4[d]**	**V5**	**V6**	**V7**	**V8[b,d]**	**V9**	**V10**	**V11[b,d]**	**V111[d]**	**V801**	**V997[c]**	
Actigraphy watch provided to subjects (if available)[m]		X						X			X				
Return of Actigraphy watch (if available)[n]			X						X				X		
CDR-CCB[o,p]	X	X	X	X	X	X	X	X	X	X	X		X		X
Alzheimer's Disease Cooperative Study – Structured Clinical Global Impression interview[d]		X						X			X				X
ADCS-CGIC[d]								X			X				X
ADAS-Cog_{13}[p]		X						X			X				X
D-KEFS[p]		X						X			X				X
MoCA[p]	X							X			X				X
PDAQ-15[d]		X						X			X				X
MDS-UPDRS[d,p]		X						X			X		X		X
NPI[d]		X						X			X				X
ESS[d]		X		X				X			X		X		X
QUIP[d]		X						X			X				X
GDS-S[d]	X										X				X
PWC-20 (Subject)											X	X	X		X
PWC-20[d] (Caregiver)											X	X	X		X
C-SSRS – Children's Version and Self-Harm Supplement Form[s]	X[q]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]		X[r]	X[r]	X[r]

Abbreviations: ADAS-Cog$_{13}$ = Alzheimer's Disease Assessment Scale – 13-Item Cognitive Subscale; ADCS-CGIC = Alzheimer's Disease Cooperative Study - Clinician Global Impression of Change; BP = blood pressure; CDR-CCB = Cognitive Drug Research Computerized Cognition Battery; C-SSRS = Columbia-Suicide Severity Rating Scale; DC = discontinuation; D-KEFS= Delis–Kaplan Executive Function System; ECG = electrocardiogram; eCOA = electronic Clinical Outcome Assessment; eCRF = electronic case report form; ED = early discontinuation; ESS = Epworth Sleepiness Scale; ET = early termination; FSH = follicle-stimulating hormone; GDS-S = Geriatric Depression Scale – Short Form; HBPM = home blood pressure monitoring; HCG = human chorionic gonadotropin; HEENT = head, ear, eye, nose, and throat; IWRS = interactive web-response system; MDS-UPDRS = Movement Disorder Society's Unified Parkinson's Disease Rating Scale; MoCA = Montreal Cognitive Assessment; NPI = Neuropsychiatric Inventory; PDAQ-15= Penn Parkinson Daily Activities Questionnaire-15; PGx = pharmacogenomic(s); PK = pharmacokinetic(s); PWC-20 = physician withdrawal checklist-20; QUIP = Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease; V = visit.

Note: Be sure that the visit allowance period takes into account the required washout duration needed for medications that are not allowed by the protocol.

[a] Every effort should be made for visits to occur on designated study days. The overall treatment period in the protocol should be maintained (visits should be scheduled based on the randomization visit). Procedures and assessments should be done in the order described in the Operations Manual.

[b] Visit 1 may be split over 2 days. In exceptional circumstances, if the clinical assessments cannot be completed within 1 day at V1, V2, V3, V8, and/or V11, those clinical assessments may be completed the next day. The Orthostatic Blood pressure measurements, in-Clinic Blood pressure measurements, the CDR-CCB, and the laboratory procedures including PK have to be completed on Day 1 of that visit. The visit interval will start from Day 1.

[c] ECGs or samples for clinical laboratory tests (hematology, clinical chemistry, and urinalysis) will only be collected if a retest is needed. All other procedures are required for each unscheduled visit.

[d] The caregiver is required to attend Visit 1 at the clinic to sign the informed consent and be informed about the study details. Caregiver's attendance will also be required at Visit 2, Visit 4, Visit 8, Visit 11, Visit 801, and the ET/DC visit to provide inputs for the PDAQ-15, ADCS-CGIC, GDS-S, MDS-UPDRS, NPI, ESS, and QUIP scales. The caregiver is required at Visit 11, ~~and~~ Visit 111 and Visit 801 to provide input for the PWC-20.

~~[e] Medical history should include timing of onset of cognitive symptoms relative to and of motor symptoms (less or equal to 1 year).~~

[f] The physical examination should include HEENT, cardiac, lung, abdomen, extremity, skin, and neurological examinations.

[g] Orthostatic BP/pulse rate will be measured as part of the vital sign assessments at every visit. At Visit 2, Visit 3, Visit 8, Visit 11, and Visit 801, these measurements will be collected at time 0 of the in-clinic BP/pulse rate monitoring. Subjects will have 3 BP/pulse rate measurements taken in the seated position approximately 1 minute apart followed by 1 BP/pulse rate measurement taken in the standing position. Subjects should be seated for at least 5 minutes and stand for at least 3 minutes prior to taking the respective measurements. If the subject feels unable to stand, vital signs only in the seated position will be recorded.

~~[h] The subject's orthostatic BP and pulse rate measurements must meet inclusion criteria [6] for the subject to proceed with dosing at Visit 3. Subjects not fulfilling inclusion criteria [6] can have their BP/pulse rate re-evaluated within 3 days of Visit 3. If inclusion criteria [6] is subsequently met (within 3 days of Visit 3), the subject may proceed with dosing. If inclusion criteria [6] is subsequently not met (within 3 days of Visit 3), the subject must be discontinued from the study.~~

~~i~~g In-clinic BP and pulse rate monitoring will be done at Visit 2, Visit 3, Visit 8, Visit 11, and Visit 801. The BP and pulse rate measurements will occur at time 0 and every 60 minutes thereafter at Visit 2, Visit 8, and Visit 11, in-clinic BP and pulse rate will be monitored for up to 6 hours; at Visit 3, for up to 8 hours and at Visit 801 for up to 2 hours.. The initial measurement, time 0 of the in-clinic BP and pulse rate monitoring, will be done as an orthostatic BP/pulse rate (refer to footnote c above), and subsequent BP and pulse rate measurements will be done in the seated position only. Time 0 for Visit 3, Visit 8, and Visit 11 will occur just prior to study drug dosing. At Visit 3, drug dosing should be initiated immediately following confirmation that subject meets inclusion criteria [6]. ~~At Visit 2, Visit 8, and Visit 11, in-clinic BP and pulse rate will be monitored for up to 6 hours; at Visit 3, for up to 8 hours and at Visit 801 for up to 2 hours.~~

~~j~~h The subject should be given the HBPM device at Visit 2. Home BP will be measured twice daily in the seated position using the HBPM equipment provided by Eli Lilly and Company (Lilly). Home BP measurements ~~will~~ should be conducted for a minimum of 7 days between Visit 2 and Visit 3, for 3 weeks between Visit 3 and Visit 6, and for a minimum of 7 days between Visit 10 and Visit 11, and Visit 11 and Visit 801. Home BP ~~will~~ should be measured twice in the morning (approximately 1 minute apart) (e.g., 8 AM) immediately following study medication dosing and twice in the evening, approximately 12 hours later (approximately 1 minute apart) (e.g., 8 PM).

~~k~~ ~~The subject should return the HBPM device at Visit 801 or at ET/DC visit, if subject is discontinued early.~~

~~l~~ ~~Laboratory tests to be performed by the central vendor.~~

~~m~~i Refer to inclusion criteria [12e] in Section 6.1.

~~n~~j PK sampling. At Visit 3, a PK sample is to be collected within 1 to 3 hours after the drug is administered at the site. At Visit 4, Visit 5, Visit 8, and ET/DC visit, the PK sample can be collected at any time during the visit. At Visit 11, the PK sample should be collected prior to the drug being administered at the site. The date and time of the PK sample collection as well as the date and time of the dose administration immediately preceding the PK sampling should be entered in the eCRF.

~~o~~ ~~First dose to be administered at the clinic on the morning of Visit 3 following the Time 0 in-clinic BP/pulse rate measurements. The subject's initial in-clinic BP/pulse rate measurements taken in the seated position must meet inclusion criteria [6] for the subject to proceed with dosing. Subjects not fulfilling inclusion criteria [6] can have their BP/pulse rate re-evaluated within 3 days of Visit 3. If inclusion criteria [6] is subsequently met (within 3 days of Visit 3), the subject may proceed with dosing. If inclusion criteria [6] is subsequently not met (within 3 days of Visit 3), the subject must be discontinued from the study.~~

~~p~~k Study drug dose to be administered at the clinic on the morning of Visit 8 and Visit 11 following the Time 0 in-clinic BP/pulse rate measurements.

~~q~~l An iPad® configured with the Lilly Trial application (Lilly Trial app) will be provided to the subjects at Visit 2 (if available). Subjects ~~will~~ should complete assessments from 2 weeks prior to dosing (starting the day following Visit 2), throughout the dosing period, and for 2 weeks after the conclusion of the treatment period (until Visit 801). This assessment ~~will~~ should be done up to twice daily. Subjects will self-select for this optional component of the protocol at Visit 1. Subjects can decide to opt out at any time during the study. In case of opt-out or ET, the subject should return the iPad to the site at the visit following the subject opt-out or at the ET/DC visit. For subjects who complete the Lilly trial application assessments throughout the study, the iPad should be returned at Visit 801. Refer to the Operations Manual for details about Opt-in and Opt-out process.

~~r~~m The actigraphy device (if available) ~~will~~ should be worn on the wrist, similar to a watch, beginning at Visit 2, for 3 separate 2-week periods of time: Visit 2 to Visit 3, Visit 8 to Visit 9, and Visit 11 to Visit 801. The site will provide the device to the subjects at Visits 2, 8, and 11.

~~s~~n Following 14 days of wearing the device, the subject ~~will~~ should bring the device back to the site at the next scheduled visit (Visit 3, Visit 9, or Visit 801).

to CDR-CCB: At least 2 training sessions are required at Visit 1. At each visit, the CDR-CCB should be assessed after the study drug has been dosed. At Visit 4, Visit 5, Visit 6, Visit 7, Visit 9, and Visit 10, if a subject has ~~,~~not taken the study drug prior to the study visit, the subject must take study drug at the site prior to the CDR-CCB ~~is assessed~~.

up The CDR-CCB, MoCA, ADAS-Cog_{13}, MDS-UPDRS (Part III), and D-KEFS scales should be conducted in the practically defined medication "on" state at all visits. The "on" state is defined as the individual best motor function as determined by the investigator or approximately 1 hour after the dose of dopaminergic therapy. Every attempt should be made to conduct these assessments in the "on" state. In the exceptional circumstance that this is not possible, the assessments could be done in the "off" state. The "on/off" state should be confirmed prior to completion of the respective scales listed above. This information will be collected in the eCOA or the eCRF. If any portion of an assessment is done in the "off" state, then that subject should be rated as in the "off" state for the whole assessment. If the subject is not on dopaminergic therapy the assessment should be documented as "on".

vq The C-SSRS "Baseline" version will be used at the Screening visit (Visit 1).

wr The C-SSRS "Since Last Visit" scale will be administered at each subsequent visit.

xs If, based on administration of the C-SSRS, it is determined that suicide-related behaviors have occurred, then the Lilly Self-Harm Follow-Up form will be used to collect additional information to allow for a more complete assessment of these behaviors.

yt All subjects who discontinue study treatment prior to a scheduled visit should have an ET/DC visit and procedures/assessments performed as soon as possible.

zu If the visit window falls on a weekend/holiday then the visit should be conducted at the next possible day.

3.2. Background

Lewy Body Dementia (LBD), including Parkinson's disease dementia (PDD) and DLB, is a progressive neurodegenerative disorder associated with alpha-synuclein deposition, Lewy body pathology, and degeneration of nigro-striatal dopaminergic neurons. According to the Parkinson's Disease Foundation, Parkinson's disease (PD) affects approximately 1 million people in the United States (U.S.) and 7 to 10 million people worldwide (Statistics on Parkinson's). It is estimated that up to 78% of of patients with PD will develop dementia (PDD) in their lifetime (Aarsland et al.2005). DLB is the second most common dementia after Alzheimer's disease (AD) and affects 1.4 million individuals in the U.S., representing an estimated 15-20% of all dementia cases worldwide (Lewy Body Dementia Association [https://www.lbda.org/go/10-things-you-should-know-about-lbd).

LBD is pathologically characterized by intraneuronal inclusions of Lewy bodies throughout subcortical and cortical brain regions, a major component of which is misfolded aggregated α-synuclein (Beyer et al. 2009). Lewy body formation and propagation is accompanied by progressive neurodegenerative processes, particularly affecting the dopaminergic and cholinergic neurons (Harding and Halliday 2001; Klein et al. 2010; Colloby et al. 2012). These neuropathological findings are largely indistinguishable between DLB and PDD and have thus led the field to consider them the same disease.

The cognitive impairments of PDD and DLB also overlap. Progressive executive dysfunction and visual-spatial abnormalities are noted in both, but memory remains relatively intact early in the course of disease (Lippa et al. 2007). Prodromal and non-motor features are similar for both conditions and include REM sleep behavior disorder, hyposmia, prominent visual hallucinations, fluctuations in arousal, autonomic dysfunction, and depression/anxiety. They share neuroimaging characteristics with overlapping patterns of atrophy, glucose utilization, and neurotransmitter changes (cortical cholinergic deficits [Colloby et al. 2016] and striatal/cortical dopaminergic deficits [Klein et al. 2010]). Although once considered as two separate entities, the constellation of supportive pathological, clinical, imaging, and neurochemical data suggest PDD and DLB fall within a spectrum of the same disease (Berg et al. 2014; Gomperts 2016; Friedman 2018; Jellinger 2018; Jellinger and Korczyn 2018).

Because of the dopaminergic fronto-striatal dysfunction and cholinergic deficits associated with LBD [Klein et al. 2010], LY3154207, a D1PAM, is a hypothesized mechanism to treat the cognitive deficits of the disorder. LY3154207 increases the affinity of dopamine for the D1 receptor, thus amplifying the response to endogenous dopamine and increasing D1 tone when and where dopamine is released. By potentiating the response to the remaining brain dopamine (or administered L-DOPA), a D1PAM should improve cognitive performance through enhancing frontal dopaminergic neurotransmission. In addition to facilitating dopamine neurotransmission, LY3154207 may be effective in improving cognitive dysfunction through activation of cortical neurons, markers of synaptic plasticity, and D1 mediated enhanced acetylcholine neurotransmitter release. Other potential effects such as reduced daytime sleepiness, enhanced motor function, improved mood, and goal-directed behaviors leading to reduced apathy (via activation of cortical and striatal D1 receptors) would also be beneficial in LBD.

4. Objectives and Endpoints

Objectives	Endpoints
Primary To test the hypothesis that LY3154207 administered at 10 mg, 30 mg, and/or 75 mg daily (or 50 mg based on interim analysis) (QD) oral dosing for 12 weeks will result in a significant improvement in cognition in subjects with mild-to-moderate LBD (PDD or DLB)~~PDD~~ compared with placebo.	Change in the CoA composite score of the CDR-CCB from baseline to Week 12
Pharmacokinetics To assess the PK of LY3154207 ~~in a population of subjects with mild-to-moderate dementia due to Parkinson's disease~~	Steady-state trough plasma concentrations of LY3154207 at Week 12
Secondary **Safety:** To evaluate the effect of LY3154207 on physical withdrawal symptoms	Change in the PWC-20 total score from Week 12 to in-clinic follow-up visit

Abbreviations: DLB = dementia with Lewy bodies; LBD = Lewy Body Dementia; PWC-20 = physician withdrawal checklist-20

5.1 Overall Design

Study HBEH is a multicenter, randomized, double-blind, parallel-group, placebo-controlled, fixed-dosage, Phase 2~~a~~ study comparing 3 dosages of LY3154207 (10, 30, or 75 mg administered orally [or 50 mg based on interim analysis] once a day [QD]) with placebo over 12 weeks in subjects with mild-to-moderate dementia associated with LBD (PDD and DLB)~~PDD~~. The study includes a Screening Period (Visits 1 to 2) of a minimum of 7 days and up to 14 days, a Pretreatment Period of a minimum of 11 days and up to 17 days (Visits 2 to 3), a 12-week Treatment Period (Visits 3 to 11), and a 14-day Safety Follow-Up Period including a telephone visit (Visit 11 + 2 days) and Visit 801 or early termination [ET]/discontinuation [DC] ~~(Visits 11 to 801).~~ Subjects who meet entry criteria will be randomized in a 1:1:1:1 ratio to LY3154207 (10 or 30 or 75 mg QD) or placebo. The primary objective of this study is to test the hypothesis that LY3154207 administration for 12 weeks will result in a significant improvement in cognition as measured by the change from baseline to Week 12 on the Continuity of Attention (CoA) composite score of the Cognitive Drug Research Computerized Cognition Battery (CDR-CCB), in subjects with mild-to-moderate dementia associated with LBD (PDD and DLB)~~PDD,~~ compared to placebo. Treatment effects with acetylcholinesterase inhibitors in LBD (PDD and DLB) subjects have been demonstrated using the CDR (Wesnes et al. 2005; Rowan et al. 2007, McKeith et al 2000). ~~The Continuity of Attention (CoA) has demonstrated a significant treatment effect in previous trials in subjects with PDD and is resistant to learning and placebo effects.~~

5.1.1.1. Screening Procedures

Screening, entry and administrative procedures, cognitive and physical assessments, vitals, safety assessments, and laboratory assessments (see Schedule of Activities) are to be performed at Visit 1. For subjects treated with dopaminergic treatment for parkinsonism symptoms, the CDR-CCB and MoCA should be conducted in the practically defined medication "on" state. The "on" state is defined as the individual's best motor function as determined by the investigator or approximately 1 hour after the dose of dopaminergic therapy. Every attempt should be made to conduct these assessments in the "on" state. In the exceptional circumstance that this is not possible, the assessments could be done in the "off" state. The "on/off" state should be confirmed prior to completion of the respective scales listed above. This information will be collected in the electronic Clinical Outcome Assessment (eCOA) or the electronic case report form (eCRF). If any portion of an assessment is done in the "off" state, then that subject should be rated as in the "off" state for the whole assessment. Subjects NOT on dopaminergic therapy should be recorded as being in the "on" state for the purpose of analysis.

Medical history should include the diagnosis, whether PDD or DLB, and the timing of onset of dementia and Parkinson's symptoms and date of diagnosis if applicable. Additionally, the relationship of the onset of dementia relative ~~of~~to motor symptoms will be assessed. Subjects without motor symptoms should report their dementia as occurring prior to motor symptoms.

The physical examination should include head, ear, eye, nose, and throat (HEENT), cardiac, lung, abdomen, extremity, skin, and neurological examinations.

5.1.1.1.1. BP and Pulse Rate

Subjects should have a BP or pulse rate at Visit 1 and Visit 3 (time 0), as determined by 3 sequential BP/pulse rate measurements in the seated position:

- Subjects <60 years old:
  - a mean systolic blood pressure (SBP) less than or equal to 140 mmHg, a mean diastolic BP less than or equal to 90 mmHg, and a mean pulse rate less than or equal to 90 beats/min in the seated position.
  - each of the 3 SBP measurement must be less than 180 mmHg.
- Subjects ≥60 years old:
  - a mean SBP less than or equal to 150 mmHg, a mean diastolic BP less than or equal to 90 mmHg, and a mean pulse rate less than or equal to 90 beats/min in the seated position.
  - each of the 3 SBP measurement must be less than 180 mmHg.

5.1.1.1.2. CDR-CBB

At Visit 1, two training sessions of the CDR-CBB will be administered to familiarize subjects with the instrument and to minimize practice effects. Subjects must be able to complete both

training sessions in order to be considered eligible for HBEH. Scores on the CDR-CCB at V1 will not be included in the analysis unless the baseline (V2) scores are incomplete or missing and then V1 scores may be used for calculation of the baseline.

5.1.1.1.3. Modified Hoehn and Yahr Scale

~~Enrolled individuals must be Hoehn and Yahr Stage 1 to Stage 4 at screening~~. The Hoehn and Yahr Scale (Hoehn and Yahr 1967) is used to describe the symptom progression of PD. The scale was originally described in 1967 and included Stages 1 through 5. It has since been modified with the addition of Stages 1.5 and 2.5 to account for the intermediate course of PD. The modified Hoehn and Yahr scale is as follows:

- Stage 0: No signs of disease
- Stage 1: Unilateral disease
- Stage 1.5: Unilateral plus axial involvement
- Stage 2: Bilateral disease, without impairment of balance
- Stage 2.5: Mild bilateral disease, with recovery on pull test
- Stage 3: Mild-to-moderate bilateral disease; some postural instability; physically independent
- Stage 4: Severe disability; still able to walk or stand unassisted
- Stage 5: Wheelchair bound or bedridden unless aided

5.1.1.1.4. Clinical Diagnostic Criteria for *PD and DLB*

Subjects must meet diagnostic criteria for either PD or DLB.

PD Criteria: Subjects should meet MDS criteria for clinically probable PD (Postuma et al. 2015) as detailed in Appendix 5. Subjects must have parkinsonism as defined by the presence of bradykinesia with either rest tremor and/or rigidity. Subjects must not have any absolute exclusion criteria. Subjects must not have greater than 2 red flags; if 1 red flag is present then it must be offset by 1 supportive criterion and if 2 red flags are present it must be offset by 2 supportive criteria. The MDS criteria does not have a criterion for the timing of dementia onset and therefore subjects may be considered PD whether the timing of dementia occurred prior to, concurrently or after parkinsonism. See Appendix 5 for the detailed list of absolute exclusion criteria, red flags and supportive criteria.

DLB Criteria: Subjects should meet the Fourth consensus report of the DLB Consortium diagnostic criteria for probable DLB (McKeith et al. 2017) as detailed in Appendix 6. In addition to dementia, subjects must have 2 or more of the 4 core clinical features of DLB (fluctuation in cognition, visual hallucinations, REM sleep behavior disorder and/or parkinsonism). Subjects with 1 core feature are eligible if they also have at least 1 indicative biomarker as detailed in Appendix 6. Typically, a diagnosis of DLB is made when dementia onset occurs before, concurrently, or in absence of parkinsonism. There is no minimal requirement for parkinsonism in subjects with DLB, who otherwise meet this criteria. See Appendix 6 for the detailed list of core features and indicative biomarkers.

Section 5.1.1.1.5 Montreal Cognitive Assessment Scale

The MoCA will be administered to subjects in Visit 1 to determine if he or she meets entry criteria for dementia. ~~Enrolled i~~Individuals must have a MoCA score of 10 to 23 at screening to be eligible for the study. The MoCA, included here as a screening cognitive assessment, is described in detail in Section 9.1.2.1.5.

Section 5.1.1.1.6. Geriatric Depression Scale Short Form

~~Enrolled individuals must have a Geriatric Depression Scale – Short Form (GDS-S) score of ≤6 at screening.~~ The GDS is a site-administered questionnaire of depression in older adults (Yesavage et al. 1983). Users respond in a "Yes/No" format. Originally developed as a 30-item scale (Long Form), it has since been shortened to a 15-item scale (Short Form), which can be completed in approximately 5 to 7 minutes (Sheikh and Yesavage 1986). Of the 15 items, 10 are indicative of depression when answered "Yes" and 5 are indicative of depression when answered "No." Caregiver's input may be needed at Visit 1 for the Geriatric Depression Scale – Short form (GDS-S).

Section 5.1.1.1.7. Columbia-Suicide Severity Rating Scale – Children's Version

The C-SSRS is a scale that captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the corresponding assessment period. The C-SSRS, included here as a screening assessment, is described in detail in Section 9.4.4. The C-SSRS "Baseline" version will be used at screening, and the findings will constitute the baseline assessment.

The C-SSRS will be administered to the patient with the study partner/study informant present or available by telephone, after the cognitive and functional assessments. Responses from both the study partner/study informant and patient will be considered when administering the scale. If a suicide-related thought or behavior is identified at any time during the study, a thorough evaluation will be performed by a study physician, and appropriate medical care will be provided.

The Lilly Self-Harm Supplement should be completed every time the C-SSRS is administered. If, based on administration of the C-SSRS, it is determined that suicide-related behaviors have occurred, then the Lilly Self-Harm Follow-Up form will be used to collect additional information to allow for a more complete assessment of these behaviors.~~The C-SSRS will be administered to the subject after the cognitive and functional assessments. Responses from subject will be considered when administering the scale. If it is determined that the subject has suicidal ideation or behavior at this baseline assessment, then the subject will not be randomized and will be discontinued from the study.~~

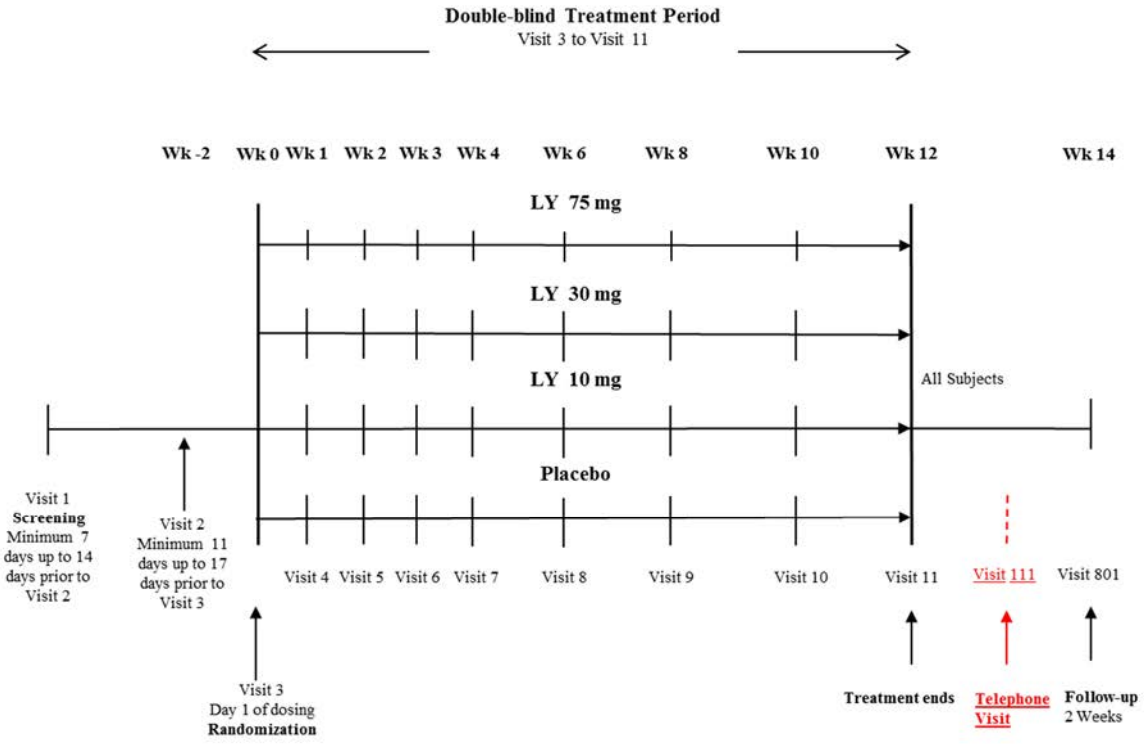

Figure HBEH.1. Illustration of study design for Clinical Protocol I7S-MC-HBEH(b).

5.1.2.1 Blood Pressure and Pulse Rate Measures

Orthostatic BP/pulse rate measurements will be collected at time 0 of the in-clinic BP/pulse rate monitoring. Subjects will have 3 BP/pulse rate measurements taken in the seated position approximately 1 minute apart followed by 1 BP/pulse rate measurement taken in the standing position. Subjects should be seated for at least 5 minutes and stand for at least 3 minutes prior to taking the respective measurements. If the subject feels unable to stand, vital signs only in the seated position will be recorded.

In-clinic BP and pulse rate measurements will occur at time 0 and every 60 minutes thereafter up to 8 hours. The initial measurement, time 0 of the in-clinic BP and pulse rate monitoring, will be done as an orthostatic BP/pulse rate (refer to orthostatic BP/pulse rate above), and subsequent BP and pulse rate measurements will be done in the seated position only.

5.1.2.2. Cognitive, Motor, and Functional Assessments

For subjects treated with dopaminergic therapy for parkinsonism symptoms, ~~The following assessments (~~CDR-CCB, Alzheimer's Disease Assessment Scale – 13-Item Cognitive Subscale [ADAS-Cog$_{13}$], Movement Disorder Society's Unified Parkinson's Disease Rating Scale [MDS-UPDRS] [Part III]) and Delis–Kaplan Executive Function System (D-KEFS) assessments~~)~~ should be conducted in the practically defined medication "on" state. The "on"

state is defined as the individual's best motor function as determined by the investigator or approximately 1 hour after the dose of dopaminergic therapy. Every attempt should be made to conduct these assessments in the "on" state. In the exceptional circumstance that this is not possible, the assessments could be done in the "off" state. The "on/off" state should be confirmed prior to completion of the respective scales listed above. This information will be collected in the eCOA or the eCRF. If any portion of an assessment is done in the "off" state, then that subject should be rated as in the "off" state for the whole assessment. Subjects NOT on dopaminergic therapy should be recorded as being in the "on" state for the purpose of analysis.

5.1.2.3 Actigraphy and iPAD Device

The actigraphy device, similar to a watch, will be placed on the wrist of the subject at Visit 2 (if available and if consented), ~~similar to a watch~~ for the 2-week period~~s~~ of time until Visit 3 (see Section 9.8.1.2 and the Operations Manual).

An iPad configured with the Lilly Trial application (Lilly Trial app) will be provided to the subjects (if available and if consented) (see Section 9.8.1.1 and the Operations Manual). Subjects should complete assessments starting the day following Visit 2, throughout the dosing period, and for 2 weeks after the conclusion of the treatment period (until Visit 801). This assessment should be done up to twice daily.

5.1.2.4 Home Blood Pressure Monitoring

The subject should be given the home blood pressure monitoring (HBPM) device at Visit 2 and instructed to measure Home BP twice daily in the seated position using the HBPM equipment provided by Lilly for a minimum of 7 days between Visit 2 and Visit 3. Home BP ~~will~~ should be measured twice in the morning (approximately 1 minute apart) (e.g., 8 AM) immediately following study medication dosing and twice in the evening, approximately 12 hours later (approximately 1 minute apart) (e.g., 8 PM).

~~An iPad configured with the Lilly Trial application (Lilly Trial app) will be provided to the subjects (if available) (see Section 9.8.1.1 and the Operations Manual). Subjects will complete assessments starting the day following Visit 2, throughout the dosing period, and for 2 weeks after the conclusion of the treatment period (until Visit 801). This assessment will be done up to twice daily.~~

5.1.3. Double-Blind Period (Visit 3 through Visit 11)

All study procedures for the respective visits ~~are~~ should ~~to~~ be completed within 1 day. In exceptional circumstances, if the clinical assessments cannot be completed within 1 day at V3, V8, and/or V11, those clinical assessments may be completed ~~on~~ the next day. The orthostatic blood pressure measurements, in-clinic blood pressure measurements, the CDR-CCB, and the laboratory procedures including PK ~~have to~~must be completed on ~~Day 1~~the first day of that visit. The visit interval will start from ~~Day 1~~the first day of visit.

Visit 3 (Day 1 of dosing) -

5.1.3.1 Orthostatic BP/Pulse Rate Measurements

Prior to dosing, ~~O~~orthostatic BP/pulse rate measurements will be collected at time 0 of the in-clinic BP/pulse rate monitoring. Subjects will have 3 BP/pulse rate measurements taken in the seated position approximately 1 minute apart followed by 1 BP/pulse rate measurement taken in the standing position. Subjects should be seated for at least 5 minutes and stand for at least 3 minutes prior to taking the respective measurements. If the subject feels unable to stand, vital signs only in the seated position will be recorded.

The mean should be calculated from ~~of~~ the 3 initial in-clinic BP/pulse rate measurements taken in the seated position, and must meet inclusion criteria [6] in order to proceed with dosing (Table HBEH.4). At Visit 3, ~~S~~subjects not fulfilling inclusion criteria [6] at their time 0 BP/pulse rate measurements can have their BP/pulse rate re-evaluated within 3 days. If inclusion criteria [6] is subsequently met (within 3 days of Visit 3), subject may proceed with dosing. If inclusion criteria [6] is subsequently not met (within 3 days of Visit 3), the subject must be discontinued. Subjects who continue to meet entry criteria will be randomized to LY3154207 (10, 30, or 75 mg QD) or placebo immediately following confirmation that subject meets inclusion criteria [6]. Subjects should be dosed immediately after randomization.

The time 0 mean BP and pulse rate will be used for the baseline measurement to assess the change threshold for the development of potentially clinically significant BP/pulse rate.

After time 0, in-clinic BP and pulse rate measurements will be taken every 60 minutes in the seated position only for up to 8 hours. Subjects who meet potentially clinically significant BP/pulse rate measurement (Table HBEH.3) at 3 consecutive timepoints -(Day 1 stopping rules) should be discontinued from the study.

Table HBEH.3. Potentially Clinically Significant Vital Sign Criteria

	Low[a]	High[a]
Systolic BP (mm Hg)	≤90 AND ≥20 decrease	≥180 AND ≥20 increase
Diastolic BP (mm Hg)	≤50 AND ≥15 decrease	≥105 AND ≥15 increase
Pulse Rate (bpm)	≤50 AND ≥15 decrease	≥120 AND ≥15 increase

Abbreviations: BP = blood pressure, bpm = beats per minute, mm Hg = millimeters of mercury

[a] Both conditions on absolute AND relative values are required for the measures to meet the criteria for potentially clinically significant (for example BP ≥180 AND ≥20 increase are both required for systolic blood pressure to meet the criteria for potentially clinically significant)

Table HBEH.4. Vital Sign Inclusion Criteria [6] for Subjects at Visit 1 and Visit 3 (time 0)

	Subjects <60 Years	Subjects ≥60 Years
Mean Systolic BP[a] (mm Hg)	≤140	≤150
Mean Diastolic BP (mm Hg)	≤90	≤90
Mean Pulse Rate (bpm)	≤90	≤90

[a] Each of the 3 SBP measurement must be less than 180 mmHg

5.1.3.2. PK Sample

A PK sample is to be collected within 1 to 3 hours after the drug is administered at the site. The date and time of the PK sample collection as well as the date and time of the dose administration immediately preceding the PK sampling will be ~~entered in the eCRF~~recorded.

5.1.3.3. Home Blood Pressure Monitoring

The subject should be instructed to take Home BP measurements twice daily in the seated position using the HBPM equipment provided by Lilly for a minimum of 7 days between Visit 3 and Visit 4. Home BP should~~will~~ be taken twice in the morning (approximately 1 minute apart) (e.g., 8 AM) immediately following study medication dosing and twice in the evening, approximately 12 hours later (approximately 1 minute apart) (e.g., 8 PM).

~~Appointments should be made for all remaining visits and should be scheduled as close as possible to the target date, relative to Visit 3~~.

5.1.3.4. Visit 4 to Visit 11

~~During the double blind period, v~~Visits will occur at weekly intervals (7 days ± 1 day) for Visit 4 through Visit 7, and will occur at biweekly intervals (14 days ± 3 days) for Visit 8 through Visit 11.

Study drug is to be administered at the clinic on the morning of Visit 8 and Visit 11 following the Time 0 in-clinic BP/pulse rate measurements.

In-clinic BP/pulse rate monitoring at Visit 8 and Visit 11 will be conducted as described in Section 5.1.2.

At each visit, the CDR-CCB should be assessed after the study drug has been administered. At Visit 4, Visit 5, Visit 6, Visit 7, Visit 9, and Visit 10, if a subject has not taken study drug prior to the study visit, the subject must take study drug at the site prior to the CDR-CCB assessment.

MoCA, ADAS-Cog13, MDS-UPDRS [Part III], and D-KEFS will be performed according to the Study Schedule.

Caregiver's inputs will be needed at Visit 4, Visit 8, Visit 11, or ET/ DC for the PDAQ-15, Alzheimer's Disease Cooperative Study – Clinician Global Impression of Change (ADCS-CGIC), MDS-UPDRS, NPI, ESS, GDS-S, and/or QUIP scales. Caregiver's input, separate from the subject, will be needed at ~~Visit 10 (in person or via telephone) and~~ Visit 11, Visit 111 and Visit 801 for the PWC-20 early termination.

5.1.4. Telephone Visit (Visit 111)

A telephone visit will be conducted 2 days following Visit 11. The PWC-20 will be assessed with the subject and caregiver, separately, at this telephone visit.

5.1.5. Follow-Up Period (Visit 801)

A follow-up visit will be performed at Visit 801, which will occur 14 days ± 3 days following the subject's last dose of study medication.

Visit 801 is expected to be of a duration of approximately 2 hours.

Caregiver's inputs will be needed at Visit 801 for MDS-UPDRS, PWC-20, and ESS.

See the Schedule of Activities (Section 2) for the timing of events and the measures to be assessed during the follow-up period.

~~The CDR-CCB assessment should be conducted in the practically defined medication "on" state. The "on" state is defined as the individual's best motor function as determined by the investigator or approximately 1 hour after the dose of dopaminergic therapy. Every attempt should be made to conduct this assessment in the "on" state. In the exceptional circumstance that this is not possible, the assessment could be done in the "off" state. The "on/off" state should be confirmed prior to assessment completion of the respective scale listed above. This information will be collected in the eCOA or the eCRF. If any portion of the assessment is done in the "off" state, then that subject should be rated as in the "off" state for the whole assessment.~~

5.2. Number of Subjects

Approximately ~~400~~ 750 subjects will be screened to achieve 340 randomized and evaluable subjects for an estimated total of 85 evaluable subjects per treatment group.

5.3. End of Study Definition

End of the study is the date of the ~~last visit or~~ last scheduled procedure shown in the Schedule of Activities (Section 2) for the last subject.

5.4. Scientific Rationale for Study Design

Study HBEH will include subjects who meet the revised MDS criteria for PD (Postuma et al. 2015) or those who meet the revised criteria for DLB, and all who have mild-to-moderate dementia as defined by a decline in cognitive function, which in the opinion of the investigator has resulted in functional impairment and a MoCA score between 10 and 23 (Trzepacz et al. 2015). ~~Per the revised MDS criteria, PDD can be diagnosed in the presence of dementia, regardless of the timing of dementia onset relative to PD diagnosis. Subjects diagnosed with~~

~~dementia with Lewy bodies (DLBs) should be considered as also having PD if they meet the MDS PD criteria. Therefore, subjects may have dementia prior to, at the time of, or subsequent to the diagnosis of PD. Unlike registration trials of symptomatic therapies in PDD (Emre et al. 2004), the current study will include some subjects who would otherwise have met the traditional criteria (dementia prior to or within 1 year of motor onset) for DLB based on the timing of their dementia (Mckeith et al. 2005). This criterion was that the dementia occurs prior to or within 1 year of Parkinson's symptoms. The 1 year rule is arbitrary and based on the historical belief that PD was not associated with dementia; however, there is increasing controversy about the validity of this traditional approach to splitting the diagnoses (Berg et al. 2014). In support of the proposed approach, both disorders share a variety of clinical, genetic, and pathological features (Lippa et al. 2007; Postuma et al. 2009; Johansen et al. 2010). Both DLB and PDD are associated with similar impairments in cognition with predominant visuoperceptual abnormalities, improvement in memory with cues, and so on. Both are associated with prominent psychosis, neuroleptic sensitivity, and alterations in arousal. Prodromal features (e.g., rapid eye movement [REM] sleep behavior disorder, olfactory loss) are the same in both conditions. Non motor symptoms with depression, anxiety, autonomic dysfunction and sleep disturbances occur with similar relative frequency in both. The same genetic mutations (alpha synuclein duplications, glucocerebrosidase mutations) are associated with the development of either condition. Finally, they have a shared pathology with alpha synuclein and Lewy body formation in the brain stem and cortex. Therefore,~~The inclusion of LBD (PDD or DLB)~~both PDD and DLB the Study~~in HBEH meets current thinking about LBD ~~PDD and DLB~~ that, apart from the timing of cognitive impairment, PDD and DLB are clinically and pathologically indistinguishable and would likely respond to similar therapeutic approaches (Aarsland et al. 2004; Ballard et al. 2006).

6.1. Inclusion Criteria

~~Study HBEH will include men and women aged 40 to 85 years with mild to moderate PDD.~~ Subjects are eligible to be included in the study only if they meet all of the following criteria (note that inclusion criteria [6] ~~to [10]~~ must be met ~~or~~ at ~~an~~ additional visits):

Type of Subject and Disease Characteristics

[1] Male and female subjects aged 40 to 85 years (inclusive).

[45] Meet diagnostic criteria for PD (Postuma et al. 2015) or DLB (McKeith et al. 2017) (See Appendix 5 and 6 for details)

[2] ~~Have idiopathic PD per MDS criteria (Postuma et al. 2015) with at least 2 years of PD symptoms.~~

[5] Are Modified Hoehn and Yahr Stages ~~1~~ 0 to 4.

[6] Have a BP or pulse rate at Visit 1 and Visit 3 (time 0), as determined by 3 sequential BP/pulse rate measurements in the seated position:

[7] If on anti-parkinsonian agents, subjects must be on stable dosage for at least ~~4~~ 3 weeks prior to Visit 1 ~~2~~, and ~~it is anticipated that no changes will be needed~~should remain on stable doses during the course of the study.

[8] If on medications affecting cognition (rivastigmine, galantamine, donepezil, memantine), subjects must be on stable dosage for at least ~~8~~ 3 weeks prior to Visit ~~2~~ 1 and ~~expected to~~should remain at a stable dosage during the course of the study.

[9] If on antidepressant medications, subjects must be on stable dosage for at least ~~8~~ 3 weeks prior to Visit ~~2~~ 1 and ~~expected to~~should remain at a stable dosage during the course of the study.

[10] If on clozapine, quetiapine, and pimavanserin to address drug-induced or disease-related psychosis, subjects must be on stable dosage for 3 ~~4~~ weeks prior to Visit 1~~2~~ and expected to remain at a stable dosage during the course of the study.

[11] If on antihypertensive medications, subjects must be on stable dosage for at least ~~3 months~~3 weeks prior to Visit 1.

[12c] Men with pregnant partners should use condoms during intercourse for the duration of the study and until ~~the end of estimated relevant potential exposure in WOCBP (below the NOAEL/10) plus 90~~3 days following the last dose of study drug~~)~~.

[12d] Men should refrain from sperm donation for the duration of the study and until their plasma concentrations are below the level that could result in a relevant potential exposure to a possible fetus, predicted to be 93~~0~~ days following the last dose of study drug ~~(below the NOAEL/10) plus 90 days~~.

[13] In the investigator's opinion is able to comply with all appointments for clinic visits, tests, and procedures, including venipuncture, computerized assessments and examinations required by the protocol.

[16] All subjects must have a reliable caregiver who is in frequent contact with the subject (defined as at least 10 hours per week) and will accompany the subject to Visit 1, Visit 2, Visit 4, Visit 8, Visit 11, Visit 111 (telephone only) and Visit 801.

6.2. Exclusion Criteria

[21] Have significant central nervous system or psychiatric disease, other than PD or DLB, that in the investigator's opinion may affect cognition or the ability to complete the study.~~may affect cognition or the ability to complete the study, including but not limited to other dementias (e.g., Alzheimer's disease [AD]).~~

[27] ~~Have a current or any previous diagnosis of bipolar disorder, schizophrenia, or other primary psychotic disorder~~. Exclusion criterion [27] has been deleted.

[28] ~~Have poorly controlled psychosis (hallucinations or delusions) that in the opinion of the investigator would interfere with the subject's ability to be compliant with the study protocol.~~ Exclusion criterion [28] has been deleted.

[29] ~~Have any other psychiatric disorder that, in the judgment of the investigator, would interfere with compliance with the study protocol.~~ Exclusion criterion [29] has been deleted.

[31] ~~Have a GDS-S score of >6 at Visit 1.~~ Exclusion criterion [31] has been deleted.

[32] Have a serious or unstable medical illness, other than ~~idiopathic~~ LBD (PDD or DLB)~~PDD~~, including cardiovascular, hepatic, respiratory, hematologic, endocrinologic, neurologic, or renal disease, or clinically significant laboratory or electrocardiogram (ECG) abnormality as determined by the investigator.

[36] Have used anticholi~~e~~nergics trihexyphenidyl and benztropine in the 4 weeks prior to screening (Visit 1) and at any time during the course of the study.

[38] ~~Are currently taking~~Have taken any medications or food, herbal or dietary supplements that are inhibitors (e.g., ketoconazole, grapefruit juice), or strong/moderate inducers of cytochrome P450 3A4 (CYP3A4) (e.g., rifampicin) or are unable or unwilling to discontinue usage of them 4 weeks prior to Visit 3. If subjects are willing and able to discontinue use of CYP3A4 inhibitors or strong/moderate inducers at least 4 weeks prior to Visit 3, they may proceed in the study. Refer to the Operations Manual for a ~~full~~ list of inhibitors and inducers of CYP3A4.

[43] Are Lilly employees, employees of ~~Quintiles IMS~~IQVIA, or employees of a third party organization involved in the conduct of the study.

[44] ~~Are unwilling or unable (e.g., visually impaired or physically unable) to comply with the use of a data collection device (e.g., HBPM, eCOA, CDR-CCB) to directly record data from the subject.~~ Exclusion criterion [44] has been deleted.

6.2.1. Rationale for Exclusion of Certain Study Candidates

CNS diseases and ~~Depression affects approximately 50% of subjects with PD and can affect cognitive performance that may confound the analysis of cognitive outcomes. Therefore, subjects with active depression will be excluded. O~~other neuropsychiatric disorders (e.g., active psychosis, substance abuse) that can affect performance on cognitive tasks and compliance with the protocol are also excluded.

Medications that negatively affect cognition (e.g., certain anticholinergics, exclusion criteria #36) and motor function (e.g., certain antipsychotics, exclusion criteria #35) will be excluded, given the potential of these medications to confound clinically relevant outcomes.

6.3. Lifestyle Restrictions

Subjects should be instructed not to donate blood or blood products during the study or for 93~~0~~ days following the last dose ~~(below the NOAEL/10) plus 90 days~~ of LY3154207. Male subjects should be instructed to not donate sperm during the study for 93~~0~~ days following the last dose of LY3154207.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. The interval between the initial screening and the rescreen should be at least 4 weeks. When the subject is rescreened, the subject must sign a new ICF, ~~and~~ be assigned a new subject identification number, and undergo all screening procedures.

7.2 Method of Treatment Assignment

Selection and Timing of Doses

The doses ~~will~~ should be administered at approximately the same time each day in the morning. At Visit 3, Visit 8, and Visit 11, the dose will be administered at the clinic. The actual date and time of the dose administrations on the day of Visit 3, Visit 4, Visit 5, Visit 8, Visit 11, and ET/DC visit will be recorded in the subject's eCRF.

7.3. Blinding

If an investigator, site personnel performing assessments, or subject is unblinded, the subject must be discontinued from the study. ~~In cases where there are ethical reasons to have the subject remain in the study, the investigator must obtain specific approval from a Lilly clinical research physician (CRP) for the subject to continue in the study.~~

In case of an emergency, the investigator has the sole responsibility of determining if unblinding of a subject's treatment assignment is warranted for medical management of the event. The subject's safety must always be the first consideration in making such a determination. Every effort should be made to notify Lilly Medical representative prior to unblinding if feasible. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

7.6. Treatment Compliance

Subject compliance with study medication will be assessed at each visit. Compliance will be assessed by counting returned capsules. ~~Deviation(s) from the prescribed~~Capsules dispen~~d~~sed and returned ~~dosage regimen~~ should be recorded in the CRF.

7.7. Concomitant Therapy

Concomitant medications to treat the underlying PD (known as antiparkinsonian agents) are permitted, provided the subject has been on a stable dosage regimen for at least ~~4~~ 3 weeks prior to Visit 1 ~~2~~, and ~~is expected to~~should remain on a stable dosage for the duration of the study.

Routine medications taken PRN are allowed. However, if in the investigator's opinion PD medications need to be adjusted to manage motor symptoms during the course of the study, the reason for change in medication should be recorded as an AE and the concomitant medication eCRF page updated accordingly. In addition, the study sponsor should be notified as soon as feasible and a notification generated.

In addition to medications for PD, drugs for common conditions in an older population, such as hypertension, hypercholesterolemia, and ischemic heart disease, are acceptable ~~at stable dosages~~. Specifically, antihypertensive medications should be stable for ~~3 months prior to screening (V1)~~3 weeks prior to V1. During the course of the study, antihypertensive medications may be adjusted for medical need. The concomitant medication eCRF page should be updated accordingly and if applicable the reason for change in medication should be recorded as an AE.

Concomitant medications to treat cognition (rivastigmine, galantamine, donepezil, memantine) and depression are permitted, if subjects have been on a stable dosage regimen for at least ~~8~~ 3 weeks prior to Visit ~~2~~ 1 and ~~is expected to~~should remain on a stable dosage for the duration of the study. Concomitant medications to treat psychosis (clozapine, quetiapine, and pimavanserin) are permitted, provided the subject has been on a stable dosage regimen for at least 4 3 weeks prior to Visit ~~2~~ 1 and ~~is expected to~~should remain on a stable dosage for the duration of the study. However, if in the investigators opinion cognitive and antipsychotic medications need to be adjusted during the course of the study to address a clinical change, the reason for change in medication should be recorded as an AE and the concomitant medication eCRF page updated accordingly. In addition, the Lilly CRP or designee must be contacted as soon as possible to determine whether the subject should continue in the study.

Subjects and their caregiver ~~will~~ should be instructed to consult ~~the investigator or other~~with the appropriate study personnel at the site prior to initiation of any new medications or supplements and prior to changing dose or discontinuing from~~of any current~~ concomitant medications or supplements.

~~**Table HBEH.4. Prohibited Concomitant Medications and Supplements**~~

~~**Drug Class**~~	~~**Allowed as Needed**~~	~~**Chronic Use Allowed**~~	~~**Conditions for Use**~~
~~All inhibitors of CYP3A4~~	~~N~~	~~N~~	~~Topical may be permitted~~
~~Strong/moderate inducers of CYP3A4~~	~~N~~	~~N~~	~~Topical may be permitted~~
~~Antipsychotics (except clozapine, quetiapine, and pimavanserin)~~	~~N~~	~~N~~	
~~Trihexyphenidyl and benztropine~~	~~N~~	~~N~~	
~~Illicit use of any drugs of abuse~~	~~N~~	~~N~~	

~~Abbreviations: CYP3A4 = cytochrome P450 3A4; N = No.~~

Additional information about concomitant medications is provided in the Operations Manual~~A complete list of prohibited concomitant medications and supplements is included~~ in the Operations Manual.

8.1.1. Permanent Discontinuation from Study Treatment

Possible reasons leading to permanent discontinuation of study treatment:

- Subject Decision
  - the subject or the subject's designee, for example, ~~parents or~~ legal guardian, requests to discontinue the investigational product.
- Day 1 stopping rules - Discontinuation due to change in acute vital signs on —Day 1 (Visit 3) ~~(Day 1 stopping rules)~~
  ~~(Day 1 of dosing)~~
  If during Day 1 (Visit 3) and following ~~of~~ study drug dosing, any of the potentially clinically significant vital signs criteria (Table HBEH.3) are met at 3 ***consecutive*** time points using in-clinic vital sign monitoring, then the subject should be discontinued from the study drug. The relative value of the potentially clinically significant vital sign criteria is calculated by comparing to the mean of the 3 seated blood pressure and pulse rate at Time 0 of Visit 3 (baseline).

~~Table HBEH.5. Potentially Clinically Significant Vital Sign Criteria~~

	Low[a]	High[a]
Systolic BP (mm Hg)	≤90 AND ≥20 decrease	≥180 AND ≥20 increase
Diastolic BP (mm Hg)	≤50 AND ≥15 decrease	≥105 AND ≥15 increase
Pulse Rate (bpm)	~~≤50 AND~~ ≥15 decrease	~~≥120 AND~~ ≥15 increase

Abbreviations: BP = blood pressure, bpm = beats per minute, mm Hg = millimeters of mercury

[a] Both conditions on absolute AND relative values are required for the measures to meet the criteria for potentially clinically significant (for example BP ≥180 AND ≥20 increase are both required for systolic blood pressure to meet the criteria for potentially clinically significant)

For vital sign measurements that meet the criteria for potentially clinically significant vital signs (Table HBEH.3) after Visit 3, management will be left to the discretion of the investigator and may include discontinuation of study drug. ~~Prior to study drug discontinuation after Visit 3, the~~The investigator should consult with the Lilly CRP or designee.

- Discontinuation due to a hepatic event or liver test abnormality

Subjects who are discontinued from the study due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via ~~CRF/electronic data entry~~eCRF.

Subjects discontinuing from the study treatment prematurely for any reason should complete an early termination visit and safety follow-up (V801) to complete AE and other follow-up

procedures per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events) and Section 9.4 (Safety).

8.1.2. Temporary Discontinuation from Study Treatment

Temporary discontinuation from study drug treatment is allowed if a short-term treatment of an excluded medication is necessary, secondary to hospitalization, personal circumstances, or to evaluate the study drug impact on an uncertain AE. Study drug may be restarted at the investigator's discretion. If temporary discontinuation is due to an AE, it should be reported to the Lilly CRP or their representative. Temporary treatment discontinuation and restarting should be documented in the eCRF. Restarting treatment after a discontinuation period that is greater than 3 consecutive days should be discussed between the investigator and Lilly CRP or their representative.

8.1.3. Discontinuation of Inadvertently Enrolled Subjects

If the sponsor or investigator identifies a subject who did not meet enrollment criteria and was inadvertently enrolled, then the subject should be discontinued from study treatment ~~unless there are extenuating circumstances that make it medically necessary for the subject to continue on study treatment~~. However, if the investigator and the sponsor CRP agree that it is medically appropriate to continue in the study, the investigator must obtain documented approval from the sponsor CRP to allow the inadvertently enrolled subject to continue in the study ~~with or without treatment with the investigational product.~~

If the subject is discontinued from the study, the subject should complete an early termination visit and safety follow-up (V801) to complete safety follow-up as outlined in Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety).

8.2 Discontinuation from the Study

Subjects discontinuing from the study prematurely for any reason should complete an early termination visit and safety follow-up (V801), to complete ~~must complete~~ AE and other safety follow-up per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety).

9.1.1. Primary Efficacy Assessments

The CoA component of the CDR-CCB has been selected as the primary endpoint for this study because it measures the ability to sustain concentration and has demonstrated a significant treatment effect in previous trials in subjects with LBD (PDD or DLB) within the time frame of the current study (Wesnes et al. 2005; Rowan et al. 2007). The battery is a simple "yes/no" computerized assessment that is feasible across a range of PD motor impairment, and as the CoA score is based on accuracy but not speed of response, it is resistant to confounding due to motor impairment (Wesnes et al. 2002). The CDR-CCB is not dependent on skill of a rater, and hence there is less inter-rater variability; learning effects can be minimized with training and it targets

domains relevant to subjects with LBD (PDD and DLB). ~~The CDR-CCB, described below, has been widely used in dementia research for more than 25 years. The CoA component of the CDR-CCB, which includes attention, concentration, and vigilance assessments, will be used as the primary efficacy measure in this study.~~ Treatment effects with acetylcholinesterase inhibitors in LBD (PDD and DLB) subjects have been demonstrated using the CDR (Wesnes et al. 2005; Rowan et al. 2007, McKeith et al 2000)~~The CoA composite score reflects the ability to sustain concentration and has demonstrated a significant treatment effect in previous trials in PDDsimilar populations subjects (Wesnes et al. 2005; Rowan et al. 2007)~~. The CoA is calculated from the CDR-CCB by summing the number of correct responses in the digit vigilance and choice reaction time tasks and then subtracting the number of digit vigilance false alarms.

~~The CDR-CCB should be assessed in the practically defined medication "on" state at all visits. The "on" state is defined as the individual best motor function as determined by the investigator or approximately 1 hour after the dose of dopaminergic therapy. Every attempt should be made to conduct this assessment in the "on" state. In the exceptional circumstance that this is not possible, the assessment could be done in the "off" state. The "on/off" state should be confirmed prior to assessment completion of the respective scales listed above. This information will be collected in the eCOA or the eCRF. If any portion of the assessment is done in the "off" state, then that subject should be rated as in the "off" state for the whole assessment.~~

9.1.2.1.3. Alzheimer's Disease Assessment Scale – 13-Item Cognitive Subscale

~~The ADAS-Cog$_{13}$ should be conducted in the practically defined medication "on" state at all visits. The "on" state is defined as the individual's best motor function as determined by the investigator or approximately 1 hour after the dose of dopaminergic therapy. Every attempt should be made to conduct this assessment in the "on" state. In the exceptional circumstance that this is not possible, the assessment could be done in the "off" state. The "on/off" state should be confirmed prior to assessment completion of the respective scales listed above. This information will be collected in the eCOA or the eCRF. If any portion of the assessment is done in the "off" state, then that subject should be rated as in the "off" state for the whole assessment.~~

9.1.2.1.4. Delis-Kaplan Executive Function System

The D-KEFS verbal fluency has shown a significant response ($p<.001$) to rivastigmine therapy in a 24-week randomized controlled trial in subjects with PDD (Emre et al. 2004). The D-KEFS verbal fluency test is preferred as a measure of executive function in PDD because it is not confounded by motor deficits. This specific measure of executive function, a domain commonly affected in LBD (PDD and DLB)~~PDD~~, will complement other measures of cognition included in Study HBEH that do not adequately assess this domain.

~~The D-KEFS should be conducted in the practically defined medication "on" state at all visits. The "on" state is defined as the individual best motor function as determined by the investigator or approximately 1 hour after the dose of dopaminergic therapy. Every attempt should be made to conduct this assessment in the "on" state. In the exceptional circumstance that this is not possible, the assessment could be done in the "off" state. The "on/off" state should be confirmed~~

~~prior to assessment completion of the respective scales listed above. This information will be collected in the eCOA or the eCRF. If any portion of the assessment is done in the "off" state, then that subject should be rated as in the "off" state for the whole assessment.~~

9.1.2.1.5. Montreal Cognitive Assessment Scale

The MoCA (available at www.mocatest.org) was developed as a brief screening instrument for mild cognitive impairment and mild AD to address limitations of the Mini-Mental State Examination (MMSE) (Nasreddine et al. 2005). The MoCA has been identified as a suitable screening instrument for the detection of cognitive impairment in PD (Hoops et al. 2009) and DLB (McKeith et al. 2017). Since development, it has been increasingly utilized to detect cognitive impairment in subjects with PD. The MoCA is divided into 7 subscores (maximum possible subscore):

Use of MoCA in the context of PD to screen for subjects with cognitive impairment is consistent with the Parkinson Study Group (PSG) Cognitive/Psychiatric Working Group and MDS recommendations; although, due to limitations of data for the MoCA on change over time or change with treatment, the PSG only reviewed the scale in the context of trials where executive functioning was not a primary outcome (Chou et al. 2010; Litvan et al. 2012). The MoCA has consistently demonstrated higher sensitivity than the MMSE for the detection of mild cognitive impairment in various subject populations including PD and DLB (Nasreddine et- al. 2005; Smith et al. 2007, Zadikoff et al. 2008; Olson et al. 2011; Freitas et al. 2012; Biundo et al. 2016; Wang et al. 2013). Using a cut-off score of less than or equal to 26 as a predictor of cognitive impairment, results from the MoCA identified from 52% to 83% of subjects with PD who had already been identified as having mild cognitive impairment (Smith et al. 2007; Hoops et al. 2009; Nazem et al. 2009). A MoCA score of 26 or less has also provided excellent discrimination between subjects who had mild cognitive impairment and those who did not (receiver operating characteristic curve analyses 78% to 90%; sensitivity 90%; specificity 75% (Dalrymple-Alford et al. 2010). Satisfactory test–retest reliability and inter-rater reliability have been demonstrated (interclass correlation coefficients 0.79 and 0.81, respectively) (Gill et al. 2008). Additionally, good correlation between the MoCA and a neuropsychological battery (assessing the domains of memory and executive function) was observed (coefficient of 0.72) (Gill et al. 2008).

~~The MoCA should be conducted in the practically defined medication "on" state at all visits. The "on" state is defined as the individual best motor function as determined by the investigator or approximately 1 hour after the dose of dopaminergic therapy. Every attempt should be made to conduct this assessment in the "on" state. In the exceptional circumstance that this is not possible, the assessment could be done in the "off" state. The "on/off" state should be confirmed prior to completion of the respective scales listed above. This information will be collected in the eCOA or the eCRF. If any portion of the assessment is done in the "off" state, then that subject should be rated as in the "off" state for the whole assessment.~~

9.1.2.1.6. Penn Parkinson's Daily Activities Questionnaire-15

The PDAQ-15 is a 15-item measure of instrumental activities of daily living (IADL) that is impacted by cognitive impairment in subjects with PDD. The PDAQ-15 is derived from the original 50-item scale, which has demonstrated test–retest reliability, construct validity, sensitivity, and specificity to PD cognitive impairment (Brennan et al. 2016a, 2016b), and the questionnaire is completed by the caregiver. The score range is 0 to 60, with higher scores indicating better function. It is derived from a larger 50-item scale that demonstrates excellent test–retest reliability and construct validity, and is both sensitive and specific in PD cognitive impairment. The PDAQ-15 demonstrates ability to discriminate between cognitively normal, mild cognitive impairment, and dementia in PD, and correlates with global measures of cognition (dementia rating scale) and performance-based functional measures. The PDAQ-15 will provide a disease-specific assessment of the effect of LY3154207 on cognitive IADL in order to understand the relationship between change in cognition and change in IADL in PDD and DLB.

9.1.2.2.1. Movement Disorder Society's United Parkinson's Disease Rating Scale

~~The MDS-UPDRS (Part III) should be conducted in the practically defined medication "on" state at all visits. The "on" state is defined as the individual best motor function as determined by the investigator or approximately 1 hour after the dose of dopaminergic therapy. Every attempt should be made to conduct this assessment in the "on" state. In the exceptional circumstance that this is not possible, the assessment could be done in the "off" state. The "on/off" state should be confirmed prior to completion of the respective scales listed above. This information will be collected in the eCOA or the eCRF. If any portion of the assessment is done in the "off" state, then that subject should be rated as in the "off" state for the whole assessment.~~

9.1.2.3. Measures of Behavioral Symptoms ~~Associated with Parkinson's Disease Dementia~~

The following measures will serve as tools to assess the impact of LY3154207 on behavioral symptoms associated with LBD (PDD and DLB)~~PDD~~ as well as the effects on motor functions.

9.1.2.3.1. Neuropsychiatric Inventory

~~The NPI assessment results will be recorded on worksheets or direct data entry.~~

9.1.3. Appropriateness of Efficacy Assessments

As previously stated, the CoA has demonstrated a significant treatment effect in ~~previous trials in PDD subjects~~similar populations (Wesnes et al. 2005; Rowan et al. 2007). The CoA is a parameter calculated using the CDR-CCB, which has been widely used in dementia research for more than 25 years. Because it is a computerized assessment system, the CDR-CCB has low inter-rater variability. Two training sessions in a single day have demonstrated an ability to minimize learning effects up to 8 weeks (Wesnes, personal communication). The CDR-CCB system also has a large normative database of over 6000 healthy volunteers from 18 to 87 years

of age, thereby making it possible to detect both the level of cognitive impairment present in subjects prior to treatment and the effect of treatment on cognitive changes (Wesnes 2008).

The secondary efficacy measures described in Section 9.1.2 are also established measures of cognitive function and related outcomes, as well as behavioral symptoms associated with PD dementia and DLB, and considered appropriate assessments for ~~the mild-to-moderate PD dementia population~~this population.

9.2.1. Serious Adverse Events

Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued and/or completed the study (the patient's final study disposition~~subject summary~~ CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

9.3. Treatment of Overdose

For this study, any dose of investigational product greater than twice participant's assigned daily dose within a 24-hour time period will be considered an overdose.

In the event of an overdose, the investigator or treating physician should use supportive therapy as necessary and contact the Clinical Research Physician (or designee) immediately.

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

~~Refer to the LY3154207 IB.~~

9.4.1. Electrocardiograms

Electrocardiograms will initially be interpreted by a qualified ~~physician~~ healthcare provider (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the subject is still present to determine whether the subject meets entry criteria at the relevant visit(s) and for immediate subject management, should any clinically relevant findings be identified.

9.4.5. Physician Withdrawal Checklist

The Penn Physician Withdrawal Checklist (PWC-20) is a 20-item checklist that will be used to assess the presence and severity of withdrawal symptoms. The PWC-20 should be assessed on the subject and caregiver, separately. The scale was originally developed to assess the severity of withdrawal symptoms in anxiolytic medication discontinuation (Rickels et al. 2008). The PWC-20 is a validated, shortened version of the original 35-item checklist, where the 20-items were selected based on their statistical ability to differentiate between placebo and active drug plus share correlation with the 35-item checklist (Schweizer et al. 1990; Rickels et al. 1990). The 20 items assess the subject's level of symptoms on a variety of withdrawal symptoms since last visit. Each of the 20 items are scored as 0 (not present), 1 (mild), 2 (moderate), 3 (severe).

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples will be collected to determine the plasma concentrations of LY3154207. Instructions for the collection and handling of blood samples will be provided by the sponsor. At Visit 3, a PK sample is to be collected within 1 to 3 hours after the drug is administered at the site. At Visit 4, Visit 5, Visit 8, and ET/DC, the PK sample can be collected at any time during the visit. At Visit 11, the PK sample should be collected prior to the drug being administered at the site. The date and time (24-hour clock time) of the PK sample collection as well as the date and time of the dose administration immediately preceding the PK sampling will be ~~entered in the eCRF~~recorded.

9.7.1. Whole Blood Sample for Pharmacogenetic Research

The collection and storage of samples for genetic studies (including samples for pharmacogenetic studies) is to continue our ongoing efforts to understand the correlation between the clinical outcome with the drug(s) under study in the clinical trial and the genetic makeup of the subject. DNA extracted from the whole blood samples collected from the subjects may be used to generate genetic data on a genome genotyping array. The genotype data may be used to perform a targeted genetic analysis of the genes of interest to understand potential safety and efficacy concerns should they arise either during this trial, future trials for this drug, or if the drug is launched and on the market. For example, genetic variations in well-known drug-metabolizing enzymes, such as cytochrome P450 (CYP), including CYP3A4, ~~CYP1A2, and so on,~~ could be a potential set of genes of interest to answer any safety concerns.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples may be used to investigate variable response to LY3154207 and to investigate genetic variants thought to play a role in ~~PD~~LBD. Assessment of variable response may include evaluation of AEs or differences in efficacy.

10.1. Sample Size Determination

Approximately ~~400~~ 750 subjects may be screened in order that 340 subjects are randomized in the study. CCI [redacted] If the true effect size for LY3154207 relative to placebo on the CoA is 0.4 with the sample size of 340 there will be over 80% probability of passing this criterion. A 20% discontinuation rate by Week 12 has been accounted for in the sample size determination.

10.2. Populations for Analyses

Population	Description
Entered ~~Enrolled~~	All subjects who sign informed consent

10.3.2.4. Concomitant Therapy

Prior medications are defined as those that stop before randomization (Visit 3~~2~~). Concomitant medications are defined as those being taken on or after randomization (Visit 3~~2~~). A summary of concomitant medications will be presented as frequencies and percentages for each treatment group. If the start or stop dates of therapies are missing or partial to the degree that determination cannot be made as to whether the therapy is prior or concomitant, the therapy will be deemed concomitant.

10.3.3.2 Secondary Efficacy Analyses

The secondary efficacy outcomes (ADCS-CGIC, PDAQ-15, ADAS-Cog_{13}, CDR-CCB PoA, D-KEFS, MoCA, NPI, ESS, and MDS-UPDRS) will be assessed at the 12-week time point ~~as the primary analysis.~~ Each of these secondary endpoints will be analyzed using an MMRM model, which will include terms for: baseline value, treatment, visit, and the relevant interaction terms. Further covariates may be included such as age, site, and the severity of PD motor function as well as severity of dementia at baseline as appropriate. The change of the score from baseline will be the dependent variable. If subscores for a particular scale are deemed clinically relevant to analysis, it will be completed as an exploratory analysis.

10.3.3.3. Tertiary/Exploratory Efficacy Analyses

The following exploratory efficacy endpoints will be analyzed using MMRM model.

- Change in ~~total~~ MDS-UPDRS ~~(sum of Parts I to III) and~~ individual subscales – non-motor experiences of daily living (Part I), motor experiences of daily living (Part II), ~~motor exam (Part III)~~, and motor complications (Part IV) subscales from baseline to Week 12
- Change in GDS-S score from screening to Week 12
- Change in QUIP score from baseline to Week 12

Exploratory Digital Biomarker Analysis: Data from digital biomarkers (Lilly Trial app and Actigraphy watch) from baseline to Week 12 will be explored using appropriate visual, univariate, and multivariate methods to understand the relationship of the biomarker endpoints to other clinical endpoints in terms of treatment effect. The data may also be used to explore the validity and reliability of these assays in ~~PDD~~ LBD subjects. If applicable, potential predictive biomarkers associated with interpretable clinical benefit may further be examined with biological evidence.

10.3.4.3. Vital Signs and Weight

- Day 1 (Visit 3) in-clinic BP and pulse rate change post first dose

Change in in-clinic BP and pulse rate from 0 up to 8 hours postdose measured on the first day of study drug dosing will be analyzed using an MMRM analysis with baseline value, treatment, time postdose (hours), and the relevant interaction terms. Two baselines will be considered: the Visit 3 pretreatment value (time 0) and the time-matched baselines from Visit 2 (hourly value 0 to 6 hours). For the second of these, there is no time-matched value for the 7- and 8-hour time points of Visit 3, so the 6-hour time point of Visit 2 will be used as their baseline value. A separate change from baseline analysis will be completed for each baseline approach.

- Change in in-clinic BP and pulse rate from baseline (Visit 2, predrug) up to Week 12 (V11)

  Change in in-clinic BP and pulse rate measured at Visit 2 (daily average 0 to 6 hours) to the in-clinic BP and pulse rate measured at Week 6/Visit 8 and Week 12/Visit 11 (daily average 0 to 6 hours) will be analyzed by an MMRM model with baseline value, treatment, and the relevant interaction terms. Analysis at 6 weeks will help to evaluate any significant changes (if any) in BP and pulse rate earlier than 12 weeks (end of study) and if they accommodate by 6 weeks.

- Daily average change in home BP measurements and pulse rate from baseline to Week 12.

10.3.4. Safety Analyses

The PWC-20 endpoint will be analyzed using an ANCOVA model with a covariate for baseline score. The primary analyses will be a change from baseline (Visit 11) to the in person follow up visit (Visit 801).

10.3.6.1. Subgroup Analyses

The CDR-CCB CoA and its component scores will be assessed based on the following subgroups: concomitant PD therapy, concomitant AChEI therapy, L~~and timing of dementia onset (less or equal to 1 year versus greater than 1 year relative to onset of motor symptoms~~ LBD (PDD or DLB), and GDS (less than or equal to 6)~~)~~. All subgroup analyses will be considered exploratory and additional subgroup analyses may be performed as suggested by the data.

10.3.7 Interim Analyses

A limited number of pre-identified individuals may gain access to the limited unblinded data, as specified in the unblinding plan. Information that may unblind the study during the analyses will not be reported to study sites or blinded study team until the study has been unblinded.

The efficacy and safety interim analyses will be completed and reviewed by an IAC.

~~Only the IAC is authorized to evaluate unblinded interim efficacy and safety analyses.~~ Study sites will receive information about interim results ONLY if they need to know for the safety of their subjects.

Safety interims will be conducted on the number of subjects on each treatment who met the potentially clinically significant vital signs criteria at 3 consecutive time points at Visit 3 (Day 1 stopping rules). This will be done after 50, 100, and 150 subjects have completed Visit 3. [redacted] Those already on 75-mg dose and passed the Day 1 stopping rules will remain on 75 mg. In the event of an unacceptable rate of subjects meeting Day 1 stopping rules at other doses, adjustments to doses may be made for subsequently randomized subjects at the discretion of the IAC. Additional efficacy analyses may be conducted at the time of these safety interim analyses or as needed to inform internal decision making.

A safety and efficacy interim analysis will be conducted when 170 randomized subjects have had the opportunity to complete Visit 11 (Week 12) assessments. The statistical analysis will include all 170 subjects in the interim analysis, which will evaluate both the efficacy and the safety. In addition, the PK data may be reviewed. An additional interim analysis of efficacy and safety may be conducted prior to study completion for internal decision making. While ~~A~~all potential efficacy analyses may be used for internal decision making, ~~but~~ they are not planned to stop the study for efficacy or futility because this is an exploratory study and there are other key endpoints being assessed, not just the primary endpoint.

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