CLINICAL TRIAL PROTOCOL

A randomized, double blind, placebo-controlled study to evaluate the impact of K0706 (Vodobatinib) on safety, tolerability, pharmacokinetics and pharmacodynamics and clinical outcomes in Dementia with Lewy Bodies (DLB)

Sponsor:	Georgetown University Medical Center
Grantor:	Sun Pharma Advanced Research Company (SPARC) Ltd. a company registered under the Companies Act,1956 (CIN: L73100GJ2006PLC047837) with its registered office at SPARC, Akota Road, Akota, Vadodara 390 020 India and a business location at 17/B, Mahal Industrial Estate, Mahakali Caves Road, Andheri East, Mumbai 400 093, India.
Study Product:	K0706 (Now known as Vodobatinib or SCC-138)
Development phase:	II
Draft or Version Number:	V 1.1 (October 2020)

Amendment 1-

Study Treatment and Dosage: The capsule formulation that was initially used will be switched over to a powder formulation, and participants will be transitioned to the powder formulation. Participants will continue to be randomized 1:1:1 to low dose and transition from 96 mg capsule to 192 mg powder, and high dose will transition from 192mg capsule to 384 mg powder and matching placebo. Note that the increase in dose from capsule to powder is not a doubling, but is on average an approximately 1.4-fold exposure increase - due to 70% availability of drug in powder compared to capsule formulation (see addendum attached).

Participants used to receive 8 capsules per day, now they will use one sachet of assigned strength.

Amendment 2- Editorial corrections:

- Consistency of numbering groups (1, 2 and 3) in section 2
- Correction of bullet numbers in Exclusion criteria
- **Amendment 3-**
  1- As per SPARC request, due to complete absence of risk of QTc prolongation in patients receiving K0706, it is recommended that the QTc range should be revised in the inclusion/exclusion criteria to be upper limit of 350-485 instead of 350-470ms
  2- The frequency of visits should be reduced from twice a month to visits as follows: Screening, Baseline, 2,4,8,12, and 16 weeks to reduce burden on patients.

Clinical Trial Protocol Template Version 1.2, December, 2022

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LIST OF ABBREVIATIONS

AEs	Adverse Events/Adverse Experience
AD	Alzheimer's Disease
ADCS-ADL	Alzheimer's Disease Co-operative Study-Activity of Daily Living
ADAS-cog	Alzheimer's Disease Assessment Scale-cognition
Abl	Abelson Tyrosine Kinase
BBB	Blood Brain Barrier
CIB	Clinical Investigator's Brochure
CNS	Central Nervous System
CRF	Case Report Form
CSF	Cerebrospinal Fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CRU	Clinical Research Unit
CML	Chronic Myeloid Leukemia
CAF	Clinical Assessment of Fluctuation
CYP	Cytochrome P
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
DLB	Dementia with Lewy bodies
DOPAC	3.4-Dihydroxyphenylacetic acid
DA	Dopaminergic
EDC	Electronic Data Capture
ELISA	Enzyme-Linked Immunosorbent Assay
FTLD	Fronto-Temporal Lobar Dementia
FDA	Food and Drug Administration
GUMC	Georgetown University Medical Center
GSRS	Gastrointestinal Symptoms Rating Scale
GI	Gastrointestinal
HVA	Homovanillic Acid
HCG	Human Chorionic Gonadotropin
HED	Human Equivalent Dose
ICH	International Conference on Harmonization
IND	Investigational New Drug Application
IHC	Immunohistochemistry
IRB	Institutional Review Board
IV	Intravenous
IAS	Irritability-Apathy Scale
IB	Investigator Brochure
LP	Lumbar Puncture
LB	Lewy Bodies
MoCA	Montreal Cognitive Assessment
MMSE	Mini Mental Status Exam
MDS	Movement Disorders Society
MSD	Multiple Single Dose
MTD	Maximum Tolerated dose
MPTP	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine

N	Number (typically refers to subjects)
NPI	Neuropsychiatric Inventory
NSE	Neuron Specific Enolase
NIH	National Institutes of Health
NCI	National Cancer Institute
OHRP	Office for Human Research Protections
OHSR	Office of Human Subjects Research
PHI	Protected Health Information
PHRC	Partners Human Research Committee
PDGF	Platelet Derived Growth Factor
PI	Principal Investigator
PPIs	Proton Pump Inhibitors
PK	Pharmacokinetics
PBAs	Problem Behaviors Assessment Short Form
PD	Parkinson's disease
RSD	Random Single Dose
SAEs	Serious Adverse Events/Serious Adverse Experience
SAD	Single Ascending Dose
SBP	Systolic Blood Pressure
SI	Site Investigator
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
SNpc	Substantia Nigra pars compacta
Src	Protein Kinase SRC
SPARC	Sun Pharma Advanced Research Company Ltd
SSRIs	Selective Serotonin Reuptake Inhibitors
TREM2	Triggering Receptors on Myeloid Cells-2
TKI	Tyrosine Kinase Inhibition
TNF	Tumor Necrosis Factor
TMT-B	Trail Making Test-B
TUG	Timed-Up and Go
VEGF	Vascular Endothelial Growth Factor
UPDRS	Unified Parkinson's Disease Rating Scale
UIS	University Information Service
WOCBP	Women of Child Bearing Potential

1- PROTOCOL SUMMARY AND RATIONALE

1.1- Study Title

A randomized, double blind, placebo-controlled study to evaluate the impact of K0706 (Vodobatinib, SCC-138) on safety, tolerability, pharmacokinetics and pharmacodynamics and clinical outcomes in Dementia with Lewy Bodies (DLB)

1.2- Version Number

Original Protocol

1.3- Study Indication

Dementia with Lewy Bodies (DLB)

1.4- Phase of Development

II

1.5- Background

Dementia with Lewy Bodies (DLB) is an alpha-synucleinopathy (1,2) and the second most common form of dementia in the elderly. DLB shares striking neuropathological and clinical similarities with both Parkinson's disease (PD) (2) and Alzheimer's disease (AD) (3,4). DLB and PD are characterized by death of dopaminergic (DA) neurons in the nigro-striatal system (5-10) and formation of intra-neuronal alpha-synuclein inclusions known as Lewy bodies (LBs) (11-13). Misfolded alpha-synuclein aggregates within LBs and SYN (alpha-synuclein) is the highest genetic risk factor for PD and DLB (1,2) followed by the microtubule associated protein tau (MAPT) (14-18). At autopsy alpha-synuclein, hyper-phosphorylated tau (p-tau) and amyloid plaques are all detected in the brains of individuals with DLB (19,20). Therefore, the neuropathology of DLB overlaps with both PD and AD, and includes alpha-synuclein accumulation in LBs, p-tau and beta-amyloid deposition (4,20-25). Potential cerebrospinal fluid (CSF) biomarkers, including alpha-synuclein, dopamine metabolites homovanillic acid (HVA) and 3,4-Dihydroxyphenylacetic acid (DOPAC) (6,26), total tau and p-tau and amyloid beta peptides (Abeta40/42) maybe commonly shared in AD, PD and DLB (25,27-29). The core clinical features of DLB, include dementia and Parkinsonism in addition to hallucinations, cognitive fluctuations and rapid eye movement (REM) sleep behavior disorders (RBD) (30-32). L-Dopa replacement therapies and acetylcholinesterase inhibitors may partially control motor and cognitive symptoms, respectively in DLB. Selective Serotonin Re-uptake Inhibitors (SSRIs) and antipsychotics manage the behavioral but worsen motor symptoms in DLB.

There is a major unmet medical need for further research into DLB to identify potential therapies for this disease and provide significant insights into the treatment of other Parkinsonian and memory disorders. A major challenge facing DLB is to develop a therapy that can halt neuronal death and alleviate cognitive, motor and behavioral symptoms. No therapeutic approach exists to alter the levels of neurotoxic proteins such as alpha-synuclein and halt DA and other neuronal death in DLB. One mechanism to degrade neurotoxic proteins is autophagy (33-37), which is a process by which the cell can degrade its own contents. There is evidence that autophagy is impaired in neurodegeneration (38-45), leading to failure of degradation of protein aggregates, including misfolded alpha-synuclein. Importantly, autophagy is exploited therapeutically in several diseases, including adult chronic myeloid leukemia (CML). Tyrosine kinase inhibitors (TKIs) induce autophagy (37,46,47), leading to destruction

of rapidly dividing tumor cells in CML (46) and degradation of neurotoxic proteins, including alpha-synuclein, beta-amyloid and p-tau in PD and AD models (37,46-49).

Sun Pharma Advanced Research Company Limited (SPARC Ltd.) is developing K0706, for the treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) that is resistant or intolerant to prior TKI therapy or Ph+ ALL that is resistant or intolerant to prior TKI therapy; and its ability to slow down progression of PD. Several ongoing Single Ascending Dose (SAD) and Multiple Single Dose (MAD) studies have shown that K0706 is potentially safe and tolerated up to 192 mg oral daily dose in early PD patients (see investigator brochure attached, **IND 127347**). No maximum tolerated dose (MTD) has been reached so far and research in cancer and patients with PD is ongoing to determine the MTD. Nonclinical pharmacology, PK, and safety pharmacology data indicate that K0706 has specific and highly potent activity on the non-receptor tyrosine kinase Abelson (Abl). K0706 shows potent activity in its in vivo models based on Abl. Furthermore, K0706 showed promising neuroprotective activity in 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) models of PD. It shows good systemic availability following oral administration in mice, rats, and dogs. It has no effect on the CNS, cardiovascular, or respiratory functions at several multiples of efficacious doses (See IB). The antiparkinson's effect of K0706 was determined in MPTP induced *Substantia Nigra pars compacta* (SNPc) neurodegeneration model in mice. Mice were treated with K0706 ME suspension, once daily, to provide equivalent doses of K0706 at 1, 3 and 10 mg/kg. Treatment was started two days prior to MPTP administration and was given for a total of 6 days from the treatment initiation day. Nilotinib, a second generation TKI with reported ability to cross the blood brain barrier was used as a reference standard TKI. The effect of K0706 and nilotinib was assessed using tyrosine hydroxylase (TH)-immunoreactivity as a marker of dopaminergic neurodegeneration at the level of SNPc. Dense TH-positive neurons were observed in the SNPc of naïve mice. Administration of MPTP caused a marked loss of SNPc dopaminergic neurons. K0706 and nilotinib administration prevented the neurodegeneration induced by MPTP in a dose-dependent manner. As assessed by percent immunoreactive area (percentage of total area covered by dopaminergic neurons in the given field), both K0706 and nilotinib mitigated the loss of TH+ neurons in SNPc by 19.38%, 47.89%, and 76.33% and 17.81%, 39.35%, and 65.13%, respectively at 1, 3 and 10 mg/kg doses. As assessed by integrated density, K0706 and nilotinib mitigated the loss of TH+ neurons in SNPc by 19.98%, 50.79%, and 82.53% and 14.07%, 39.98%, and 69.88%, respectively at 1, 3 and 10 mg/kg doses. In conclusion, results suggest promising neuroprotective activity of K0706 in MPTP model of PD (see IB, section 5.2). Nilotinib and Bosutinib that target the wild type Abl tyrosine kinase were also shown to penetrate the brain and promote autophagic degradation of neurotoxic proteins, leading to survival of DA neurons and improvement of motor and cognitive behavior in animal models of alpha-synucleinopathy and other neurodegenerative diseases (37,46-53). Therefore, the use of TKIs, including K0706, is a novel strategy that promotes autophagy to clear neurotoxic protein aggregates in neurons (47,49-51,53-57).Taken together these data suggest that K0706 may induce autophagic clearance of neurotoxic proteins and protect DA neurons in individuals with DLB.

Based on pre-clinical evidence of the efficacy of K0706 in models of PD involving loss of DA SN neurons, and the promising safety and tolerability effects of K0706 in CML and PD patients, this phase II study will evaluate the effects of K0706 on safety, tolerability and potential biomarker outcomes in individuals with DLB. Allometric scaling was used to extrapolate mouse to human dose of drugs according to US Food and Drug Administration (FDA) guidelines (58). This allometric conversion takes into consideration the biochemical, functional systems and variation of pharmacokinetics (PK) in different species. Using allometric scaling and an average human body weight of 70kg an oral dose of 15-30mg/kg once daily in mice corresponds to an oral human equivalent dose (HED) of 85-160 mg in

human (58), which is within the tolerated dose in both CML and PD. Therefore, the effects of 96 mg K0706 capsules (192 mg powder) and 192 mg K0706 capsules (384 mg powder) versus matching placebo taken daily by mouth for 12 weeks (3 months), followed by a 4 week wash-out period will be evaluated in individuals diagnosed with DLB. The data obtained from this study will serve as a proof of concept for future placebo-controlled, double-blind studies in patients diagnosed with DLB, AD, or PD.

Hypothesis: K0706 is safe and tolerable and will alter CSF and plasma biomarkers in DLB patients.

a- Primary outcomes: **Safety and tolerability Go/NoGO (25% discontinuations)**
Safety and tolerability will be determined using the occurrence of adverse events (AEs) of interest, including myelosuppression, urinary, pancreatic and hepatic disorders, QTc prolongation as per SPARC Ltd Investigator Brochure (IB) and Addendum.

b- Secondary outcomes: Determine K0706 plasma and CSF pharmacokinetics and 2) pharmacodynamics, including changes of DLB related CSF and plasma biomarkers, including HVA, DOPAC, Abeta40/42, total tau, ptau231/181 and total and oligomeric alpha-synuclein.

c- Clinical outcomes will include assessment of (**A**) cognitive and behavioral function via Montreal Cognitive Assessment (MoCA), the Trail Making Test (TMT)-B, AD Assessment Scale-Cognitive subscale (ADAS-cog), AD Cooperative Study-Activity of Daily Living (ADCS-ADL), Neuropsychiatric Inventory (NPI), and Clinical Assessment of Fluctuation (CAF), Irritability-Apathy Scale (IAS) and Problem Behaviors Assessment short (PBA-s) form. We will also determine the effects of K0706 on (**B**) motor function via the Unified Parkinson's Disease Rating Scale (UPDRS)-I-III and timed-up-and-go (TUG).

1.6- Objectives and Endpoints

1- Primary outcomes: **Safety and tolerability Go/NoGO (25% discontinuations)**

Safety and tolerability using the occurrence of adverse events (AEs) of interest, including gastrointestinal (GI), myelosuppression, hepatic and kidney disorders as per SPARC Ltd, IB.

Safety will be measured using the occurrence of AEs and serious adverse events (SAEs) deemed to be possibly, probably, or definitely related to the study drug. AEs of interest are defined as GI disorders, hepatotoxicity and pancreatitis, and myelosuppression (Table 1). These AEs will be tracked over the course of the trial and reviewed by an independent Data and Safety Monitoring Board (DSMB) at scheduled meetings and in real time and on case-by-case basis.

Tolerability for a given participant will be defined as the ability of participants to remain on treatment. Overall tolerability of the drug will be defined as an acceptable number of up to 25% discontinuations.

Possible side effects of K0706 may include: diarrhea, nausea, low blood cell counts, rash, vomiting, stomach pain, respiratory tract infection, fever, abnormal liver function, tiredness or weakness, cough, and headache. GI hemorrhage and effusions (including pleural effusion, pericardial effusion, ascites) or pulmonary edema. Cardiovascular disorders, including ischemic heart, cerebrovascular and peripheral arterial occlusion are rarely seen in a limited number of patients according to IB. Therefore, K0706 must be administered with caution and the guidelines for monitoring K0706 toxicity will be according to Common Terminology Criteria for AEs (CTCAE, Version 4.0) that is used commonly used to monitor safety and tolerability with this class of TKIs.

- Gastrointestinal Toxicity will be monitored on a bi-weekly basis and managed via withholding, reducing the dose or discontinuation of K0706 according to Table 1.
- Myelosuppression: Blood counts will be monitored on a bi-weekly basis and managed via withholding, reducing the dose or discontinuation of K0706 according to Table 1.
- Hepatic Toxicity: Liver enzymes will be monitored on a bi-weekly basis and managed via withholding, reducing the dose or discontinuation of K0706 according to Table 1.
- Fluid Retention: Patients will be monitored on a bi-weekly basis and managed via withholding, reducing the dose or discontinuation of K0706 according to Table 1.
- Renal Toxicity: Patients will be monitored on a bi-weekly basis and managed via withholding, reducing the dose or discontinuation of K0706 according to Table 1.

Table 1- Monitoring laboratory tests for drug safety and stopping rules or withdrawal will follow the classification of organ toxicity according to standardized definitions of AEs published by the National Cancer Institute (NCI) of the National Institutes of Health (NIH), using CTCAE, Version 4.0:

Stopping and/or withdrawal rules in Table 1 apply to any SAE as stated. These rules apply to individual SAEs. i.e. if the SAE is not the same recurrent SAE (e.g. cardiovascular) but a different SAE (e.g hepatic), dose reduction is allowed as long as the participant still takes the study medication 75% or more of the 12-week (3 months) treatment period or a minimum of 9 weeks of treatment. If participants are off study medication more than 9 weeks of the treatment period, they will be withdrawn.

In the event of an SAE ≥ Grade 3 according to CTCAE, study medication must be withheld immediately without un-blinding, and necessary lab tests and/or EKGs must be repeated after

7 days and if symptoms disappear and/or are less than grade 3, the same dose of study drug will be resumed only once within 2 weeks. If the same SAE recurred drug dose will be reduced only once per SAE from 192 mg capsule (or 384 mg powder) to 96 mg (192 mg powder) and from 96 mg to 48 mg (96 mg powder). The same one-time dose reduction shall take place in the event of another or different SAE. Any participant who receives the drug less than 9 weeks in total during the 12-week (3-months) treatment period must be withdrawn and recorded as withdrawal due to SAE.

Assessments	Toxicity Criteria	Endpoints
Myelosuppression ≥Grade 3	Thrombocytopenia and Neutropenia	Perform complete blood counts (CBC) every two-weeks or as needed. Withhold K0706 for hematological toxicities if absolute neutrophil count (ANC) <1.0 x 10^9 /L and/or platelet count <50 x 10^9 /L. Monitor blood counts every 7 days and if problem resolves resume treatment within 2 weeks. If myelosuppression recurs after resumption of the same dose, reduce K0706 dose and if problems recurs with lower dose K0706 must be discontinued and patients must be withdrawn.
Gastrointestinal (GI) disorders ≥ Grade 3	GI ulcer, stenosis, constipation, diarrhea, distention, pain, hemorrhage, mucositis, bloating, colitis, dry mouth, fistula, dysphagia, perforation	Perform physical and laboratory exams and administer the Gastrointestinal Symptoms Rating Scale (GSRS) at every scheduled visit. If GI symptoms occur withhold K0706 for 7 days and resume treatment within 2 weeks and monitor for return of symptoms. If symptoms return after 2 weeks of resumption of the same dose, reduce K0706 dose and if symptoms return with lower dose K0706 must be discontinued and patients must be withdrawn.
Hepatotoxicity ≥Grade 3	Elevated hepatic transaminases	Withhold treatment and monitor hepatic transaminases, including gamma-glutamyltransferase (GGT) alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase every 7 days. If transaminase level returns to baseline, resume treatment. If hepatotoxicity recurs after resumption of the same dose, reduce K0706 dose and if problems recur, K0706 should be discontinued and patients must be withdrawn.
Bilirubin ≥ Grade 3	Elevated Bilirubin	Withhold treatment and monitor bilirubin every 7 days. If bilirubin level returns to baseline, resume K0706 treatment. If bilirubin elevation recurs after resumption of the same dose reduce K0706 dose and if problem recurs K0706 should be discontinued and patients must be withdrawn.
Pancreatitis≥ Grade 3	Elevated serum lipase and amylase	Withhold treatment and monitor lipase and amylase every 7 days. If lipase and amylase levels return to baseline, resume K0706 treatment. If pancreatic toxicity recurs after resumption of same dose, reduce

		K0706 dose and if problem recurs K0706 should be discontinued and patients must be withdrawn.
Renal ≥ Grade 3	Renal or urinary disorder	Withhold K0706 if urinary proteins ≥3.5g/24 hours (proteinuria) or protein/creatinine ratio is ≥3.4; there is renal hemorrhage or transfusion, free hemoglobin in the urine (hematuria), creatinine > 3 x baseline or >4.0mg/dL; or development EGFR or CrCL 29-15ml/min/1.73m$^{2.}$ If renal toxicity recurs after resumption of treatment, K0706 should be discontinued and patients must be withdrawn.
QT Prolongation ≥ Grade 3	EKGs with a QTc ≥≥485ms and/or an increase of QTc ≥ 60 ms from baseline	Withhold K0706, and perform an analysis of serum potassium and magnesium, and if below lower limit of normal, correct with supplements to within normal limits. Concomitant medication usage must be reviewed, and if clinically indicated, concomitant medications causing QTc prolongation should be decreased or discontinued. Patients with prolonged QTc ≥60 ms change from baseline or QTc ≥≥485 ms should be withdrawn from the study unless there is a causative electrolyte abnormality that has been corrected or CYP inhibitor that may be withdrawn. Resume K0706 treatment within 2 weeks if QTcF returns to <485ms and to within 20 ms of baseline. If QTcF returns to ≥≥485 ms following dose reduction or withholding, K0706 must be discontinued.

1.7- Rationale to advance to Phase II K0706 trial in DLB

This proposal will evaluate the effects of K0706, which a TKI that targets Abl in patients with DLB. There is mounting pre-clinical evidence of the efficacy of K0706 in models of PD and promising safety and tolerability effects of K0706 have been demonstrated in several in CML patients and PD (**NCT02970019 and NCT03655236**). Currently there is no disease-modifying treatment that can slow or halt the progression of DLB. This study may have a large impact on the field of neurodegenerative research as it tests a novel mechanism of action (autophagy). This study tests a novel strategy that may be applicable to a number of neurodegenerative diseases, including other dementias caused by accumulation of neurotoxic protein aggregates (a potential broad-spectrum anti-neurodegenerative drug). This study will provide critical safety and tolerability and potential biomarkers data to test in future larger placebo-controlled, double-blind studies of DLB and other patients and will guide future development of putative disease-modifying therapies in neurodegeneration.

2- Study Design

This is a phase II randomized, double-blinded, placebo-controlled study to evaluate the effects of 96mg (192mg powder) K0706 and 192mg (384 mg powder) K0706 on safety, tolerability, pharmacokinetics and pharmacodynamics in individuals with DLB (MoCA ≥14). A total of 45

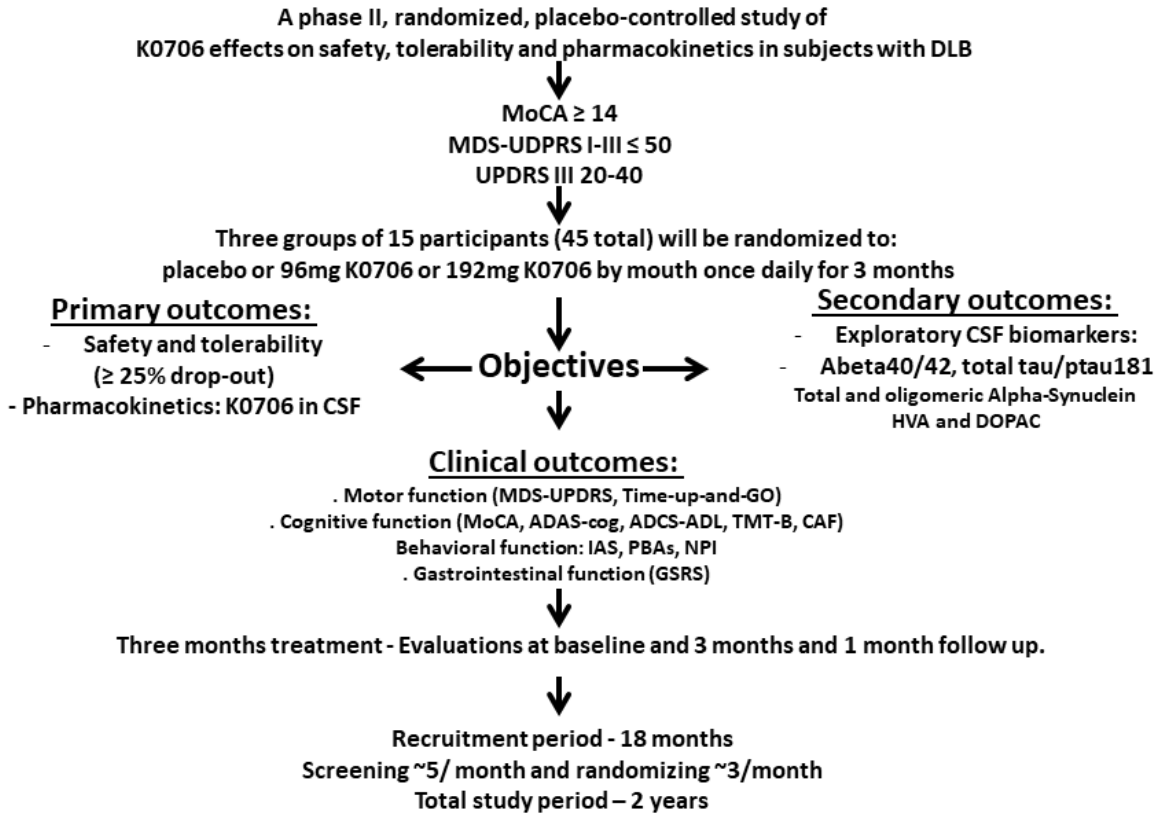

Chart 1- Study design of a randomized, double blind placebo controlled, phase II trial of K0706 in DLB.

participants will be randomized 1:1:1 into 3 groups (n=15/per group) to be treated with oral daily doses of placebo (group 1), 96 mg K0706 capsules (192mg powder) (group 2) and 192mg K0706 capsules (384mg powder) (group 3) for 12 weeks, followed by 4-week wash-out period.

2.1- Treatment: A total of 45 participants will be randomized 1:1:1 into 3 groups (n=15/per group) to be treated with oral daily doses of 96 mg capsule (192mg powder) and 192mg capsule (384mg powder) and matching placebo for 12 weeks, followed by 4-week wash-out period.

2.2- Drug Administration: K0706 powder will be taken orally in water after fasting for at least 2 hours once daily for 3 months and 1 month wash out. Study partners must provide written informed consent prior to screening. This phase II study will primarily examine the effects of K0706 on safety and tolerability and biomarker outcomes.

2.3- Dosing Guidelines

Participants will be randomized 1:1:1 into 3 groups (n=15 per group):

- Group 1: Take one sachet of placebo daily
- Group 2: Take one sachet of 192 mg K0706 powder daily (comparable to 96mg capsule)
- Group 3: Take one sachet of 384 mg K0706 powder daily (comparable to 192 mg capsule)

The capsule formulation that was used initially will be switched over to a powder formulation. Randomized participants will continue on the capsule and only new participants will be transitioned to the powder formulation.

Study drug will be dispensed every month during study visits. Each participant will receive one box (kit) of the assigned strength. Each box has 31 sachets to last for one month and any visit windows. Patient only uses one sachet per day. The packaging of each sachet and kit is identical so the participant and study partner and investigator would not know the dose. Participants will receive a total of 3 boxes (3 months) for the duration of treatment.

- Participants must record the date and time they take the sachet in a daily medication dairy
- Participants must return all unused/damaged sachet at every visit
- At some visits participants may be asked to take the study drug on the day of the visit
- Study drug must be dissolved in water as instructed on the labelled drug package and taken on empty stomach, in standing position, at least 2 hours after fasting and with no food least 1 hour after following drug administration.
- Participants should space out K0706 from calcium and magnesium containing medications and supplements (e.g., Tums, milk of magnesia) by at least 2 hours.
- Study drug will be administered for 3 months or 12 weeks once daily

Dosing, Administration and Drug Interactions. Cytochrome p (CYP) inhibition IC_{50} for CYP1A2, 2B6, 2C9, 2C19, 2D6 and 3A4 were >100 uM, no CYP related drug-drug interaction (DDI) was predicted for K0706 according to IB. For CYP2C8, the reversible IC_{50} was >10 uM.. Similarly, there was no DDI potential predicted with respect to irreversible potential for CYP1A2, 2B6, 2C9, 2C19, 2D6 and 3A4. K0706 may also inhibit CYP2C8. With regards to transporters, the IC50 for phospho-glycoprotein-P (P-gp) inhibition was 2.4 uM, BCRP 6.9 uM and organic anion transporters (OAT)3 >10 uM. Simulation predicted DDI potential for the drugs which are substrates for P-gp and breast cancer resistance protein (BCRP) when co-administered with K0706. No DDI was possible for OAT3 substrates.

2.4- Planned Exposure (e.g. Duration of the study administration)

We anticipate this project to be completed in 2 years (24 months); including 12-18 months (12 months) for pre-screening and enrolment and 6 months for post treatment evaluation and data analysis.

2.5- Number of Planned Subjects and Treatment Plan

Up to 150 subjects will be screened for the study with the goal of enrolling 45 for treatment, including 15 participants with DLB on placebo (group 1) and 15 participants on 96 mg capsule or 192 mg powder K0706 (group 2) and 15 participants on 192mg capsule or 384 mg powder K0706 (group 3).

2.6- Study Population

This study will be conducted in DLB patients with 2.5≥Hoehn & Yahr≤3 and UPDRS I-III ≤50 and 15≥UPDRS III (motor) ≥40 and MoCA≥14. Eligible participants must be stable on MAO-B inhibitors (Rasagiline or Selegiline) for 4 weeks and must not be on ≥800mg Levodopa daily. Participants must be stable on acetylcholinesterase inhibitors and other medications for at least 6 weeks.

3- VISIT SCHEDULE AND ASSESSMENTS

Screening process. The screening visit (Table 2) will determine study eligibility. Potential participants and their study partners and legally authorized representative (LAR) must review and sign an informed consent form (ICF) prior to any study-related procedures. Information regarding demographics, concurrent medications, and medical history will be gathered from the participant and study partner. Prior to any study-related activities, participants and LAR will be thoroughly informed on all aspects of the study and will be requested to sign an ICF. Prior to obtaining written informed consent, information will be given at a complexity level that is understandable by the subject in both oral and written form by staff.

Visits/Week	Screening	Baseline	2w	4w	8w	12w	16w (wash-out)	
Consent	X							
Demographics	X							
Vitals	X	X	X	X	X	X	X	
H&P	X	X	X	X	X	X	X	
Neuro Exam	X	X	X	X	X	X	X	
EKG	X	X	X	X	X	X	X	
Blood draw *	X	X	X	X	X	X	X	
Urine	X	X	X	X	X	X	X	x
CSSRS	X	X	X	X	X	X	X	
Pregnancy test	X	X	X	X	X	X	X	
UPDRS I-III	X	X				X	X	
MoCA	X	X				X	X	
ADAS-Cog		X				X	X	
ADCS-ADL		X				X	X	
TUG		X				X	X	
TMT-B	X	X				X	X	
PBAs		X				X	X	
IAS		X				X	X	
CAF		X	X	X	X	X	X	
GSRS		X	X	X	X	X	X	
NPI		X				X	X	

LP and blood draw	**X**	**X**

Table 2- A detailed schedule of 7 visits and the assessments done at each visit. History and Physical (H&P), Electrocardiograms (EKG), Columbia Suicide Severity Rating Scale (CSSRS), Montreal Cognitive Assessment (MoCA), Trail Making Test (TMT)-B, AD Assessment Scale-Cognitive subscale (ADAS-cog), AD Cooperative Study-Activity of Daily Living (ADCS-ADL), Neuropsychiatric Inventory (NPI), and Clinical Assessment of Fluctuation (CAF), Gastrointestinal Symptoms Rating Scale (GSRS), Irritability-Apathy Scale (IAS), Problems Behavior Assessment Short (PBAs) form. Movement Disorders Society-Unified Parkinson's Disease Rating Score (MDS-UPDRS)-I-III, timed-up-and-go (TUG) and Lumbar Puncture (LP).

Blood draw* Standard blood chemistry, include cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), albumin, total protein, alkaline phosphatase, total bilirubin, creatinine, calcium, chloride, sodium, potassium, magnesium, inorganic phosphorus, bicarbonate, creatine phosphokinase (CPK), gamma-glutamyl transferase (γ-GT), lactate dehydrogenase (LDH), lipase, amylase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), vitamin B12, and glucose and protein/creatinine ratio in the urine. A standard hematology panel including, complete blood count (CBC) with differential counts will be performed. Hemoglobin (Hb), hematocrit, red blood cell count, platelet count, and white blood cell (WBC) with differential count will be measured. Prothrombin time-international normalized ratio (PT-INR) will be measured for assessment of coagulation.

Additional **blood draws** will be performed 30 minutes before LPs at baseline and 3 months. LPs are mandatory at baseline line and end of study visit. LP must be performed within 2 hours from the last Levodopa dose or in ON-STATE.

Study drug will be dispensed at the end of baseline visit and at end of every visit.
Visits should be scheduled as indicated on the protocol (screening,baseline,2, 4,8,12, and 16 weeks)(± 3 days).
Women of child-bearing potential must be willing to take a pregnancy test at every visit.
Unscheduled or miscellaneous visits are allowed if necessary.
EKGs should be done in triplicates

Monitoring and laboratory tests (EKG, blood draw and urine), vital signs and comprehensive physical and neurological exams will be performed at screening and every other visit. Standard blood chemistry, include cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), albumin, total protein, alkaline phosphatase, total bilirubin, creatinine, calcium, chloride, sodium, potassium, magnesium, inorganic phosphorus, bicarbonate, creatine phosphokinase (CPK), gamma-glutamyl transferase (γ-GT), lactate dehydrogenase (LDH), lipase, amylase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), vitamin B12, and glucose, protein/creatinine ratio in the urine. A standard hematology panel including, complete blood count (CBC) with differential counts will be performed. Hemoglobin (Hb), hematocrit, red blood cell count, platelet count, and white blood cell (WBC) with differential count will be measured. Prothrombin time-international normalized ratio (PT-INR) will be measured for assessment of coagulation. Should treatment with any HMG-CoA (or 3-hydroxy-3-methylglutaryl-coenzyme A) reductase inhibitor (a lipid lowering agent) be needed to treat lipid elevations, evaluate the potential for a drug-drug interaction before initiating therapy as certain HMG-CoA reductase inhibitors are metabolized by the CYP3A4 pathway. If test results warrant therapy, local standards of practice and treatment guidelines will be followed.

At screening, MoCA, TMT-B and UPRDS-III (only) will be performed to determine eligibility (see below). The C-SSRS will be performed at screening and every visit. Participants who drop out prematurely have to have a close out visit and if they finish more than 80% of drug treatment LP should be performed. Drugs should be dispensed to participants at the end of the baseline visit and participants should start their first day of study drug the same day. Drugs will be dispensed every visit until the next visit.

Baseline visit will be scheduled 2-4 weeks after screening and results from all screening procedures will be reviewed and all inclusion/exclusion criteria must be met prior to baseline assessments. Monitoring and laboratory tests (EKG, blood draw and urine), vital signs and comprehensive physical and neurological exams will be performed at baseline and every other visit thereafter. Blood for biomarker studies will be collected half an hour before LP at baseline. Participants will then be randomized 1:1:1 into 96mg capsule or 192 mg powder K0706 (group1), 192mg capsule or 384 mg powder K0706 (group 2) or placebo (Group 3) and receive their study drug at the end of their visit. LPs are mandatory at baseline and 3-month visits (end of treatment). MoCA, TMT-B and UPRDS I-III will be performed to determine eligibility. The C-SSRS will be performed at baseline and every visit.

GI disorders will be assessed using the GSRS. **Cognitive assessments** will be performed via MoCA (global cognition), and TMT-B (executive function). The MoCA and TMT-B will be done at both screening and baseline to ensure subjects can perform these tests and to minimize practice effects on baseline score. ADCS-ADL will measure activities of daily living and ADAS-cog will measure global cognitive change. Cognitive fluctuations will be measured via CAF. **Motor assessments** will be performed via UPDRS I-III and Timed-Up and Go (TUG). **Psychiatric assessments** will be performed using NPI, PBAs and IAS. Any AEs that occur will also be recorded at each visit.

Visits at 24, and 8 weeks. Monitoring and laboratory tests (EKG, blood draw and urine), vital signs and comprehensive physical and neurological exams will be performed. GI disorders will be assessed using the GSRS. The C-SSRS and CAF will also be performed. Any AEs that occur will also be recorded at each visit.

12 weeks end of treatment and 16 weeks wash out visit- after the termination of treatment all study procedures will be performed, LP is mandatory at 12 weeks visit. LP must be performed within 2 hours from the last Levodopa dose. CSF collection via LP and blood draw will be performed for biomarker pharmacokinetics, pharmacodynamics and biomarkers measurement (CSF alpha-synuclein (total and oligomeric), CSF total tau/p-tau18, HVA and DOPAC. Blood will also be collected for monitoring laboratory tests as indicated above.

Medication Compliance Check. Site staff will remind subjects to bring unused study drug with them **at each visit** as well as the completed drug compliance diary. Site staff will count the number of capsules remaining at each in-person clinic visit for which the subject brings the unused drug with him/her. This information will be recorded in the subject specific drug accountability form. The total number of returned medication will be reviewed against the drug compliancy diary. If drug compliance is determined to be problematic site staff will review with the subject the importance of using the study drug as per protocol. Any dose adjustments will be documented on the drug exposure form (indicating start and stop date). Additionally, site staff will check the subject's overall compliance with the study requirements. This will also include checks of protocol compliance, and concomitant medication use, in addition to the proper use of study drug in order to assess the reliability of subject generated data.

4- Drug, Drug Related Risks and Potential Side Effects

Active Ingredients:

K0706 has molecular formula of C27H20ClN3O2. Detailed information about physical, chemical and pharmaceutical properties and formulation is given in Section 4 of IB. K0706 is almost white to light yellow crystalline powder, with partition coefficient: 6.5 (Log P, theoretical) and M=melting range of 244-248°C. It is non hygroscopic. K0706 formulation is hard gelatin capsule filled with white to off white

blend. Film coated tablets or white powder. K0706 excepients include Polyvinyl caprolactam – polyvinyl acetate – polyethylene glycol graft co-polymer (Soluplus®), auxiliary excipients like glidants, disintegrants and coating agents

Inactive ingredients:
Polyvinyl caprolactam – polyvinyl acetate – polyethylene glycol graft co-polymer (Soluplus®), auxiliary excipients like glidants, disintegrants and coating agents

Risk Summary
K0706 is a Abl tyrosine kinase inhibitor. Abl tyrosine kinase inhibitors such as Imatinib mesylate (Gleevec), Dasatinib, Nilotinib, Ponatinib are used in the treatment of Philadelphia positive leukemias. AEs detailed in attached IB have been observed with the use of approved Abl tyrosine kinase inhibitors. While some of the observed AEs are common between the Abl tyrosine kinase inhibitors used and contribute as a class effect, specific adverse reactions are associated with the structure of the Abl tyrosine kinase inhibitors used. Since K0706 is being developed as a tyrosine kinase inhibitor for the treatment of Philadelphia positive leukemias, AEs commonly observed with the approved Abl tyrosine kinase inhibitors class of drugs may be observed with the clinical use of K0706. The following AEs have been reported during clinical studies and clinical use of Abl TKIs like Imatinib mesylate, Dasatinib, Nilotinib, Ponatinib and Bosutinib. Similar AEs could be associated with the use of K0706.

- Fluid retention: Participants should be monitored for development of signs and symptoms of fluid retention.
- Myelosuppression: Participants should be monitored with complete blood counts regularly.
- Cardiac arrhythmias: Participants should be monitored and instructed to report signs and symptoms of slow or rapid heart rate. Drugs known to prolong the QT interval and strong CYP3A4 inhibitors should be avoided.
- Heart failure: Participants should be monitored for signs or symptoms consistent with cardiac dysfunction and should be treated appropriately.
- Hepatotoxicity: Participants should be monitored liver function tests regularly.
- Pancreatitis: Participants should be monitored for pancreatic diseases and caution is recommended in subjects with a history of pancreatitis
- Hemorrhage: Caution should be indicated to subjects requiring medications that inhibit platelet function or anticoagulants.
-Tumor lysis syndrome: Participants should be monitored for clinically significant dehydration and treatment of high uric acid levels and corrected when necessary.
- Participants should be monitored for compromised wound healing and gastrointestinal perforation.

Animal Data
Nonclinical toxicology studies with K0706 demonstrated a safety profile that supports administration to human subjects as summarized in IB section 5.2.2.1. The safety of single-dose orally administered K0706 was evaluated in the CNS, cardiovascular and respiratory systems. A placebo formulation containing all excipients, but not containing K0706, was used for comparisons. The effect of K0706 on the CNS and respiratory systems was studied in rats by performing an Irwin functional observational battery (FOB) tests (BRP1_14_056) and evaluating respiratory functions (BRP1_14_072). The effect of K0706 on the cardiovascular system was evaluated in vitro using hERG assays (BRS_hERGK+_K0706 and BRP1_15_066) and in vivo using telemetry-instrumented beagle dogs (BRP1_14_107) to evaluate electrocardiogram (ECG) parameters, hemodynamic parameters, and body temperature. Summaries of the safety pharmacology program are presented in IB section 5.2.2.1.

Pregnancy: Women should be advised of the potential hazard to the fetus and to avoid becoming pregnant.

Overdosage. No studies with K0706 have been performed. Participants must stop taking the medication and immediately report over-dosage to study team as soon as possible and check into an emergency department nearby if any signs of AEs appear.

5- PATIENT POPULATION

5.1- Number of Patients & Centers

This is a single center study at Georgetown University Medical Center (GUMC) Translational Neurotherapeutics Program (TNP) with total duration of 2 years and open enrollment for 24 months due to COVID-19 interruption of enrollment. We currently have no competing trials for DLB and we anticipate efficient recruitment to this study. We will recruit DLB patients from our Movement Disorders and Memory Disorders clinics at MedStar Georgetown University Hospital (MGUH). We have a registry of over 400 potential participants diagnosed with mild to moderate DLB and their study partners. This study will determine the blinded effects of K0706 on safety and tolerability, cerebrospinal fluid (CSF) and plasma biomarkers and clinical outcomes. The data obtained will serve as a feasibility study for future placebo-controlled, double-blinded studies in DLB and AD patients. Study procedures will be conducted at GUMC Clinical Research Unit (CRU) of Georgetown-Howard Universities Center for Clinical and Translational Science (GHUCCTS). GHUCCTS encompasses MedStar Health Research Institute (10 hospitals), including Georgetown University Hospital (GUH), Howard University, the Washington DC VA Medical Center (with its hospital and five clinics) and the Oak Ridge National Laboratory. CRU GHUCCTS is NIH-funded and combines the five institutions into one research powerhouse, creating one of the largest clinical trials networks in the country. Any satellite clinic interested in considering participants to enroll in this study should contact the study co-ordinator and the candidate will be consented and screened at the CRU where the entire study visits will take place.

There are no competing clinical trials for DLB in the greater Washington-Baltimore area. We will advertise to community support groups and websites (Clinicaltrials.gov). Only patients that meet all inclusion/exclusion criteria and are willing to make all visits will be included in the study. Our program has had significant success with recruitment and retention in clinical trials because of the active clinical involvement at GUH and in the satellite centers, including McLean Medical Center, Montgomery Hospital and Washington Hospital Center. Most patients will be local to study center, but any patient who qualifies and can commit to all study visits will be allowed enrollment into the study regardless of residence. Overall we do not anticipate any issues in recruiting or maintaining 45 patients in this clinical trial for 3-month treatment. We will also advertise in our newsletters and websites.

5.2- Inclusion Criteria

1) Written informed consent
2) Capable of providing informed consent and complying with study procedures. Subjects who are unable to provide consent may use a Legally Authorized Representative (LAR)
3) Age of 25-90 years, medically stable
4) Clinical diagnosis of DLB according to McKeith et al (32) with both dementia MoCA≥14 and Parkinsonian defined as bradykinesia in combination with rest tremor, rigidity or both UPDRS I-III ≤ 50 and UPDRS-III between 20-40.

5) Dementia and Parkinsonism must be present with at least one other symptom such as fluctuation, visual hallucinations or REM sleep behavioral disorder (RBD)
6) Stable on Levodopa no more than 800mg daily, acetylcholinesterase inhibitors, dopamine agonists for at least 6 weeks
7) Stable on monoamine oxidase inhibitors (MOA-B) for at least 4 weeks before enrollment and during the trial
8) Stable concomitant medical and/or psychiatric illnesses in the judgement of the PI
9) QTc interval 350- 485ms, inclusive
11) Participants must be willing to undergo LP at baseline and 3 months after treatment.

5.3- Exclusion Criteria

1) Medical history of liver or pancreatic disease, GI ulcers and Chron's disease, kidney, GI, or blood problems
2) Abnormal liver function defined as AST and/or ALT > 100% the upper limit of the normal
3) Renal insufficiency as defined by a serum creatinine > 1.5 times the upper limit of normal or proteinuria
4) History of HIV, clinically significant chronic hepatitis, or other active infection
5) hypokalemia, hypomagnesaemia, or long QT syndrome- QTc≥≥485 ms or concomitant drugs known to prolong the QTc interval and history of any cardiovascular disease, including myocardial infarction or cardiac failure, angina, arrhythmia
6) History or presence of significant cardiac conditions including: cardiovascular or cerebrovascular event (e.g. myocardial infarction, unstable angina, or stroke), congestive heart failure, first, second- or third-degree atrioventricular block, sick sinus syndrome, or other serious cardiac rhythm disturbances, any history of Torsade de Pointes.
7) Treatment with any of the following drugs at the time of screening or the preceding 30 days, and/or planned use over the course of the trial: Treatment with Class IA or III antiarrhythmic drugs (e.g. quinidine), treatment with QT prolonging drugs (*www.crediblemeds.org)*- excluding SSRIs (e.g. Citalopram, Escitalopram, Paroxetine, Sertraline, Duloxetine, Trazodone, etc.). Should treatment with any of these agents be required, therapy with K0706 should be interrupted.
8) Females must not be lactating, pregnant or with possible pregnancy
9) Clinical signs indicating syndromes other than DLB including, AD idiopathic PD, corticobasal degeneration, supranuclear gaze palsy, multiple system atrophy, chronic traumatic encephalopathy, signs of frontal dementia, history of stroke, head injury or encephalitis, cerebellar signs, early severe autonomic involvement, Babinski sign
10) Current evidence or history in past two years of epilepsy, focal brain lesion, head injury with loss of consciousness or DSM-IV criteria for any active major psychiatric disorder including psychosis, major depression, bipolar disorder, alcohol or substance abuse
11) Evidence of any significant clinical disorder or laboratory finding that renders the participant unsuitable for receiving an investigational drug including clinically significant or unstable hematologic, hepatic, cardiovascular, pulmonary, gastrointestinal, endocrine, metabolic, renal or other systemic disease or laboratory abnormality.
12) Active neoplastic disease, history of cancer five years prior to screening, including breast cancer (history of skin melanoma or stable prostate cancer are not exclusionary)
13) Contraindications to LP: prior lumbosacral spine surgery, severe degenerative joint disease or deformity of the spine, platelets < 100,000, use of Coumadin/warfarin, or history of a bleeding disorder.
14) Must not be on any immunosuppressant medications

15) Must not be enrolled as an active participant in another clinical study.

5.4- Randomization and Registration will be performed by an internet based randomization module. Randomization of the subjects to the 3 treatment groups will be performed in a stratified manner. The chance for randomization to the groups is 1:1:1 for placebo: 96mg capsule or 192 mg powder K0706:192mg capsule or 384 mg powder K0706.

5.5- Blinding. The investigators will be blinded to the dosage. Medications for any patient will be labeled by the CRU with a package medical identification number (Med. Id). A patient specific patient identification number (Pat. Id.) will be assigned to each patient. The investigator will have to note the Pat.Id on the designated medication package number after randomization. Drug dispensation will take place during the scheduled visits.

5.6- Un-blinding may occur for emergency purposes in case an AE or SAE makes it necessary for the treating physician to unblind the study treatment– if possible prior contact will be made with the clinical trials co-coordinator (CTC) or project manager. If this is not feasible, the CTC will be contacted within 24 hours after un-blinding. The CTC should not be made aware of what the treatment assignment was. If un-blinding occurs the subject is automatically withdrawn and the procedure for withdrawal will be followed.

5.7- Withdrawal of subjects. In accordance with the Declaration of Helsinki, each subject is free to withdraw from the study at any time without giving reasons for her/his decision. The investigator may also withdraw the subject at any time in the interest of the subject's safety, including severe study-related toxicity as detailed in Table 1 or in the case of un-blinding as described above. The primary reason for withdrawal (e.g. subject wish, safety, withdrawal of consent, etc.) must be recorded in the subject's medical record and on the withdrawal form in the electronic Case Report Form (eCRF). Should a subject decide to withdraw after administration of study drug, or should the investigator decide to withdraw the subject, all efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible.
A study subject will be discontinued from participation in the study if:

- Any clinical AE, laboratory abnormality, concurrent illness, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject.
- The participant meets any exclusion criteria (either newly developed or not previously recognized).

Subjects are free to withdraw from participation in the study at any time upon request.

5.8- Handling of Withdrawals
A subject may choose to discontinue participation in the study at any time. Subjects who permanently discontinue study drug should complete early study drug termination procedures per protocol. The subject should then return any unused study drug and will be asked to return to the study site for a final safety visit.

5.9- Termination of Study
This study may be prematurely terminated if, in the opinion of the principal investigator(s) (PIs), there is sufficient reasonable cause.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects.
- Enrollment is unsatisfactory.
- Insufficient adherence to protocol requirements.
- Data are not sufficiently complete and/or evaluable.

Other reasons for termination of study are:

- Grantor' changes its Business Strategy and no longer wants to support the study
- Investigational Product for the study is not available from the 'Grantor'.

5.10- Protocol Adherence

The Principal Investigators (PIs) agree to adhere to the protocol detailed in this document and agrees that any changes to the protocol must be approved by the site Institutional Review Board (IRB). The PIs will be responsible for enrolling only those study subjects who have met protocol eligibility criteria.

6- SAFETY MONITORING AND REPORTING

The AE definitions and reporting procedures provided in this protocol comply with all applicable regulations and ICH guidelines. The PI(s) will carefully monitor each subject throughout the study for possible AEs. All AEs will be documented on CRFs designed specifically for this purpose. It is also important to report all AEs, especially those that result in permanent discontinuation of the investigational product being studied, whether serious or non-serious.

6.1- All Non-Serious Adverse Events

An AE is any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with a study, use of a drug product or device whether or not considered related to the drug product or device.

Adverse drug reactions (ADR) are all noxious and unintended responses to a medicinal product related to any dose. The phrase “responses to a medicinal product” means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. Therefore, a subset of AEs can be classified as suspected ADRs, if there is a causal relationship to the medicinal product.

Examples of AEs include: new conditions, worsening of pre-existing conditions, clinically significant abnormal physical examination signs (i.e. skin rash, peripheral edema, etc.), or clinically significant abnormal test results (i.e. lab values or vital signs), with the exception of outcome measure results, which are not being recorded as AEs in this trial (they are being collected, but analyzed separately). Stable chronic conditions (i.e., diabetes, arthritis) that are present prior to the start of the study and do not worsen during the trial are NOT considered AEs. Chronic conditions that occur more frequently (for intermittent conditions) or with greater severity, would be considered as worsened and therefore would be recorded as AEs.

AEs are generally detected in two ways:

Clinical → symptoms reported by the subject or signs detected on examination.

Ancillary Tests → abnormalities of vital signs, laboratory tests, and other diagnostic procedures (other than the outcome measures, the results of which are not being captured as AEs).

If discernible at the time of completing the AE log, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the PI and recorded on the AE log. However, if an observed or reported sign, symptom, or clinically significant laboratory anomaly is not considered by the Site Investigator to be a component of a specific disease or syndrome, then it should be recorded as a separate AE on the AE log. Clinically significant laboratory abnormalities, such as those that require intervention, are those that are identified as such by the PI.

Subjects will be monitored for AEs from the time they sign consent until completion of their participation in the study (defined as death, consent withdrawal, loss to follow up, and early study termination for other reasons or following completion of the entire study).

6.2- All Serious Adverse Events

An SAE is defined as an adverse event that meets any of the following criteria:

1. Results in death.

2. Is life threatening: that is, poses an immediate risk of death as the event occurred.
    a. This serious criterion applies if the study subject, in the view of the PI or Sponsor, is at immediate risk of death from the AE as it occurs. It does not apply if an AE hypothetically might have caused death if it were more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization.
    a. Hospitalization for an elective procedure (including elective PEG tube/g-tube/feeding tube placement) or a routinely scheduled treatment is not an SAE by this criterion because an elective or scheduled "procedure" or a "treatment" is not an untoward medical occurrence.
4. Results in persistent or significant disability or incapacity.
    a. This serious criterion applies if the "disability" caused by the reported AE results in a substantial disruption of the subject's ability to carry out normal life functions.
5. Results in congenital anomaly or birth defect in the offspring of the subject (whether the subject is male or female).
6. Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.
7. Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

An inpatient hospital admission in the absence of a precipitating, treatment-emergent, clinical AE may meet criteria for "seriousness" but is not an adverse experience, and will therefore, not be considered an SAE. An example of this would include a social admission (subject admitted for other reasons than medical, e.g., lives far from the hospital, has no place to sleep).

The PI is responsible for classifying AEs as serious or non-serious.

6.3- All Reports of Drug Exposure during Pregnancy.
There have been no studies or reports detailing K0706 exposure during pregnancy. However, this TKI is likely to provide a toxicity profile similar to other well-studied and FDA-approved TKIs, including Gleevec, Nilotinib, Bosutinib, Ponatinib and others. Females of child bearing potential will undergo a pregnancy test at every visit and will be advised not to get pregnant during the study period as K0706 may present potential harm to the fetus.

6.4- All reports of misuse and abuse of K0706 and other medication.
Site staff will check the subject's overall compliance with the study requirements. This will also include checks of protocol compliance, K0706 and concomitant medication use, in addition to the proper use of study drug in order to assess potential risks of drug abuse or misuse. The PI shall report within 24 hours of discovery any drug misuse experience to the IRB, FDA and study sponsor Sun Pharma Advanced Research Company Ltd.,

6.5- Assessment and Recording of Adverse Events
The PIs will carefully monitor each subject throughout the study for possible AEs. All AEs will be documented on CRFs designed specifically for this purpose. All AEs will be collected and reported in the electronic data capture (EDC) system. The PIs shall promptly review all information relevant to the safety of the investigational product, including all SAEs. Special attention will be paid to those that

result in permanent discontinuation of the investigational product being studied, whether serious or non-serious.

6.6- Assessment of Adverse Events

At each visit (including telephone interviews), the subject will be asked if they have had any problems or symptoms since their last visit in order to determine the occurrence of AEs. If the subject reports an AE, the Investigator will probe further to determine:

1. Type of event
2. Date of onset and resolution (duration)
3. Severity (mild <grade 1, moderate <grade 2, severe <grade 3) according to CTCAE (
4. Seriousness (does the event meet the above definition for an SAE)
5. Causality, relation to investigational product and disease
6. Action taken regarding investigational product
7. Outcome

6.7- Relatedness of Adverse Event to Investigational Product

The relationship of the AE to the investigational product should be specified by the PIs, using the following definitions:

1. Not Related: Concomitant illness, accident or event with no reasonable association with treatment.

2. Unlikely: The reaction has little or no temporal sequence from administration of the investigational product, and/or a more likely alternative etiology exists.

3. Possibly Related: The reaction follows a reasonably temporal sequence from administration of the investigational product and follows a known response pattern to the suspected investigational product; the reaction could have been produced by the investigational product or could have been produced by the subject's clinical state or by other modes of therapy administered to the subject. (Suspected ADR)

4. Probably Related: The reaction follows a reasonably temporal sequence from administration of investigational product; is confirmed by discontinuation of the investigational product or by re-challenge; and cannot be reasonably explained by the known characteristics of the subject's clinical state. (Suspected ADR)

5. Definitely Related: The reaction follows a reasonable temporal sequence from administration of investigational product; that follows a known or expected response pattern to the investigational product; and that is confirmed by improvement on stopping or reducing the dosage of the investigational product, and reappearance of the reaction on repeated exposure. (Suspected ADR)

6.8- Recording of Adverse Events

All clinical AEs are recorded in the AE Log in the subject's study binder. Study staff should fill out the AE Log and enter the AE information into the EDC system within 48 hours of the site learning of a new AE or receiving an update on an existing AE. Entries on GUMC MEDUSA database and the AE Log (and into the EDC) will include the following: name and severity of the event, the date of onset, the date of resolution, relationship to investigational product, action taken, and primary outcome of event. The PI shall report within 24 hours of discovery any serious adverse experience whether or not considered related to the study to the IRB, FDA and Sun Pharma Advanced Research Company Ltd.. The OI shall also report SAEs to the DSMB. Serious adverse experiences should also be reported immediately by telephone and subsequently in writing within 48 hours of the occurrence to the following:
Sponsor: Sun Pharma Advanced Research Company Ltd.,
The Institutional Review Board will be notified of such adverse experiences

The minimum necessary information to be provided at the time of the initial report will include the following:

Study identifier	A description of the event	Whether study was discontinued
Study Center	Date of onset	The reason why the event is classified as serious
Subject number	Current status	Investigator assessment of the association between the event and study treatment

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file/site binder.

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up

7- STUDY MONITORING

7.1- Safety Monitoring

The study PIs will review safety data throughout the trial and may stop the trial for safety if they determine that there is a significant difference in the rate of a particular AE that would indicate a risk that is greater than the possible benefit of the study drug.

Unanticipated problems involving risks to subjects or others including adverse events will be reported to the Partners Human Research Committee (PHRC) in accordance with PHRC unanticipated problems including AEs reporting guidelines.

7.2- Data Safety Monitoring Board (DSMB) will be formed at the time of the initiation of the study and will include medical experts on TKI effects on GI toxicity (TBD), neurologist (TBD), a clinical pharmacologist (TBD) and a biostatistician (TBD). No investigator involved in the trial will be a member of the DSMB. The DSMB will review the protocol to identify any necessary modifications. If modifications are necessary, revisions will be reviewed by the DSMB prior to its recommendation on initiation of the project. The DSMB, based on its review of the protocol, will identify the data parameters and format of the information to be regularly reported. The DSMB will be informed of the occurrence of any SAEs and immediately notified of fatal or life-threatening events. The DSMB may at any time request additional information from the PIs. The DSMB will be provided with data blinded to treatment status, but they may request un-blinded data if there is a safety concern. Based on the review of safety data, the DSMB will make recommendations regarding the conduct of the study. These may include amending safety monitoring procedures, modifying the protocol or consent, terminating the study or continuing the study as designed. The discussions and decisions of the DSMB will be summarized in written reports and provided to the PIs. The DSMB will meet in person or by conference call on a quarterly basis or as necessary when requested by the PI or the medical monitor.

At the initiation of the study, a DSMB will be immediately formed and an independent study monitor, will directly communicate with the DMSB that will create a charter outlining all duties to develop stopping rules for serious and potentially serious irreversible adverse events. The DSMB will also provide boundaries for when to terminate the study or end participation of an individual patient. The stopping rules should include stopping rules as in Table 1 and other criteria related to:
GI disorders, Pancreatitis, myelosuppression, renal disorders and QT prolongation (select a method for QT correction (typically Frederica's method) and include in the protocol), develop individual stopping rules for withdrawal from the study for QT prolongation, and create algorithms for the follow-up of abnormal blood tests that potentially signal the start of a drug induced event (e.g. neutropenia or thrombocytopenia). The DSMB will monitor each patient in real-time and on a case-by-case basis and unblind any case when necessary in consultation with the study monitor.

7.3- Study monitor and auditing will ascertain adherence to the study protocol by investigators and ensure proper documentation and investigator blinding of biomarker data processing and deposition. This study will be monitored by a clinical monitor. The monitors will maintain liaison with the investigators by telephone, letter, email and personal visits in order to assure the sponsors that the clinical study is completed according to the protocol requirements and that Good Clinical Practices are being followed according to 21 CFR parts 50, 56, 812, FDA Guidelines and the ICH E6 Guideline. The PI will allocate adequate time for such monitoring activities. The PI will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related

documents and study related facilities (device testing location), and has adequate space to conduct the monitoring visit.

Auditing inspections will serve to verify strict adherence to the protocol and the accuracy of the data management, in accordance with the federal regulations. The PI will permit study-related monitoring and audits by the IRB, the sponsor Sun Pharma Advanced Research Company Ltd., and government regulatory bodies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc) at regular intervals throughout the study. The PI will ensure the capability for inspections of applicable study-related facilities (device testing location). Participation as a PI in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

The investigator should be aware that representatives of the FDA might also inspect the study site and subject records. If contacted for an audit of this study by any regulatory agency, the investigator should notify the sponsor immediately.

Study monitor will ascertain adherence to the study protocol by investigators and ensure proper documentation and investigator blinding of biomarker data processing and deposition.

8- INSTITUTIONAL REVIEW BOARD (IRB)

This study will be conducted in compliance with current Good Clinical Practices (GCP) and Title 21Part 56 of the United States of America Code of Federal Regulations (CFR) relating to IRBs.

8.1- Ethical Conduct of Study

The study will be conducted in accordance with GCP defined by the International Conference on Harmonization (ICH) and the ethical principles of the Declaration of Helsinki.

8.2- Subject Information and Consent

This study will be conducted in compliance with Title 21 Part 50 of the United States of America Code of Federal Regulations (CFR), Federal Regulations and ICH Guidance Documents pertaining to informed consent. At the first visit, prior to initiation of any study-related procedures, subjects will be informed about the nature and purpose of the study, participation/termination conditions, and risks and benefits. Subjects will be given adequate time to ask questions and become familiar with the study prior to providing consent to participate. Subjects will give their written consent to participate in the study and will be provided with a copy of the fully executed consent form for their records.

9- Statistical Methods and Data Analysis

9.1- Sample size determination

This is a proof-of-concept study and we will examine incidence of AEs and SAEs by dosage.

Safety: No formal sample-size calculation for 45 subjects was performed. Safety of each dose will be judged by the absence of events of major concern, including GI disorders, QTc prolongation and myelosuppression.

Tolerability: If we define a dose as tolerable when we observe no more than 25% intolerance or the discontinuation ratio is greater than 25%.

9.2- Analyses plan

Safety: The frequency of AEs classified by MedDRA system organ class and preferred term and clinically significant changes in EKG and laboratory parameters will be summarized as simple proportions with exact 95% confidence bounds. The proportion of participants experiencing each type of event will be compared by Fisher's exact test.

Tolerance: The proportion tolerant of each dose will be estimated with exact confidence intervals.

Target Engagement: The measurements of biomarkers at baseline and the change from baseline to 3 months will be summarized in terms of mean and standard deviation. The relationship between 3-month changes in tau, ptau, alpha-synuclein and abeta40/42 levels or other biomarkers and 3-month changes in clinical outcomes will be summarized as simple correlations with a visual verification that correlations within each dose roughly match correlations across doses, i.e., absence of Simpson's paradox.

10-ANIMAL DATA WITH K0706 IN MODELS OF NEURODEGENERATION.

Nonclinical pharmacology, PK, and safety pharmacology data indicate that K0706 has specific and highly potent activity on Abl and several Abl mutations. K0706 shows potent activity in its in vivo models based on Abl. Furthermore, K0706 showed promising neuroprotective activity in MPTP model of Parkinson's disease. It shows good systemic availability following oral administration in mice, rats, and dogs. It has no effect on the CNS, cardiovascular, or respiratory functions at several multiples of efficacious doses (See IB). The antiparkinson's effect of K0706 was determined in 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced SNPc neurodegeneration model in mice. Mice were treated with K0706 ME suspension, once daily, to provide equivalent doses of K0706 at 1, 3 and 10 mg/kg. Treatment was started two days prior to MPTP administration and was given for a total of 6 days from the treatment initiation day. Nilotinib, a second generation TKI with reported ability to cross the blood brain barrier was used as a reference standard TKI. The effect of K0706 and nilotinib was assessed using TH-immunoreactivity as a marker of dopaminergic neurodegeneration at the level of SNPc. Dense TH-positive neurons were observed in the SNPc of naïve mice. Administration of MPTP caused a marked loss of SNPc dopaminergic neurons. K0706 and nilotinib administration prevented the neurodegeneration induced by MPTP in a dose-dependent manner. As assessed by percent immunoreactive area (percentage of total area covered by dopaminergic neurons in the given field), both K0706 and nilotinib mitigated the loss of TH+ neurons in SNPc by 19.38%, 47.89%, and 76.33% and 17.81%, 39.35%, and 65.13%, respectively at 1, 3 and 10 mg/kg doses. As assessed by integrated density, K0706 and nilotinib mitigated the loss of TH+ neurons in SNPc by 19.98%, 50.79%, and 82.53% and 14.07%, 39.98%, and 69.88%, respectively at 1, 3 and 10 mg/kg doses. In conclusion, results suggest promising neuroprotective activity of K0706 in MPTP model of PD (see IB, section 5.2). Nilotinib and Bosutinib that target the wild type Abl tyrosine kinase were also shown to penetrate the brain and promote autophagic degradation of neurotoxic proteins, leading to survival of DA neurons and improvement of motor and cognitive behavior in animal models of alpha-synucleinopathy and other neurodegenerative diseases (37,46-53). Therefore, the use of TKIs is a novel strategy that promotes autophagy to clear neurotoxic protein aggregates in neurons (47,49-51,53-57).Taken together these data suggest that K0706 may induce autophagic clearance of neurotoxic proteins and protect DA neurons in individuals with DLB. Please see IB and supplemental investigational drug attachments for more details.

11-PRIOR AND CONCOMITANT THERAPY

Throughout the study, the subject may be prescribed concomitant medications or treatments deemed necessary to provide adequate supportive care, provided that the medications are licensed in the United States. All concomitant medications and/or treatments received by a subject should be recorded on the appropriate source document and eCRF.

Prohibited and contra-indicated medications in those receiving K0706 are listed in the inclusion/exclusion criteria and detailed below.

11.1- Prohibited Medications and Contraindications

Prohibited Medications

Prohibited medications for study subjects are as follows:

- Milk and calcium appear to reduce the absorption of K0706. Participants should space out K0706 from calcium and magnesium containing medications and supplements (e.g., Tums, milk of magnesia) by at least 2 hours.
- St John's Wort

Pregnancy & Nursing Mothers

There are no adequate and well-controlled studies in pregnant women. Subjects or partners of male subjects must not become pregnant during the study or 3 months after stopping study drug. If a female subject becomes pregnant, study treatment must be discontinued immediately. Caution should be exercised; therefore, no subject should nurse their infant while participating in this study.

12-CLINICAL ASSESSMENTS AND OUTCOME MEASURES

12-1. Clinical Variables

Assessments will be performed at visits as noted above throughout the study for clinical evaluation. In addition to the assessments evaluated below, subjects will provide information on their demographics, past medical history, including DLB, as well as concomitant medication usage.

12.2- Vital Signs, Height & Weight

Vital signs, including systolic and diastolic blood pressure, pulse rate (radial artery)/minute, respiratory rate/minute, temperature and weight will be assessed at specified visits. Height will be measured and recorded at the Screening Visit only.

Medical history will be assessed as follows:

- History of DLB (inquiring on date of diagnosis and first symptoms)
- DLB treatment history
- Smoking history
- Important medical information for inclusion/exclusion
- Significant medical and surgical history (e.g. Allergy/Immunologic, Cardiovascular, Dermatological, ENT, Gastrointestinal, Gynecologic/Urologic, Hepatobiliary, Hermato/Lymphatic, Metabolic/Endocrine, Musculoskeletal, Neurologic, Ophthalmologic, Psychiatric, Pulmonary, renal, and Other)

Questioning of Comorbidities will be done using the Charlston Comorbidity Index and should be done at every visit after Baseline:

Metastatic solid tumor:	no/yes
AIDS:	no/yes
Moderate-to-severe liver disease:	no/yes
Hemiplegia:	no/yes
Moderate-to-severe renal failure:	no/yes
Moderate-Diabetes with endorgan damage:	no/yes
Neoplasia:	no/yes
Leukemia:	no/yes
Lymphoma:	no/yes
Myocardial infarct:	no/yes
Congestive heart failure:	no/yes
Peripheral vascular disease:	no/yes
Cerebrovascular disease:	no/yes
Dementia:	no/yes
Chronic pulmonary disease:	no/yes
Connective tissue disease:	no/yes
Ulcer disease:	no/yes
Mild liver disease:	no/yes
Diabetes:	no/yes

- Concomitant medications will be recorded at every visit after baseline.

12.3- Clinical Laboratory Assessments

The following safety laboratory tests will be performed during the study:

Standard blood chemistry, including Cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), albumin, total protein, alkaline phosphatase, total bilirubin, creatinine, calcium, chloride, sodium, potassium, magnesium, inorganic phosphorus, bicarbonate, creatine phosphokinase (CPK), gamma-glutamyl transferase (γ-GT), lactate dehydrogenase (LDH), lipase, α-amylase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), thyroid stimulating hormone (TSH), vitamin B12, glycated urea, uric acid. A standard hematology panel including, complete blood count (CBC) with differential counts will be performed. Hemoglobin (Hb), hematocrit, red blood cell count, platelet count, and white blood cell count with differential count will be measured. In addition, prothrombin time-international normalized ratio (PT-INR) will be measured for assessment of coagulation.

- Serum hCG for women of childbearing potential (WOCBP)

Additional testing may be ordered if needed, to further assess an AE, or if there is any suspicion that a subject may be pregnant, throughout the course of the study.

12.4- Physical Examination

A physical examination will be performed and recorded. A full physical examination (including vital signs) will be performed by a trained physician as indicated in the schedule of assessments (Table 2). The Physical examination will include:

- General appearance
- Abdomen
- Cardiovascular systems
- Lungs
- Lymph nodes
- Musculoskeletal systems
- Skin (with special attention to dermatological tolerability)
- Extremities
- Head, ears, eyes, nose, throat, and mouth
- Thyroid gland
- Vital signs:
    - Body weight (Kg or pound)
    - Height (cm or inch) (at the Screening Visit only)
    - Blood pressure systolic and diastolic (mmHg)
    - Heart rate (bpm)

12.5- Neurological Examination

A neurological examination will be performed and recorded as detailed in Table 2. Neurological examination will include:

- Cranial nerves
- Motor functions
- Sensation
- Coordination
- Speech

12.6- Adverse Events
AEs will be documented at each study visit, including the Screening Visit once the ICF has been signed by the subject. Information on AEs of study medication and on inter-current events will be determined at each visit by direct questioning of the subjects' review of concomitant medications, and vital sign results. AEs are incidents or complaints that do not require hospitalization, SAEs require hospitalization (see section 13).

12.7- MDS-UPDRS (includes Hoehn & Yahn staging) is used to follow the longitudinal course of PD and it is the most commonly used scale in the clinical study of PD. UPDRS motor section in particular is used to follow the progression of a person's PD. The UPDRS is made up of these sections: Part I: evaluation of mentation, behavior, and mood. Part II: self-evaluation of the activities of daily life (ADLs) including speech, swallowing, handwriting, dressing, hygiene, falling, salivating, turning in bed, walking, and cutting food. Part III: clinician-scored monitored motor evaluation. Part IV: complications of therapy. Part V: *Hoehn and Yahr* staging of severity of Parkinson's disease. Part VI: Schwab and England ADL scale

12.8- TMT-B. The Trail Making Test (TMT) is a *neuropsychological test* of visual attention and task switching (Reitan, 1958). It consists of two parts in which the subject is instructed to connect a set of 25 dots as quickly as possible while still maintaining accuracy. The test can provide information about visual search speed, scanning, speed of processing, mental flexibility, as well as executive functioning. The Trail Making Test B (TMT-B) has been shown to be sensitive to changes in cognitive ability in HD, and has been used in an HD clinical trial (Huntington Study Group Reach2HD Investigators, 2015).

12.9- MOCA is designed as a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains, including attention and concentration, executive functions, memory, language, visuo-constructional skills, conceptual thinking, calculations and orientation. It has excellent psychometric properties and has become a widely used screening instrument for mild cognitive impairment (Smith, Gildeh & Holmes, 2007). It is administered by a nurse or clinician and takes 10 - 20 minutes.

12.10- C-SSRS
The US FDA recommends the use of a suicidality assessment instrument that maps to the Columbia Classification Algorithm for Suicide Assessment (C-CASA). The C-CASA was developed to assist the FDA in coding suicidality data accumulated during the conduct of clinical trials of antidepressant drugs. One such assessment instrument is the Columbia Suicide Severity Rating Scale (C-SSRS). The C-SSRS involves a series of probing questions to inquire about possible suicidal thinking and behavior.

Only investigators who have been fully trained in the administration of the C-SSRS and GDS will assess subject suicidality and depression. As part of training, investigators are prepared to respond to and manage instances in which patients express suicidal ideation or exhibit suicidal behavior.
At the Baseline Visit, the C-SSRS *Baseline* version will be administered. This version is used to assess suicidality over the subject's lifetime and specifically for the previous 6-month time period.
At each visit and the Final Safety visit, as applicable, the *Since Last Visit* version of the C-SSRS will be administered. This version of the scale assesses suicidality since the subject's last visit.
Information obtained from: *http://www.cssrs.columbia.edu/*

12.11- TUG- Timed Up and Go (TUG) is an assessment of mobility, balance, walking ability, and fall risk (Podsiadlo et al, 1991). It uses the time that a person takes to rise from a chair, walk three meters, turn around, walk back to the chair, and sit down. It requires both static and dynamic balance.

12.12- NPI. The behavioral outcome measure for this trial is the NPI. The NPI is a well-validated, reliable, multi-item instrument to assess psychopathology in AD based on interview with the study partner. The NPI evaluates both the frequency and severity of 10 neuropsychiatric disturbances. Frequency assessments range from 1 (occasionally, less than once per week) to 4 (very frequently, once or more per day or continuously) as well as severity (1=mild, 2=moderate, 3=severe). The overall score and the score for each subscale are the product of severity and frequency.

12.13- ADAS-Cog aims to evaluate cognitive impairment in the assessment of AD. Recommended for second stage or more detailed assessments and/or for particular research evaluations rather than for applications in routine care settings. It takes 30-45 min and administered by an interviewer. Requires additional training. ADAS-cog was included in this LBD study to better capture potential changes in ADL and non-ADLs and severity of cognitive impairment.

12.14- ADCS-ADL is an activity of daily living inventory developed by the ADCS to assess functional performance in participants with AD. Using a structured interview format, study partners are queried as to whether participants attempted each item in the inventory during the prior 4 weeks and their level of performance. The ADCS-ADL scale discriminates well between normal participants and those with mild AD and it has good test-retest reliability. The ADCS-ADL includes some items from traditional basic ADL tests (e.g., grooming, dressing, walking, bathing, feeding, toileting) as well as instrumental (complex) activities of daily living (e.g., shopping, preparing meals, using household appliances, keeping appointments, reading).

12.15- CAF consists of seven items of confusional behavior (falls, fluctuation, drowsiness, attention, disorganized thinking, altered level of consciousness, communication), scores for which are summed to provide a severity score for fluctuating confusion ranging from 0 to 21.

12.16- IAS was developed to measure apathy and irritability in patients with dementia, including AD and HD (Chatterjee 2005). The IAS is a 28-item self-administered questionnaire collecting information about different aspects of irritability and apathy utilizing a 0-3 scale for each item to indicate severity. Both a patient and a study partner version can be administered. The IAS will be completed separately by Subjects and Study Partners (Chatterjee 2005).

12.17- PBA-s is a structured interview in which a trained interviewer rates the frequency and severity of neuropsychiatric symptoms through observation and the reporting of the Subject and Study Partner. Symptoms rated include depressed mood, suicidal ideation, anxiety, irritability, angry or aggressive behavior, apathy, perseverative thinking or behavior, obsessive-compulsive behaviors, delusional or paranoid thinking, hallucinations, and disoriented behavior. Each behavioral problem is rated for both severity and frequency on a 0-4- point scale; severity and frequency ratings are then multiplied to provide an overall score for each symptom.

12.18- CSF and Blood Biomarkers

Subjects will also be asked to provide blood samples for biomarker analysis per Schedule of Activities. Blood samples will be stored in a sample repository at Georgetown University Medical Center (GUMC) laboratory for Dementia and Parkinsonism, where bio fluids will be indefinitely stored and may be used

for further biomarker validation studies. All samples will be labeled with a code. The code will not include any identifiable information. Any analysis performed on these samples is for research purposes only. Unused samples will remain in the biorepository for future DLB-related research. There is no scheduled date on which the samples will be destroyed. Samples may be stored for research until they are used, damaged, decayed or otherwise unfit for analysis. Subjects have the option of declining participation in this portion of the study at any time by withdrawing their consent to have their sample used. However, it will not be possible to destroy samples that may have already been used.

13- BIOMARKERS

13-1- Rationale for CSF and plasma biomarkers.

DLB is the second most common type of dementia that causes motor and non-motor symptoms. DLB is characterized by loss of DA-producing neurons in the substantia nigra (SN) *pars compacta* and formation of intracellular inclusions known as Lewy bodies (LBs) that primarily contain aggregated *alpha*-synuclein. Cerebrospinal fluid (CSF) levels of alpha-synuclein oligomers longitudinally increase in DLB compared to aged-matched controls (59-61). Additionally, the ratio of oligomeric to total alpha-synuclein also increases in the CSF of DLB patients when compared to control and this increased ratio has been associated with motor decline (62,63). Homovanillic acid (HVA) and 3,4-Dihydroxyphenylacetic Acid (DOPAC) are two primary metabolites of DA and can be used as a CSF marker of DA metabolism. Decreased CSF levels of DOPAC have been shown to be an early marker for DLB (64), and similarly HVA has been shown to be decreased in the CSF of DLB patients compared to controls (65). Measuring CSF HVA and DOPAC as well as alpha-synuclein levels may provide an important pharmacodynamics effect of K0706 treatment in LBD.

The R47H and other variants of triggering receptors on myeloid cells (TREM)-2, which result in loss of TREM2 function, are strong risk factors for PD and DLB (66-68). Activated microglia in the SN proliferate and produce reactive oxygen species and pro-inflammatory cytokines, resulting in progressive degeneration of DA neurons in PD (69,70). TREM2 may regulate microglial response and phagocytosis. TREM2 inhibits inflammatory responses in microglia via suppression of NF-kB pathways and activation of innate immunity (71), while TREM2 loss of function results in reduced microglial phagocytosis (72-74). Therefore, measuring TREM2 levels in the CSF may provide another important pharmacodynamics effect indicating neuro-inflammation and the phagocytic activity of microglia to potentially reduce alpha-synuclein levels after K0706 treatment of DLB patients. The biomarkers proposed include CSF levels of total and oligomeric alpha-Synuclein, total tau and p-tau$_{181/231}$, which are identified as potential CSF biomarkers for PD and DLB pathology.

Several studies indicate that reduction of CSF alpha-Synuclein is associated with alpha-Synuclein pathology in the CNS (75-77). CSF alpha-Synuclein, which probably comes from a neuronal source, has a lower level than the highly abundant presence of peripheral alpha-Synuclein (78). However, only a few studies have investigated CSF alpha-Synuclein levels in patients with neuropathologically confirmed alpha-Synucleinopathies (79,80). CSF alpha-Synuclein is reduced in de novo PD patients compared with healthy individuals (81), and it is lower in patients with advanced alpha-Synucleinopathies compared to other neurological disorders (80). Therefore, we expect K0706 to reduce the decrease in CSF total and oligomeric alpha-Synuclein level indicating reduced cell death, which will also be compared with direct markers of cell death, including neuron specific enolase (NSE), S100B and Phosphorylated neurofilaments.

Tau pathology is also frequently found in the CNS of DLB patients and have been associated with the development of cognitive impairment and PD dementia (82). Several studies also demonstrate increased levels of CSF total tau and p-tau181 levels (79,83,84) in PD and DLB patients, but another study report slightly decreased or normal levels of CSF total tau and p-tau (85). The CSF variably as reported in the literature in CSF tau levels may be due to disease stage and/or differences in diagnostic criteria. Therefore, we will measure CSF tau in this study as another marker of cell death and compare tau with NSE and S100B at baseline and 3 months in a placebo-controlled study.

Other candidate biomarkers for DLB include catechol amines, such as dopamine and noradrenaline, and their metabolites. Levels of CSF HVA and DOPAC, which are the end byproduct of the neuronal metabolite of dopamine is reduced in PD and DLB (86,87), reflecting diminution of stores of central dopamine. We will measure CSF HVA and DOPAC at baseline, 3 months to evaluate dopamine metabolism. We expect K0706 to increase HVA and DOPAC levels, reflecting an increase in central dopamine stores. We will also measure changes in exploratory biomarkers of pathophysiology, which may show K0706 effects on biomarker levels that will help us to build a better clinical development program going forward.

CSF, plasma DLB biomarkers: Blood draw (15ml) and lumbar puncture (LPs) to obtain CSF (~15ml) will be performed on all patients at baseline and 3 months after treatment. Blood will be drawn 0.5hr before LP s outlined above. Plasma will be isolated immediately after blood draw and will be aliquoted and stored at -80^{o}C. CSF will be aliquoted and stored at -80^{o}C. Freeze and thaw cycles will be avoided. To avoid CSF contamination with blood, the first 1 mL of CSF collection will be discarded and all samples will be centrifuged at 1000g for 15 minutes. Samples that contain a detectable level of Hemoglobin will be eliminated from alpha-Synuclein and HVA evaluation.

Plasma and CSF sample preparation for Mass Spec to determine K0706 pharmacokinetics
Plasma and CSF samples (20 µl) will be thawed initially on ice at room temperature and transfused to Eppendorf tubes containing 100µl of water. 500µl extraction solvent, Acetonitrile/Methanol (50:50) containing the internal standard (5ng/mL of K0706_13C_2H3) will be added to the sample. The mixture will be vortexed and incubated for 20min on ice to accelerate protein precipitation. After incubation, the samples will be vortexed and centrifuged at 13,000 rpm for 20 min at 4^{O}C. The supernatant is freeze-dried using speed vacuum and reconstituted in 200µL of Methanol: Water (50:50) and processed by Mass Spectrometry.

13.2- Pharmacokinetics. Plasma and CSF will be collected 1-4 hours after oral administration of K0706 to determine the pharmacokinetic parameters of K0706 after dosing with 96mg and 192mg. Quantitation of K0706 will be performed using multiple reactions monitoring mass spectrometry. The samples will be resolved on an Acquity UPLC BEH C18 1.7µm, 2.1 x 50 mm column online with a triple quadrupole mass spectrometer (Xevo-TQ-S, Waters Corporation, USA) operating in the multiple reaction monitoring (MRM) mode (The sample cone voltage and collision energies will optimized for both analytes to obtain maximum ion intensity for parent and daughter ions using “IntelliStart” feature of MassLynx software (Waters Corporation, USA). The instrument parameters will be optimized to gain maximum specificity and sensitivity of ionization for the parent and daughter ions. Signal intensities from all MRM Q1/Q3 ion pairs for both analytes are ranked to ensure selection of the most intense precursor and fragment ion pair for MRM-based quantitation. The metabolite ratios are calculated by normalizing the peak area of endogenous metabolites within tissue samples normalized to the internal standard K0706_13C_2H3. SPARC Ltd will also perform PK studies in their designated laboratories by Q2 labs, Ithaca, NY.

13.3- Phospho Abl (Pan-tyrosine) ELISA. PathScan® Phospho-c-Abl (panTyr) solid phase sandwich ELISA will be performed on human CSF and plasma. A c-Abl rabbit antibody will be coated on the microwells. 100 ul of CSF or plasma will be added to designated wells. After sample incubation for 2hrs at 37^0C, Abl protein (phospho and nonphospho) will be captured by the coated antibody. Following extensive washing, a phospho-tyrosine (pan-tyrosine) detection antibody will be added to each well to detect captured tyrosine-phosphorylated Abl and c-Abl protein. Samples will be incubated with detection antibody for 1hr at 37^0C. Following extensive washing, anti-mouse IgG, HRP-linked antibody will be added and incubated for 10 minutes at 37^0C to recognize the bound detection antibody. HRP substrate, TMB will be added to develop color. The magnitude of the absorbance for this developed color is proportional to the quantity of tyrosine-phosphorylated Abl and c-Abl protein in the samples.

13.4- Cell death and exploratory biomarkers. NSE and S100B (glia and neurons), total Tau and phosphorylated Tau will be measured using Millipore ELISA at baseline and after 3 months K0706 treatment. K0706 may have a modulatory effect on myeloid cells (88), which can either proliferate and differentiate into peripheral macrophages or become myeloid-derived glia that cross the BBB and produce neurotrophic and/or inflammatory markers, including TREM2. K0706 may affect CNS glial progenitor cells. Our preclinical data show K0706-induced alterations of peripheral and CNS inflammatory makers. Therefore, we will perform unbiased multiplex ELISA (Millipore) to profile a panel of 44 plasma and CSF markers, including interleukins (IL)- 1α&β, 2, 3, 4, 5, 6, 7, 8 (CXCL8), 9, 10, 12, 13, 15, 17 α, and chemokines (C-C) including, CXCL10, CCL2, CL7, CCL22, CCL3, CCL4, platelet-derived growth factor (PDGF)-AA, PDGF-AB/BB, CCL5, CX3CL1 (fractalkine), Tumor necrosis growth factor (TNF)-α, transforming growth factor (TGF)-α, and vascular endothelial growth factor (VEGF), GFAP, phosphorylated neurofilaments, glial fibrillary acidic protein (GFAP) and TDP-43.

13.5- Alpha-Synuclein ELISA. Solid phase alpha-Synuclein sandwich ELISA (Cat#SIG38974, Biolegend) will be performed on CSF and plasma. To avoid repetitive freeze and thaw cycles, immediately after LP and blood draws, 15 mL CSF and 5mL plasma will be aliquoted on ice into 0.5mL tubes and stored at -80ºC. Fresh aliquots were used to perform or repeat ELISA. Total alpha- Synuclein rabbit monoclonal antibody (amino acids 118-123) will be coated on the microwells and 200µl CSF or plasma will be added to designated wells. CSF samples will be diluted 1:10 while plasma samples will be diluted 1:50. After overnight sample incubation at 2-8ºC, alpha-Synuclein will be captured by the coated antibody. After washing, a biotinylated mouse monoclonal alpha-Synuclein (amino acids 103-107) detection antibody will be added to each well to detect the captured alpha-Synuclein (amino acids 118-123). Samples will be incubated with 50µl of detection antibody for 2hrs at room temperature. After washing, 200µl of streptavidin HRP will be added and incubated for 1hr at room temperature to recognize the bound biotinylated detection antibody. Samples will then washed and incubated with 100µl of chemiluminescent substrates. Plates will be shaken for 10-15 seconds and read immediately by a luminometer. The magnitude of the luminescence is proportional to the quantity of alpha-Synuclein in the samples. **Oligomeric alpha-synuclein ELISA measurement.** Solid phase human *alpha*-synuclein oligomer sandwich ELISA (Cat# MBS730762, Mybiosource) was performed on CSF. To avoid freeze-thaw cycles, immediately after LP and blood draws, 15ml of CSF and 10 ml of plasma were aliquoted on ice into 0.5ml tubes and stored at –80°C. Fresh aliquots were used to perform ELISA. All samples were analyzed side-by-side using same reagents. 50 µl of standards or CSF samples were added to the appropriate wells. 5 µl of balance solution was dispensed into samples only and mixed well. 100 µl of conjugate was added to each well. Sample solution was mixed well and incubated for one hour at 37°C. After washing, samples were incubated with 50 µl substrate-A and 50 µl substrate-B per well, including blank control well. Sample solution was incubated for 10-15 minutes at 37°C before

50 µl of stop solution was added to each well including blank control well. To determine the Optical Density (O.D.), samples were read at 450 nm using a microplate reader immediately.

13.6- Homovanillic Acid and DOAPC ELISA. A 100µl CSF or plasma samples will be incubated with 100µl HRP-conjugate reagent and incubated for 1hr at 37ºC using solid phase sandwich ELISA (MyBioSource, Cat# MBS064661). All samples at baseline and 3 months will be analyzed side-by-side using same reagents. After washing, 50µl of chromogen solution A and 50µl of chromogen solution B will be added to the solution and incubated for 15min at 37ºC. The reaction will be stopped with 50µl stop solution and the optical density will be read at 450nM. The magnitude of the absorbance is proportional to the quantity of CSF and plasma HVA.HVA and DOPAC levels will be confirmed by LC-MS.

13.7- Total Tau and p-Tau181 measurement. Solid phase human total Tau sandwich ELISA (Invitrogen, Cat# KHB0042) and p-Tau181 (Invitrogen, Cat# KH0061) will be performed on CSF samples. All samples at baseline and 3 months will be analyzed side-by-side using same reagents. A monoclonal Tau or p-Tau181 capture antibodies will be coated onto micro-wells. 50µl of CSF will be added to each well, allowing human Tau or p-Tau181 antigen to bind to the immobilized capture antibody, and incubated for 2hrs at room temperature. After 2hr incubation, samples will be washed and incubated with 100µl of total Tau or p-Tau181 detection antibody and incubated for 1hr at room temperature. After washing, 100µl of HRP labeled anti-rabbit IgG will be added to each well and incubated for 30min at room temperature. Samples will be washed to remove all unbound enzyme and100µl TMB, a HRP substrate, will be added to develop color. The magnitude of the absorbance for this developed color is proportional to the quantity of CSF total Tau or p-Tau181.

13.8- Human Neurodegenerative Disease Panels. We will use a multiplex Xmap technology that uses magnetic microspheres internally coded with two fluorescent dyes to measure markers of neurodegeneration. All samples at baseline and 3 months will be analyzed side-by-side using same reagents. Through precise combinations of these two dyes, multiple proteins are measured within the sample. Each of these spheres is coated with a specific capture antibody. The capture antibody binds to the detection antibody and a reporter molecule, completing the reaction on the surface of the bead. 25µL of CSF or plasma will be incubated overnight at 4ºC with 25µL of a mixed bead solution, containing human total Tau, pTau231 and NSE (Millipore, Cat#: HND1MAG-39K) or S100B, Aβ42, and Aβ40 (CSF Aβ40 is diluted 1:10). After washing, samples will be incubated with 25µL detection antibody solution for 1.5hrs at room temperature (Millipore, CAT#: HND4MAG-36K), 25µL of Streptavidin-Phycoerythrin will be added to each well containing the 25µl of detection antibody solution. Samples were then washed and suspended in 100µl of sheath fluid. Samples will be then run on MAGPIX with Xponent software. The Median Fluorescent Intensity (MFI) data will be analyzed using a 5-parameter logistic or spline curve-fitting method for calculating analyte concentrations in samples.

14- DATA COLLECTION

All data collected as part of this study will be entered into a secure data management site maintained by Georgetown University Information Service (UIS). All data will be stored on a UIS and IRB approved databases, including long-term storage on Amazon Web Service (WAS) and will be deposited on MEDUSA for an external and independent data analysis and monitoring. Data will also be stored at a secured database for Sun Pharma Advanced Research Company Ltd (SPARC). Data will be stored in EDC maintained by GUMC. This platform facilitates:

1. Capture of clinical and research data from neurologic patients for individual projects in a structured and secure system;
2. Aggregating and sharing uniform, de-identified and/or anonymized datasets for secondary analyses.

14.1- Role of Data Management

Data Management (DM) is responsible for the development, execution and supervision of plans, policies, programs, and practices that control, protect, deliver, and enhance the value of data and information assets.

All data will be managed in compliance with applicable Sponsor and regulatory requirements. Site personnel will collect, transcribe, correct, and transmit the data onto source documents, Case Report Forms (CRFs), and/or other forms used to report, track and record clinical research data. DM is responsible for developing, testing, and managing clinical data management activities.

14.2- Data Entry and Checks

The site personnel are instructed to enter information into the EDC. Data capture is the responsibility of the staff at the site under the supervision of the PIs. During the study, the PIs must maintain complete and accurate documentation for the study. The EDC provides password protection. An edit checking and data clarification process will be put in place to ensure accuracy of the data. Logic and range checks as well as more sophisticated rules may be built into the eCRFs to provide immediate error checking of the data entered. The system has the capability to automatically create electronic queries for forms that contain data that are out of range, out of window, missing or not calculated correctly.

14.3- Data Lock Process

The platform will have the ability to lock the project-specific visits to prevent any modification of data once the project is closed. Once this option is activated, every user will have Read-Only access to the data.

14.4- Data handling and record keeping

The PIs are responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported. Data reported in the eCRF derived from source documents should be consistent with the source documents and discrepancies should be explained.

14.5- Confidentiality

The EDC software and MEDUSA databases and patient data reside on Georgetown University IRB-approved servers and a secure database for Sun Pharma Advanced Research Company Ltd (SPARC). Physical and software access to the servers and security is provided by GUMC investigators.

14.6- Retention of Records

Research records will be retained in accordance with site IRB policies.

14.7- Publications

The PIs will be responsible for publications of results from this trial. Responsibilities will include the following:

- Analyze and interpret data gathered in this study, and write publications from these data.
- Submit manuscripts to selected journals and address peer reviewers' comments.
- Submit abstracts to selected meetings and present data at the meetings.
- Determine authorship on the basis of the Uniform Requirements for Manuscripts.

15- LITERATURE REFERENCES

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