Protocol MP-101-01(b)

Tolerability, Pharmacokinetics, and Efficacy of MP-101 in the Treatment of Patients with Dementia-Related Psychosis and/or Agitation and Aggression

NCT03044249

Approval Date: 13Feb2018

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Confidential Information

MP-101

A Phase 2, double-blind, randomized, parallel, 10-week study of MP-101 (1 MP-101 dose arm), compared with placebo in patients with dementia-related psychosis and/or agitation and aggression. The starting dose will be 20 mg per day, with titration to a target dose of 60 mg per day.

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Protocol Approval Date: December 19, 2016
Protocol Amendment (a) Approval Date: February 24, 2017
Protocol Amendment (b) Approval Date: February 13, 2018

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1. Synopsis

Title of Study:
Tolerability, Pharmacokinetics, and Efficacy of MP-101 in the Treatment of Patients with Dementia-Related Psychosis and/or Agitation and Aggression

Rationale:
MP-101 (formerly known as LY2979165 ammonium monohydrate) is the alanine prodrug of LY2812223, a selective orthosteric metabotropic glutamate (mGlu) 2 receptor agonist. Study MP-101-01 is a Phase 2, multicenter, double-blind, randomized, parallel, 10-week study of MP-101 (1 MP-101 dose arm), compared to placebo in patients with dementia-related psychosis and/or agitation and aggression.

There are currently no approved therapies for the treatment of dementia-related psychosis and/or agitation and aggression. Antipsychotics are commonly prescribed off-label despite an association with increased risk of cerebral vascular adverse events such as stroke, increased all-cause mortality, as well as more rapid progression to severe dementia.

Metabotropic glutamate 2 receptors are localized in presynaptic terminals throughout the cortex and limbic brain structures. Activation of mGlu2 receptors suppresses excessive presynaptic release of glutamate; this excessive release may contribute to the development of psychosis. Administration of MP-101 produces potent preclinical antipsychotic, anti-stress, and analgesic effects.

The objectives of Study MP-101-01 are to assess the tolerability, pharmacokinetics (PK), and efficacy of MP-101 in patients with dementia-related psychosis and/or agitation and aggression.

Objectives and Endpoints:

Primary Objective and Endpoint

- To test the hypothesis that oral administration of once daily (QD) MP-101 will improve psychotic symptoms and/or agitation and aggression in patients with dementia when compared to placebo
    - Endpoint: Change from baseline to 10-week treatment endpoint in the Neuropsychiatric Inventory (NPI)-Psychosis subscale (combination of 2 items: hallucinations and delusions) and/or in the agitation/aggression domain.

Secondary Objectives and Endpoints

- To assess whether MP-101 is superior to placebo in the following: neuropsychiatric disturbances, caregiver distress, anxiety
    - Endpoints: Change from baseline to 10-week treatment endpoint in the following: Clinical Global Impression of Improvement (CGI-I); NPI Total Score; NPI-Core Total (combination of 3 items: hallucinations, delusions, and agitation/aggression); NPI Caregiver Distress; NPI domain of anxiety;
- To determine if MP-101 is safe and tolerable in patients with dementia-related psychosis and/or agitation and aggression
    - Endpoints: Treatment-emergent adverse events (TEAEs); Unified Parkinson's Disease Rating Scale Part III
- To assess the PK of MP-101 and its primary active metabolite, LY2812223, in patients with dementia-related psychosis and/or agitation and aggression

- Endpoint: Plasma PK data

Exploratory Objectives and Endpoints

- To assess whether MP-101 is superior to placebo in changes in patient behavior and caregiver burden
  - Endpoints: Change from baseline to 10-week treatment endpoint in the following: NPI domains of depression/dysphoria, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, sleep and nighttime behavior disorders, and appetite and eating disorders; Mini-Mental State Examination (MMSE); Zarit Burden Interview-22 (ZBI-22)
- To explore the effect of 5-hydroxytryptamine serotonin 2A receptor (HTR2A) and apolipoprotein E (APOE) genotypes on response to treatment
  - Endpoints: HTR2A single nucleotide polymorphism (SNP) rs7330461 genotype data; HTR2A SNP rs6313 (102T/C) genotype data; APOE genotype data
- To explore exposure-response relationships with efficacy and safety clinical endpoints as needed
  - Endpoints: Efficacy and safety clinical endpoints, as needed

Summary of Study Design:

Study MP-101-01 is a Phase 2, multicenter, double-blind, 1:1 randomized, parallel, 10-week study of MP-101 (1 MP-101 dose arm) compared to placebo in patients with dementia-related psychosis and/or agitation and aggression. All patients will be randomized to receive either placebo or MP-101. Randomization will be stratified by MMSE score and estimated glomerular filtration rate value.

Treatment Arms:

Patients will be randomized to the MP-101arm or the placebo arm at Visit 2 (Week 0). Patients in the MP-101 arm will begin dosing at 20 mg QD of study drug. If in the opinion of the investigator, the patient cannot tolerate the initial 20-mg QD dose of study drug (administered for the first week of dosing and assessed at or before Visit 3 [Week 1]) the patient will be discontinued from the study. Study drug intolerance will be determined by the investigator and includes TEAEs of special interest identified from prior studies, e.g., dizziness, nausea, and vomiting.

At Visit 3 (Week 1), the dose of MP-101 (or equivalent placebo) will be increased to 40 mg. If intolerance is reported at a dose of 40 mg between Visit 3 (Week 1) and Visit 4 (Week 2), the patient will be discontinued from the study.

At Visit 4 (Week 2), the dose of MP-101 (or equivalent placebo) will be increased to 60 mg. If intolerance is reported at a dose of 60 mg between Visits 4 (Week 2) and Visit 5 (Week 4), the patient will be asked to return for an unscheduled visit for down-titration to 40 mg. Patients down-titrated to 40 mg prior to Visit 5 (Week 4) will remain at this dose for the remainder of the study.

At Visit 5 (Week 4), the dose of MP-101 (or equivalent placebo) will be maintained at 60 mg. If intolerance is reported at a dose of 60 mg at Visit 5 (Week 4), the patient will be down-titrated to 40 mg and will remain at this dose for the remainder of the study. If intolerance is reported at a dose of either 40 mg or 60 mg beyond Visit 5 (Week 4) the subject will be discontinued from the study.

In order to maintain blinding, patients randomized to the placebo arm will undergo the identical up-titration procedures, with similar down-titration rules as described above.

Number of Patients:
Approximately 100 patients will be enrolled to obtain approximately 80 patients in the Evaluable population.

Statistical Analysis:
The primary treatment effect will be measured as the difference in the percentage of patients with a response on either the NPI-Psychosis or Agitation/Aggression subscales at the end of the treatment period. A patient with a 30% improvement from baseline on a subscale will be considered a responder for that subscale. A patient with a psychosis diagnosis at screening will be considered an overall responder with a response on the NPI-Psychosis subscale, a patient with a diagnosis of agitation/aggression at screening will be considered an overall responder with a response on the NPI-Agitation/Aggression subscale, and a patient with both diagnoses will be considered an overall responder with a response on either subscale. The primary analysis will use a one-sided Fisher's exact test with a 5% type 1 error rate. The primary population for analysis will include all randomized patients who take at least 1 dose of double-blind study treatment and complete Visit 5 (Week 4) with NPI efficacy data (i.e., the Evaluable population).

The primary analyses will be performed with patients grouped by treatment arm (i.e., MP-101 or placebo) regardless of their final dose level.

2. Schedule of Activities

Schedule of Activities for Protocol MP-101-01

	Screen	Treatment Period (10 Weeks)							Follow-up	ET
Visit Number	**V1**	**V2**	**V3[a]**	**V4**	**V5**	**V6**	**V7[a]**	**V8**	**V9**	
Week	**-1 to -5**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**11**	
Days from Randomization (target)	**-1 to-35**	**0**	**7**	**14**	**28**	**42**	**56**	**70**	**77**	
Visit Window (± days from target)				**2**	**2**	**2**		**2**	**2**	
Study site visit	x	x		x	x	x		x	x	x
Informed Consent (before any procedures/tests)	x									
Clinical Assessments										
Demographics, height	x									
Weight	x	x		x	x	x		x	x	x
Vital signs (BP and pulse)	x	x		x	x	x		x	x	x
Medical history and physical exam	x									
Neurological exams	x	x						x		x
TUG (if applicable)	x	x		x	x	x		x	x	
Concomitant medications	x	x	x	x	x	x	x	x	x	x
Inclusion/exclusion review	x	x[b]								
Hepatitis B surface antigen, Hepatitis C antibody, HIV	x									
Randomization		x								
Investigational product dispensing		x		x	x	x				
Dose administration at site		x		x	x					
Investigational product accountability				x	x	x		x		x
Symptom directed physical exam		x		x	x	x		x	x	x
Habits (alcohol, caffeine, nicotine, tobacco)	x	x	x	x	x	x	x	x		x
Safety Measures										
Adverse event assessment	x	x	x	x	x	x	x	x	x	x
C–SSRS[c]	x	x		x	x	x		x	x	x
Single 12-lead ECG	x	x		x	x			x	x	x
Efficacy and Outcome Measures										
NPI	x[b]	x[b]		x	x	x		x	x	x
CGI-S		x								
CGI-I					x			x	x	x
ZBI-22		x			x			x		
MMSE	x	x			x			x		x
UPDRS Part III		x			x			x	x	x
Laboratory Samples										
Clinical chemistry and hematology	x	x		x		x		x		x
Urinalysis	x	x						x		x
Plasma sample collection for PK analysis (see Table 9.1)				x	x	x		x		x
Plasma and serum collection for biomarker research		x				x		x		x
Blood for epigenetic research		x				x		x		x
Blood for assessment of APOE and HTR2A SNPs[d]		x								
Blood for pharmacogenetic research[d]		x								

Study Schedule Protocol MP-101-01 (continued)

Abbreviations: APOE = apolipoprotein E; BP = blood pressure; CGI-I=Clinical Global Impressions of Improvement; CGI-S=Clinical Global Impressions of Severity; C-SSRS= Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; ET = early termination; HIV = human immunodeficiency virus; HTR2A = 5-hydroxytryptamine serotonin 2A receptor; MMSE = Mini-Mental State Examination; NPI = Neuropsychiatric Inventory; PK = pharmacokinetic, SNP = single nucleotide polymorphism; TUG = Timed Up and Go test; UPDRS = Unified Parkinson's Disease Rating Scale; V = visit; Zarit Burden Interview-22= ZBI-22.

[a] Phone call.

[b] Patients must have at least one of the following at Visit 1 (screening) and Visit 2 (Week 0):

- an NPI score of ≥4 on either delusions or hallucinations individual items
- an NPI score of ≥6 on the Psychosis Subscale (combined delusions and hallucinations)
- an NPI score of ≥4 on agitation/aggression domain

[c] During screening, the "Lifetime/Recent-Clinical" version of the C-SSRS will be used. The "Since Last Visit-Clinical" version will be used for all subsequent assessments.

[d] Samples should be collected at V2, if possible, but may be collected at an alternate visit if they cannot be collected at V2.

3. Introduction

MP-101 (formerly known as LY2979165 ammonium monohydrate) is the alanine prodrug of LY2812223, a selective orthosteric metabotropic glutamate (mGlu) 2 receptor agonist. The objectives of Study MP-101-01 are to assess the tolerability, pharmacokinetics (PK), and efficacy of MP-101 in the treatment of patients with dementia-related psychosis and agitation/aggression.

Dementia is characterized by multiple cognitive deficits severe enough to interfere with daily functioning and affects approximately 6.5% of people over the age of 65 (Matthews et al. 2013) Dementia can be caused by numerous neurodegenerative disorders including (but not limited to) Alzheimer's disease (AD), dementia with Lewy bodies (DLB) and frontotemporal dementia (FTD). While cognitive impairment is the hallmark symptom of dementia, behavioral and psychological disturbances are almost invariably present at some point during the illness (Steinberg et al. 2008; Lyketsos et al. 2002) Among the most disturbing and burdensome of these symptoms are psychosis (hallucinations and delusions) as well as aggression and agitation (Rocca et al. 2010). These types of neuropsychiatric symptoms are among the most complex, stressful, and costly aspects of care and lead to poor health outcomes, including excess morbidity, mortality, hospital stays, and early placement in a nursing home (Kales et al. 2015; Wancata et al. 2003). There are currently no approved therapies for dementia-related psychosis or agitation/aggression. Antipsychotics are commonly prescribed off-label despite an association with increased risk of cerebral vascular adverse events (AEs) such as stroke, increased all-cause mortality (Wooltorton 2002, 2004; Hermann et al. 2004; Smith and Beier 2004), as well as more rapid progression to severe dementia (Schneider et al. 2006).

Metabotropic glutamate receptors are plasma-membrane-associated, G-protein-coupled proteins that modulate neuronal excitability function via presynaptic, postsynaptic, and glial mechanisms. There are currently 8 members of the mGlu receptor family (mGlu1-mGlu8) that vary in their primary sequence, tissue localization, agonist/antagonist pharmacology, and signal transduction pathways (Conn and Pin 1997). The mGlu2 and mGlu3 receptors are heavily distributed within cortical and limbic structures of the brain (e.g., prefrontal cortex, hippocampus, and amygdala) and localize predominantly on presynaptic nerve terminals (Tamaru et al. 2001). Activation of mGlu2/3 receptors by glutamate, or by other exogenous agonists, leads to the inhibition of synaptic glutamate release, thereby dampening downstream postsynaptic excitation. The mGlu2/3 receptor agonists are effective in animal models associated with hyper-glutamatergic tone (e.g., states associated with psychosis and stress/anxiety). Acute intraperitoneal administration of MP-101 produces potent antipsychotic, anti-stress, and analgesic effects in the rat. These effects are consistent with the known preclinical behavioral attributes of mGlu2/3 receptor agonists which have been tested in patients and have demonstrated clinical efficacy in schizophrenia and generalized anxiety disorder (Patil et al. 2007; Dunayevich et al. 2008). Additionally, MP-101 produces an mGlu2-dependent antidepressant-like effect in the mouse forced swim assay; potency and efficacy are comparable to that observed with the antidepressant imipramine.

Pimavanserin is a 5-hydroxytryptamine (serotonin) 2A (5-HT2A/HTR2A) receptor antagonist which has demonstrated efficacy in the treatment of psychosis in Parkinson's disease patients (Cummings et al. 2014) and has advanced to a Phase 3 study for dementia-related psychosis. Significant neuroanatomical overlap exists between mGlu2(3) and 5-HT2A receptors and strong pharmacological evidence supports interactions along key neural pathways (Marek et al. 2000). In rodent models, MP-101 has similar clinical effects to pimavanserin, providing further support for study of MP-101 for the treatment of patients with dementia-related psychosis.

As of December 2016, MP-101 has been administered to 116 healthy male subjects as single and multiple oral doses for up to 14 days in 3 clinical studies. These studies included: 1) a single-ascending dose (SAD) study in the 20- to 150-mg dose range (Study I4S-EW-HHCA [HHCA]), 2) a multiple-ascending dose (MAD) study in the 20 to 400 mg once daily (QD) dose range (Study I4S-EW-HHCB [HHCB]) and 3) a pharmacodynamic (PD) biomarker study evaluating the effect of single doses of MP-101 on the ketamine-induced magnetic resonance imaging (MRI) signal (Study I4S-EW-HHCC [HHCC]). The SAD study included a food effect evaluation and cerebrospinal fluid (CSF) sampling, and the MAD study included CSF sampling. In the MAD study, after multiple QD dosing of MP-101 in the 20- to 400-mg dose range, conversion of MP-101 to its active metabolite, LY2812223, was extensive; plasma exposure to MP-101 was generally <1% that of LY2812223. Plasma LY2812223 exposure at steady-state was dose proportional over the 20- to 400-mg dose range, and showed minimal accumulation in the 20-mg QD cohort. In plasma, the LY2812223 time of maximum concentration (t_{max}) at steady-state was approximately 4 hours, and terminal half-life ($t_{1/2}$) was approximately 11 hours, with the majority of drug eliminated within 24 hours. After administration of single 20- to 150-mg MP-101 doses, the mean urine recovery of LY2812223 in the first 24 hours postdose ranged from 44% to 62%, suggesting renal excretion is a major elimination pathway for LY2812223 (Study HHCA). After multiple QD dosing at 150 mg, CSF exposure to LY2812223 was achieved in all subjects by 7 hours postdose on Day 14 and ranged from 38 nM to 141 nM (Study HHCB).

The most common AEs reported in the 3 clinical studies were (in order of decreasing frequency): dizziness, vomiting, nausea, tiredness, and headache. In the MAD study, vomiting appeared to be a "first-dose" effect for most subjects (1 subject also had an episode of vomiting on Day 2, which did not recur with continued dosing). Nausea also tended to occur during the first 3 days of dosing, whereas dizziness tended to be reported later during dosing and at higher MP-101 doses (150 and 250 mg), but nausea did not persist with ongoing dosing. There were no significant changes in vital signs (blood pressure [BP] and heart rate), electrocardiograms (ECGs; including corrected QT interval [QTc]), and safety laboratory tests (biochemistry, hematology, and urinalysis) in subjects receiving MP-101.

To date, there have been no adverse drug reactions associated with administration of MP-101 in healthy subjects, for which AEs were mild (summarized above). In an elderly patient population with dementia-related psychosis and agitation/aggression, the mild AEs reported in healthy subjects may present a greater safety concern. Adverse events include reports of dizziness which could lead to gait instability and falls in an elderly dementia population. The risk for gait

instability will be assessed for ambulatory patients throughout Study MP-101-01 with the Timed Up and Go (TUG) test. Similarly, transient vomiting, unrelated to the dose, was reported in healthy subjects in the SAD and MAD studies. There is a greater risk of dehydration or aspiration in dementia patients. To improve patient safety, MP-101 exposure will be reduced in Study MP-101-01 (60-mg maximal dose in dementia patients vs. 400-mg QD dose in healthy subjects).

More detailed information about the known and expected benefits, risks, serious adverse events (SAEs), and reasonably anticipated AEs of MP-101 can be found in the Investigator's Brochure (IB).

4. Objectives and Endpoints

4.1. Primary Objective and Endpoint

- To test the hypothesis that oral administration of QD MP-101 will improve psychotic symptoms and/or agitation/aggression in patients with dementia when compared to placebo
    - Endpoint: Change from baseline to 10-week treatment endpoint in the Neuropsychiatric Inventory (NPI)-Psychosis subscale (combination of 2 items: hallucinations and delusions) and/or in the agitation/aggression domain.

4.2. Secondary Objectives and Endpoints

Secondary objectives and endpoints in patients with dementia-related psychosis and/or agitation and aggression are as follows:

- To assess whether MP-101 is superior to placebo in the following: neuropsychiatric disturbances, caregiver distress, and anxiety
    - Endpoints: Change from baseline to 10-week treatment endpoint in the following: Clinical Global Impression of Improvement (CGI-I); NPI Total Score; NPI-Core Total (combination of 3 items: hallucinations, delusions, and agitation/aggression); NPI Caregiver Distress (NPI-D) and NPI domains of anxiety
- To determine if MP-101 is safe and tolerable
    - Endpoints: Treatment-emergent adverse events (TEAEs); Unified Parkinson's Disease Rating Scale (UPDRS) Part III
- To assess the PK of MP-101 and its primary active metabolite, LY2812223
    - Endpoint: Plasma PK data

4.3. Exploratory Objectives and Endpoints

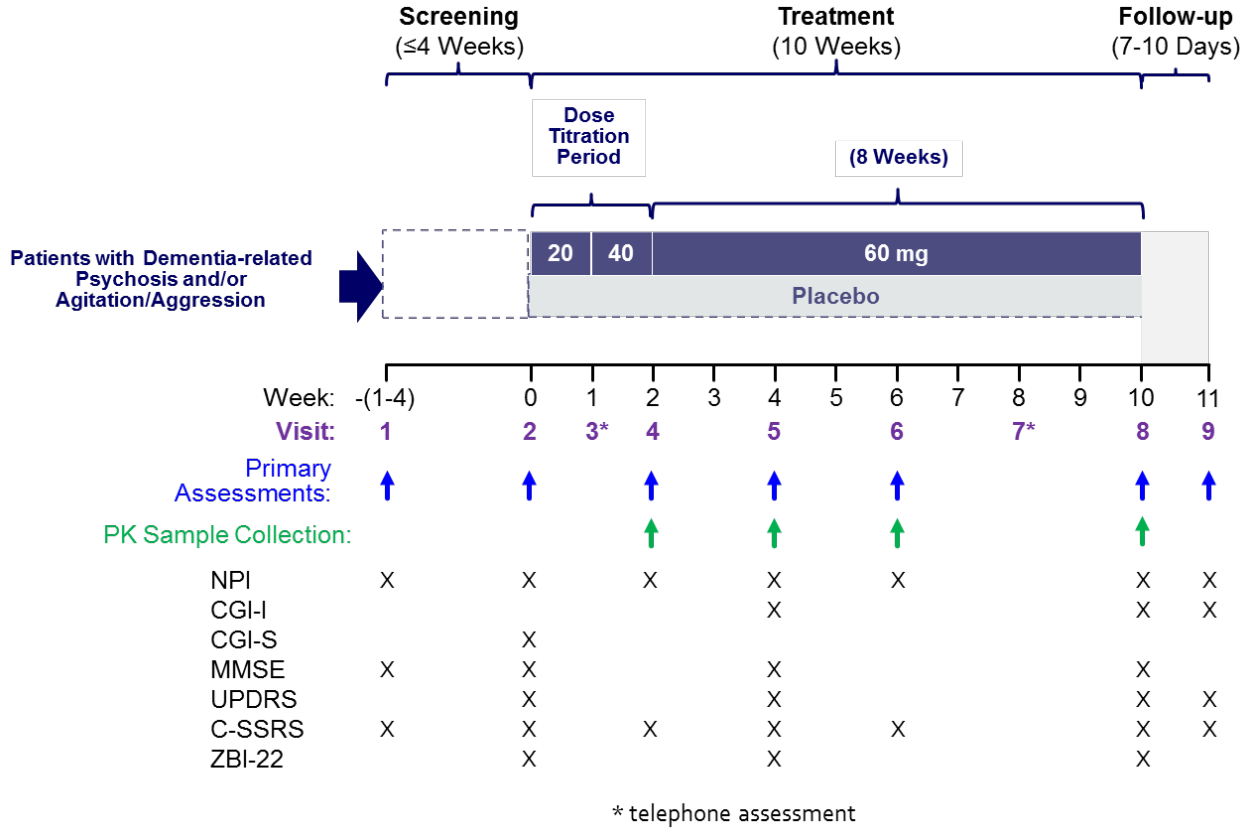
- To assess whether MP-101 is superior to placebo in changes in patient behavior and caregiver burden
    - Endpoints: Change from baseline to 10-week treatment endpoint in the following: NPI domains of depression/dysphoria, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, sleep and nighttime behavior disorders, and appetite and eating disorders; Mini-Mental State Examination (MMSE); Zarit Burden Interview-22 (ZBI-22)
- To explore the effect of HTR2A and apolipoprotein E (APOE) genotypes on response to treatment
    - Endpoints: HTR2A single nucleotide polymorphism (SNP) rs7330461 genotype data; HTR2A SNP rs6313 (102T/C) genotype data; APOE genotype data
- To explore exposure-response relationships with efficacy and safety clinical endpoints as needed
    - Endpoints: Efficacy and safety clinical endpoints, as needed

5. Study Design

5.1. Overall Design

Study MP-101-01 is a Phase 2, multicenter, double-blind, randomized, parallel, placebo-controlled, 10-week study of MP-101, consisting of screening, treatment, and follow-up periods, in patients with dementia-related psychosis and/or agitation and aggression. All patients will be randomized 1:1 to receive either placebo or MP-101.

Figure 5.1. Illustrates the study design



Abbreviations: CGI-I=Clinical Global Impressions of Improvement; CGI-S=Clinical Global Impressions of Severity; C-SSRS = Columbia Suicide Severity Rating Scale; MMSE = Mini-Mental State Examination; NPI = Neuropsychiatric Inventory; PK = pharmacokinetic; UPDRS = Unified Parkinson's Disease Rating Scale; ZBI-22 = Zarit Burden Interview-22.

Figure 5.1. Illustration of study design for protocol MP-101-01.

5.2. Number of Participants

Approximately 100 patients will be enrolled to obtain approximately 80 patients in the Evaluable population (see Section 10.2).

5.3. End of Study Definition

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

5.4. Scientific Rationale for Study Design

The primary objective of this study is to test the hypothesis that MP-101, when administered at a target dose of 60 mg QD, will improve psychotic symptoms and/or agitation and aggression in patients with dementia when compared to placebo.

A randomized, double-blind, placebo-controlled design will be utilized in this study. Randomization minimizes systematic bias in the selection and assignment of patients to study therapy and provides justification for inferential statistical methods to be used on data from this study. Strategies to minimize placebo response include 1:1 randomization, blinding, and centralized rater training. Using an appropriate concurrent placebo arm enables direct statistical estimation of benefits and harms due to study therapy and minimizes bias in the assessment and interpretation of observed treatment effects. The details regarding dose selection are described in Section 5.5.

5.5. Justification for Dose

The MP-101 oral dose range of 20 to 60 mg QD was selected based on current in vitro, preclinical, and clinical PK and PD data. The dose titration scheme of 20 mg QD for the first week and 40 mg QD for the second week, with a final titration to 60 mg QD on the third week, is intended to minimize nausea and vomiting.

Pharmacokinetic data from 3 previous clinical studies of MP-101 (SAD and MAD studies in healthy subjects [Studies HHCA and HHCB], and a biomarker study of ketamine-induced pharmacological magnetic resonance imaging [phMRI] signal in healthy male subjects [Study HHCC]), were used to simulate LY2812223 CSF exposure levels. In all prior clinical studies in healthy subjects, MP-101 doses up to 400 mg QD for 14 days were generally well tolerated.

A dose of 60 mg demonstrated target engagement (phMRI study) and was predicted to achieve a range of LY2812223 CSF concentrations (median maximum observed drug concentration [C_{max}] approximately 30 nM, 90% confidence interval [CI]: 10 nM to 80 nM) that would exceed the mGlu2 cyclic adenosine monophosphate (cAMP) half maximal effective concentration (EC_{50}) of 5.6 nM for 24 hours, and the mGlu2 cAMP concentration for maximum achievable response concentration (EC_{100}) of approximately 50 nM for at least 10 hours, in healthy subjects with normal renal function (Eli Lilly and Company, data on file). In the CSF sampling cohort in Study HHCB, CSF exposure to LY2812223 at steady-state was achieved in all subjects at approximately 7 hours postdose, and ranged from 38 nM to 141 nM.

This study population includes patients with impaired renal function (lower estimated glomerular filtration rate [eGFR] limit = 45 ml/min/1.73m^2). In a patient with an eGFR of 45 ml/min/1.73m^2, the mean predicted plasma LY2812223 C_{max} at steady-state for a 60 mg QD MP-101 dosing regimen is approximately 3600 nM (90% CI: 2800 nM to 4800 nM). These

values are lower than those observed at steady-state for a 400 mg QD dose in Study HHCB (geometric mean LY2812223 C_{max} during a dosing interval at steady-state: 10900 nM; 90% CI: 7880 nM to 15600 nM); where MP-101 doses up to 400 mg were well tolerated. Concentrations in CSF may be expected to be higher for this population as well, in a manner consistent with the plasma concentrations. These estimations assume that MP-101 and LY2812223 are primarily renally eliminated in this patient population, and that LY2812223 exposure is dose proportional.

Based on these data, a 60-mg dose would be expected to provide efficacious CSF exposures in this population, in addition to adequate safety to be able to test this dose in Phase 2 studies.

6. Study Population

Eligibility of patients for study enrollment will be determined following screening, which will include a full medical history, physical examination, clinical laboratory testing, and an ECG.

Enrollment must be within 35 days of screening.

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

6.1. Inclusion Criteria

Patients are eligible for inclusion in the study only if they meet all of the following criteria at screening:

Type of Patient – Patient and Disease Characteristics

[1] Males or females (of non-childbearing potential) ≥50 years of age

Note: Females of non-childbearing potential are defined as women ≥60 years of age, postmenopausal women ≥50 and <60 years of age who have had a cessation of menses for at least 12 months, or women who are congenitally or surgically sterile (i.e., have had a hysterectomy or bilateral oophorectomy or tubal ligation).

To confirm postmenopausal status for women ≥50 and <60 years of age who have had a cessation of menses for at least 12 months, follicle stimulating hormone levels will be assessed and must be ≥40 mIU/mL.

Note: Males must agree to use 2 forms of highly effective birth control (see below) with female partners of childbearing potential while enrolled in the study, and for at least 28 days following the last dose of investigational product.

The following birth control methods are considered highly effective:

- Oral, injectable, or implanted hormonal contraceptives
- Condom with a spermicidal foam, gel, film, cream, or suppository
- Occlusive cap (diaphragm or cervical/vault caps) with a spermicidal foam, gel, film, cream, or suppository
- Intrauterine device
- Intrauterine system (e.g.,, progestin-releasing coil)
- Vasectomized male (with appropriate postvasectomy documentation of the absence of sperm in the ejaculate).

[2] Ambulatory (with or without walking device) with a stable gait as assessed with a TUG test (Okumiya et al. 1998; Nordin et al. 2006) that must be completed in

≤30 seconds. The test may be repeated once with instruction. Patients in wheelchairs are also eligible and do not need to complete the TUG test.

[3] Have an MMSE score of 10 to 24.

[4] Meets clinical criteria for one of the following disorders: dementia associated with Parkinson's disease, dementia with Lewy bodies, possible or probable Alzheimer's disease, frontotemporal degeneration spectrum disorders, vascular dementia.

[5] Must be able to communicate verbally.

[6] At Visit 1 (screening) and Visit 2 (Week 0) have at least ONE of the following:

- an NPI score of ≥4 on either delusions or hallucinations individual items
- an NPI score of ≥6 on the Psychosis Subscale (combined delusions and hallucinations)
- an NPI score of ≥4 on agitation/aggression domain

[7] Have a reliable caregiver to accompany the patient to all study visits. This caregiver must provide written informed consent to participate and be in frequent contact with the patient (defined as spending at least 4 hours/day at least 4 days/week with the patient and who is knowledgeable about the patient's daytime and nighttime behaviors). The caregiver must be able to communicate with site personnel, and in the opinion of the investigator, must understand the written protocol-specified questionnaires. If a caregiver cannot continue, one replacement caregiver will be allowed if the above criterion is met.

[8] Must be on a stable dose of cholinesterase inhibitor and/or memantine, if applicable.

[9] If taking antipsychotic drugs or any drug intended to treat psychosis, must be on a stable treatment regimen for ≥1 month prior to the baseline visit (Visit 2). Note: If the patient has recently stopped taking antipsychotic drugs or any drug intended to treat psychosis, he or she must have discontinued treatment at least 4 weeks before Visit 1 (screening).

[10] Have venous access sufficient to allow for blood sampling per the protocol.

[11] Have clinical laboratory test results within normal reference range for the population or investigative site, or results with acceptable deviations that are judged to be not clinically significant by the investigator.

[12] Are capable of participating in all study assessments in the opinion of the investigator.

Informed Consent

[13] Are able and willing to provide consent (patients and caregivers).

6.2. Exclusion Criteria

Patients will be excluded from participating in the study if they meet any of the following criteria:

Diagnostic Assessments

[14] Have a history of significant psychotic disorders (including, schizophrenia, delusional disorder, substance abuse psychosis that lasted over 6 months, major depressive disorder or bipolar disorder with psychotic episodes).

[15] Has a history of ischemic stroke within the last 12 months or any evidence of hemorrhagic stroke.

Medical Conditions

[16] Have renal impairment as defined by eGFR <45 ml/min/1.73m^2 using the Chronic Kidney Disease Epidemiology Collaboration Cystatin C Equation (Grubb et al. 2010; Peralta et al. 2011; Inker et al. 2012).

[17] Have significant cardiovascular, respiratory, gastrointestinal, renal, hematologic, or oncologic comorbidities that could impact patient safety and study participation over 10 weeks.

[18] Have a history of seizures (other than remote history of childhood febrile seizure) or other condition that would place the patient at increased risk of seizures. Patients taking anticonvulsants for seizure control are also excluded.

[19] Are, in the investigator's judgment, at risk for suicide, including patients who have answered 'yes' to either Question 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) or Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the Suicidal Ideation portion of the Columbia Suicide Severity Rating Scale (C-SSRS), or answered 'yes' to any of the suicide-related behaviors (actual attempt, interrupted attempt, aborted attempt, preparatory act or behavior) on the Suicidal Behavior portion of the C-SSRS; and the ideation or behavior occurred within a month of Visit 1 (screening).

[20] Have a Fridericia's corrected QT interval (QTcF) >450 ms (males) or 470 ms (females) at Visit 1 (screening).

Prior/Concurrent Clinical Trial Experience

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

[22] Have participated, within the last 30 days, in a clinical trial involving an investigational product. If the previous investigational product has a long half-life, 3 months or 5 half-lives (whichever is longer) must have passed.

Other Exclusions

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

[24] Are Mediti Pharma, Inc. or Eli Lilly and Company employees or immediate family members of employees; or are employees of any third-party involved in the study who require exclusion of their employees. This pertains to both caregivers and patients.

[25] In the opinion of the investigator or sponsor, are unsuitable for inclusion in the study.

6.3. Lifestyle and/or Dietary Requirements

Throughout the study, patients may undergo medical assessments and review of compliance with requirements before continuing in the study.

Study participants should be instructed not to donate blood or blood products during the study or for 8 weeks following the study.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened 1 time with sponsor approval. The time period from screen fail to rescreen will be determined by the investigator. If rescreening is performed, a new informed consent form (ICF) must be signed, and the patient will be assigned a new identification number. Additionally, all screening procedures must be conducted at rescreen to ensure all eligibility criteria are met.

At screening and throughout the study, procedure/lab retests may be conducted at the discretion of the investigator and do not constitute a rescreen.

7. Treatment

7.1. Treatment Administration

This study compares 60-mg MP-101 versus matching placebo administered orally QD for 10 weeks. Table 7.1 shows the treatment regimens.

Three capsules of 20-mg MP-101 and/or placebo will be ingested with 240 mL of room temperature water with the patient in an upright position. Doses should be administered at approximately the same time in the morning each day. For all visits that include PK sampling, the approximate start and stop times of food consumption prior to dosing and up to 4 hours postdose will be recorded as detailed in Section 9.5.1.

Table 7.1. Treatment Regimens

	Dose		
Treatment Arm	**Week 0**	**Week 1**	**Week 2 through Week 9**
MP-101	20-mg MP-101 QD (1 × 20-mg caps and 2 placebo caps)	40-mg MP-101 QD (2 × 20-mg caps and 1 placebo cap)	60-mg MP-101 QD[a] (3 × 20-mg caps)
Placebo	Placebo QD (3 placebo caps)	Placebo QD (3 placebo caps)	Placebo QD (3 placebo caps)

Abbreviations: caps = capsule; QD = once daily; TEAE= treatment-emergent adverse event.

[a] Refer to Figure 7.1 for the dose titration schedule.

The investigator or designee is responsible for:

- explanation of the correct use of the investigational product(s) to the patient/caregiver/site personnel,
- verification that instructions are followed properly,
- maintenance of accurate records of investigational product receipt, dispensing and collection, and
- return of all unused and used medication to Mediti Pharma, Inc. or its designee at the end of the study.

Note: In some cases, sites may destroy the material if, during the investigative site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose of clinical trial materials.

7.1.1. Packaging and Labeling

The specific dose strength of the drug product (DP), MP-101 DP, corresponds to the free acid equivalent (i.e., 20-mg MP-101 DP is equivalent to 20-mg LY2979165 free acid equivalent).

MP-101 will be provided in a wallet design (blister pack) containing blister strips. Each wallet will contain 9 rows of 3 capsules each. Placebo capsules that look identical to MP-101 capsules, but contain no active ingredient, will also be provided.

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

7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomized in a 1:1 ratio (MP-101:placebo) to double-blind treatment at Visit 2 (Week 0). Assignment to treatment arms will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). The IWRS will be used to assign blister packs containing double-blind investigational product to each patient. Blister packs will be dispensed at Visits 2, 4, 5, and 6, (Weeks 0, 2, 4, and 6, respectively). During the patient's visit, the site will access the IWRS for the correct blister pack numbers to dispense.

Randomization will be stratified by baseline MMSE score and eGFR value:

- MMSE < 16 or MMSE $\geq$ 16
- eGFR <60 or eGFR $\geq$ 60

7.2.1. Timing of Dose Administration

The dose will be administered at approximately the same time in the morning each day. Patients will record the actual time of each dose of study drug and the time of food consumption before and after each dose; this information will be collected.

7.3. Blinding

Blinding will be maintained throughout the conduct of the trial until all data are verified to an acceptable level of quality and locked.

Select individuals may gain access to unblinded data prior to the final database lock to initiate the final population PK model development. The individuals and unblinded data will be specified in the unblinding plan section of the Statistical Analysis Plan (SAP) or a separate unblinding plan document.

If, in the opinion of the investigator or the Mediti Pharma, Inc. clinical research physician (CRP) or designee, unblinding of patients is necessary for the management of adverse or other clinically relevant events, the patients' treatment code will be made available.

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

If an investigator, site personnel performing assessments, or patient is unblinded, the patient must be discontinued from the study. In cases where there are ethical reasons to have the patient remain in the study, the investigator must obtain specific approval from a Mediti Pharma, Inc. or designated CRP for the patient to continue in the study.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety is the primary consideration in

making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Mediti Pharma, Inc. CRP prior to unblinding, unless a delay compromises patient safety. If a patient's treatment assignment is unblinded, Mediti Pharma, Inc. must be notified immediately.

Upon completion of the study, all codes must be returned to Mediti Pharma, Inc. or its designee.

7.4. Dose Titration

Figure 7.1 illustrates the dose titration schedule.

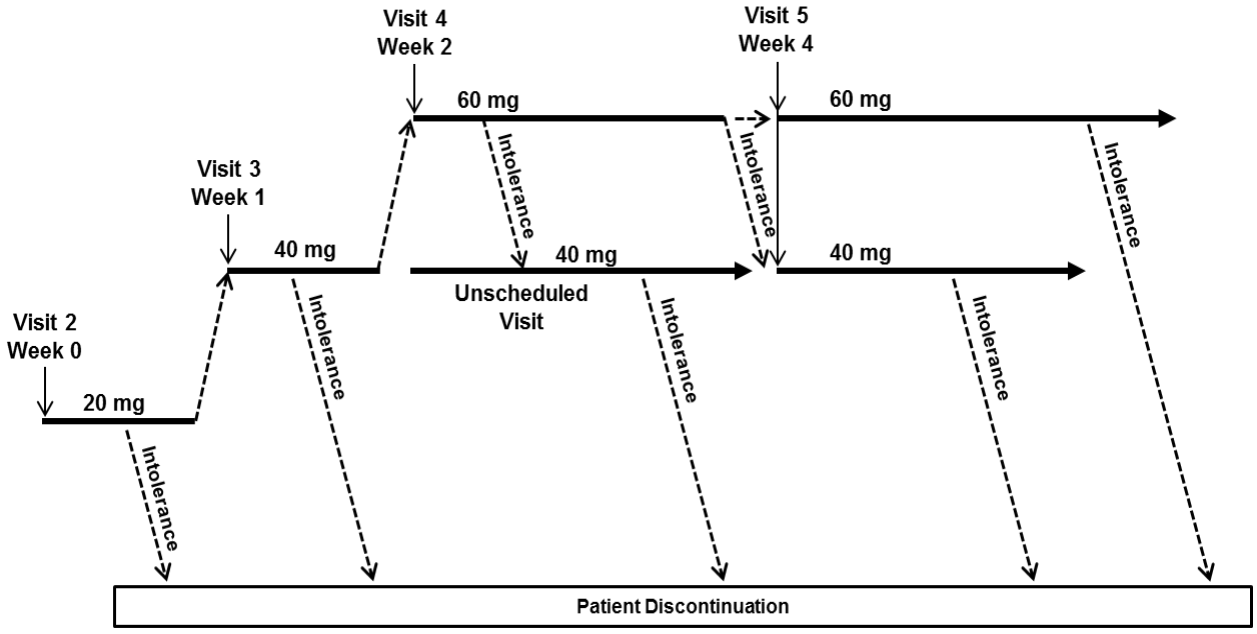


Figure 7.1. Dose titration schedule for protocol MP-101-01.

At Visit 2 (Week 0), patients will be randomized to the MP-101 arm or the placebo arm. All patients will start at a dose of 20 mg or equivalent placebo (Figure 7.1). If intolerance is reported at a dose of 20 mg between Visit 2 (Week 0) and Visit 3 (Week 1), the patient will be discontinued from the study. Intolerance is defined as the inability to tolerate TEAEs such as dizziness, nausea, and vomiting, which in the opinion of the investigator are possibly related to MP-101.

At Visit 3 (Week 1), the dose of MP-101 (or equivalent placebo) will be increased to 40 mg. If intolerance is reported at a dose of 40 mg between Visit 3 (Week 1) and Visit 4 (Week 2), the patient will be discontinued from the study.

At Visit 4 (Week 2), the dose of MP-101 (or equivalent placebo) will be increased to 60 mg. If intolerance is reported at a dose of 60 mg between Visits 4 (Week 2) and 5 (Week 4), the patient will be asked to return for an unscheduled visit for down-titration to 40 mg. Patients down-titrated to 40 mg prior to Visit 5 (Week 4) will remain at this dose for the remainder of the study.

At Visit 5 (Week 4), the dose of MP-101 (or equivalent placebo) will be maintained at 60 mg. If intolerance is reported at a dose of 60 mg at Visit 5 (Week 4), the patient will be down-titrated to 40 mg and will remain at this dose for the remainder of the study. If intolerance is reported at a dose of either 40 mg or 60 mg beyond Visit 5 (Week 4), the subject will be discontinued from the study.

7.5. Preparation/Handling/Storage/Accountability

Only participants enrolled in the study or their designated caregivers may receive investigational product and only authorized site staff may supply study treatment. All study treatments should be stored in an environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (such as receipt, reconciliation and final disposition records). A Mediti Pharma, Inc. delegate (e.g., site monitor) will conduct an accountability assessment.

7.6. Treatment Compliance

Patient compliance with investigational product will be assessed at each visit. Compliance will be assessed by direct questioning and documentation of returned capsules. Patient compliance with study drug will also be recorded in the patient diary.

Patients who are noncompliant will be discontinued from the study. A patient will be considered noncompliant if he or she misses more than 5 consecutive days of investigational product at 60 mg, or more than 10 cumulative days of investigational product at 60 mg during the study. Similarly, a patient will be considered noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of medication.

7.7. Concomitant Therapy

Patients on stable concomitant medication at the time of study entry (e.g., AChEIs) should continue their regular, unchanged dose throughout the study. Any medication used during the course of the study must be documented. A list of Excluded Concomitant Medications is presented in Table 7.2. Questions concerning the excluded medications should be directed to the sponsor. Use of any of the listed medications would result in either a screen fail (see Section 6.2) or discontinuation from the study.

Patients with worsening psychosis or agitation/aggression requiring rescue therapy will be withdrawn from the study.

Table 7.2. List of Excluded Concomitant Medications

Drug Class
Opioids, tramadol, ketorolac except occasional use as needed
Antiemetics (except occasional use as needed metoclopramide, domperidone, other dopamine receptor blockers)
Antihistamines (except occasional use as needed)
Hydroxyzine (except occasional use as needed)
Hypnotics
Lithium
Psychostimulants (modafanil)
Skeletal muscle relaxants (except occasional use as needed)

7.8. Treatment after the End of the Study

MP-101 will not be made available to patients after conclusion of the study.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

8.1.1. Permanent Discontinuation from Study Treatment

Discontinuation of dosing for abnormal liver tests should be considered by the investigator when a patient meets 1 of the following conditions, after consultation with the Sponsor designated medical monitor:

- alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8 × upper limit of normal (ULN)
- alanine aminotransferase or AST >5 × ULN for more than 2 weeks
- alanine aminotransferase or AST >3 × ULN and total bilirubin level (TBL) >2 × ULN or prothrombin time >1.5 × ULN
- alanine aminotransferase or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- alkaline phosphatase (ALP) >3 × ULN
- alkaline phosphatase >2.5 × ULN and TBL >2 × ULN
- alkaline phosphatase >2.5 × ULN with the appearance of fatigue, nausea, vomiting, right-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

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

- the occurrence of worsening psychosis and/or agitation or aggression requiring rescue therapy
- the occurrence of an SAE that in the opinion of the investigator would preclude the patient from continuing in the study
- the occurrence of a clinically significant event, which is defined as a moderate (Grade 2) AE, laboratory result, ECG finding, or vital sign change based on the Common Terminology Criteria for Adverse Events v4.03 (CTCAE) or most current version, that in the opinion of the investigator would preclude the patient from continuing in the study. Clinically significant events of special interest include vomiting or “dizziness” associated with balance and gait instability as assessed for ambulatory patients using the TUG test

For patients who discontinue the investigational product early, sites will make every reasonable effort to ensure that patients have procedures performed as shown in the Schedule of Activities (Section 2).

8.1.2. Discontinuation of Inadvertently Enrolled Patients

If the sponsor or investigator identifies a patient who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the Mediti Pharma, Inc. CRP or designee and the investigator to determine if the patient may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the Mediti Pharma, Inc. CRP or designee to allow the inadvertently enrolled patient to continue in the study with or without treatment with investigational product.

8.2. Discontinuation from the Study

Patients may be discontinued in the following circumstances:

- enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- investigator decision
    - the investigator decides that the patient should be discontinued from the study
    - if the patient, for any reason, requires treatment with another therapeutic agent that is intended for the treatment of psychosis, discontinuation from the study occurs prior to introduction of the new agent
- patient decision
    - the patient and/or caretaker requests patient withdrawal
- sponsor decision

If a patient discontinues the study early, the site will make every reasonable effort to have the patient return for an early termination visit to have end-of-study procedures performed as shown in the Schedule of Activities (Section 2). If the patient does not return, this will not be considered a protocol deviation.

8.3. Patients Lost to Follow-up

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

9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities, detailing the study procedures and their timing.

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

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

Investigators must document their timely review of each laboratory safety report.

9.1. Efficacy Assessments

9.1.1. Primary Efficacy Assessment

The primary endpoint is the response on the NPI-Psychosis subscale items of delusions and hallucinations and/or the agitation/aggression domain.

Neuropsychiatric Inventory (NPI; Cummings et al. 1994).
The NPI is a tool for assessing psychopathology in patients with brain disorders (i.e., AD and other dementias). Information is obtained from an informed caregiver who is familiar with the patient's behavior. Ten behavioral and 2 neurovegetative areas are included in the NPI: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, sleep and nighttime behavior disorders and appetite and eating disorders. An initial question assesses the 10 items and 2 neurovegetative evaluations of the scale. If the answer to the initial question is 'no', no further questions are pursued. If the answer is 'yes', sub questions are asked; ratings of the frequency and severity of the behavior(s) are determined by the caregiver according to the criteria provided with each behavior. Distress induced in the caregiver by each behavior is also rated. Therefore, a total of 4 scores are computed for each behavior type: frequency, severity, total (frequency × severity), and caregiver distress (Cummings 2009).

9.1.2. Secondary Efficacy Assessments

The secondary endpoints are listed below.

Clinical Global Impression of Improvement (CGI-I; Guy et al. 1976)

The CGI-I is a 7-point scale that requires the clinician to assess how much the patient's illness has improved or worsened relative to baseline (Visit 2). The scale ranges from 1 (very much improved) to 7 (very much worse).

Neuropsychiatric Inventory (NPI; Cummings et al. 1994)
Neuropsychiatric disturbances, caregiver distress, and other key parameters of patient behavior in this study will be measured using the NPI total score, the NPI Domains of anxiety, sleep and

nighttime behavior disorders, and the NPI Caregiver Distress (NPI-D) score. A detailed description of NPI scoring can be found in Section 9.1.1.

Mini-Mental State Examination (MMSE; Folstein et al. 1975)
The MMSE is a brief assessment used to assess cognitive function. The assessment is a simple, 30-question, pen-and-paper test that evaluates attention, orientation, memory, registration, recall, calculation, language, and the ability to draw a complex polygon (Arevalo-Rodriguez et al. 2015). The range for the total MMSE score is 0 to 30, with lower scores indicating greater impairment.

Unified Parkinson's disease Rating Scale Part III (UPDRS; Fahn, 1987)
Part III of the UPDRS is an investigator-scored scale used to assess the motor symptoms of patients with Parkinson's disease. The investigator indicates if the patient is receiving medication for treating Parkinson's disease symptoms (specifically levodopa, and the time since the last dose) and the patient's clinical response to the medication. The investigator rates the patient on 14 items based on observation or the performance of a task the patient performs (even in the context of any comorbidities) on a 5-point scale. The scores range from 0 to 4, with higher scores indicate greater impairment.

9.1.3. Exploratory Efficacy Assessments

The exploratory endpoints are listed below.

Neuropsychiatric Inventory (NPI; Cummings et al. 1994)
Changes in patient behavior as measured by the following NPI domains: depression/dysphoria; elation/euphoria, apathy/indifference, disinhibition, irritability/liability, aberrant motor behavior, and appetite and eating disorders. A detailed description of NPI scoring can be found in Section 9.1.1.

Zarit Burden Interview-22 (ZBI-22; Zarit et al. 1980)

Changes in caregiver burden will be assessed using the Zarit Burden Interview-22 (ZBI-22). The ZBI-22 is a 22-point scale used to assess caregiver burden in the dementia patient population (Zarit et al. 1980). Each of the 22 items is rated on a scale of 0 to 4, where 0 = never, 1 = rarely, 2 = sometimes, 3 = frequently, 4 = nearly always. The total score of the ZBI-22 is the sum of those 22 items.

9.2. Adverse Events

Investigators are responsible for monitoring the safety of patients who have entered this study and for notifying Mediti Pharma, Inc. or its designee to any event that is deemed clinically significant, even if this event may be considered an unanticipated benefit to the patients.

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

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

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

After the ICF is signed, study site personnel will record, via CRF, the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. Additionally, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs.

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

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

The investigator answers yes/no when making this assessment.

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

If a patient's investigational product is discontinued as a result of an AE, study site personnel must report this to Mediti Pharma, Inc. or its designee via CRF or designated data transmission methods, clarifying, if possible, the circumstances leading to discontinuation of treatment.

9.2.1. Serious Adverse Events

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

- death
- initial or prolonged inpatient hospitalization
- considered life-threatening
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason: important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious based on best medical judgment

Study site personnel must alert Mediti Pharma, Inc., or its designee, of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

As with AEs, SAE reporting begins after the patient has signed informed consent.

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

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

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

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

9.2.2. Complaint Handling

Mediti Pharma, Inc. collects product complaints on investigational products and drug delivery systems used in clinical trials in order to ensure the safety of study participants, monitor quality, and facilitate process and product improvements.

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

9.3. Treatment of Overdose

Patients receiving more than 60 mg/day of MP-101 (or placebo) will be noted in the CRF. It is not expected that doses of up to 400 mg/day will result in any TEAEs or SAEs in patients based on prior studies in healthy subjects. Patients who receive more than 60 mg/day will be monitored for side effects and treated appropriately for emergent symptoms (e.g., hydration or inpatient monitoring when appropriate). There are no specific antidotes for MP-101. Significant misdosing or TEAEs related to misdosing may result in discontinuation from the study, but will remain at the discretion of the investigator after consultation with the Mediti Pharma, Inc. CRP or designee. Patients with SAEs related to misdosing or overdose will be discontinued from the study.

9.4. Safety

9.4.1. Physical and Neurological Examination

Physical and neurological examinations will be conducted according to the Schedule of Activities (Section 2) and as clinically indicated.

Body weight and height will be recorded. Physical examinations will include assessment of general appearance, skin, head and neck, lymph nodes, thyroid, abdomen (bowel sounds and liver and spleen palpation), back (costovertebral angle tenderness), and musculoskeletal, cardiovascular, and respiratory systems. Neurological examinations will include assessment of mental status, cranial nerves, muscle strength, tone, and bulk, motor and sensory systems, muscle stretch reflexes, coordination, and balance and gait. Gait and balance will be assessed with the TUG test (Appendix 5) for ambulatory patients. The physical and neurological examination will be performed by a physician, nurse practitioner, or physician's assistant holding appropriate delegation.

If a clinically meaningful change is noted during the study, an additional full neurological examination will be performed as soon as possible, along with any other medical follow-up deemed necessary by the investigator.

Any clinically significant change from baseline (Visit 2 [Week 0]) on follow-up physical and neurological examinations should be reported to Mediti Pharma, Inc. or its designee as an AE via CRF.

9.4.2. Vital Signs

For each patient, vital signs measurements should be conducted according to the Schedule of Activities (Section 2) and the provided study-specific recommendations

Blood pressure and pulse rate should be measured after at least 5 minutes in the supine position.

Orthostatic BP measurements are to be obtained if the patient complains of orthostatic lightheadedness. Blood pressure will be obtained with the patient supine for 5 minutes and then after 3 minutes standing. Additional vital signs may be measured during each study period if warranted and agreed upon between the sponsor and investigator.

Any clinically significant findings from vital signs measurement that result in a diagnosis and that occur after the patient receives the first dose of study treatment should be reported to Mediti Pharma, Inc. or its designee as an AE via CRF.

9.4.3. Electrocardiograms

For each patient, a single 12-lead digital ECG will be collected according to the Schedule of Activities (Section 2) and the provided study-specific recommendations.

Electrocardiograms should be recorded before collecting any blood for safety or PK tests, when possible. Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. Electrocardiograms may be obtained at additional times, when deemed clinically necessary. All ECGs recorded should be stored at the investigational site.

Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the

patient is still present, to determine whether the patient meets entry criteria at the relevant visit(s) and for immediate patient management, should any clinically relevant findings be identified.

If a clinically significant finding is identified (including, but not limited to, changes in QTcF from baseline) after enrollment, the investigator will determine if the patient can continue in the study. The investigator or qualified designee is responsible for determining if any change in patient management is needed, and must document his/her review of the ECG printed at the time of collection. Any new clinically relevant finding should be reported as an AE.

Any clinically significant findings from ECGs that result in a diagnosis and that occur after the patient receives the first dose of the investigational product, should be reported to Mediti Pharma, Inc., or its designee, as an AE via CRF.

9.4.4. Laboratory Tests

For each patient, laboratory tests detailed in Appendix 2 should be conducted according to the Schedule of Activities (Section 2) and the study-specific laboratory manual.

Any clinically significant findings from laboratory tests that result in a diagnosis and that occur after the patient receives the first dose of investigational product should be reported to Mediti Pharma, Inc. or its designee as an AE via CRF.

9.4.5. Other Tests

9.4.5.1. Columbia Suicide Severity Rating Scale

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

Terms captured by the use of the C-SSRS can be mapped to Columbia Classification Algorithm for Suicide Assessment (Posner et al. 2007) to facilitate future pooling of data.

The first time the scale is administered in this study, the C-SSRS "Lifetime/Recent-Clinical" version will be used, and the findings will constitute the baseline assessment. The "Since Last Visit-Clinical" version will be used for all subsequent assessments. If a suicide-related thought or behavior is identified at any time during the study, a thorough evaluation will be performed by a study physician, and appropriate medical care will be provided. If, based on administration of the C-SSRS, it is determined that suicide-related behaviors have occurred, then the additional information will be collected to allow for a more complete assessment of these behaviors.

9.4.6. Safety Monitoring

The Mediti Pharma, Inc. CRP or designee, and Chorus will monitor safety data throughout the course of the study. Chorus will oversee the formal and periodic safety reviews conducted during the study.

These safety reviews include the review of SAEs within time frames mandated by company procedures, as well as the review of evolving aggregate safety data within the study by appropriate methods. This review will include the assessment of:

- trends in safety data
- adverse events including monitoring of vomiting or dizziness associated with balance and gait instability as assessed using the TUG test

If a patient experiences elevated ALT ≥3 × ULN, ALP ≥2 × ULN, or TBL ≥2 × ULN, clinical and laboratory monitoring should be initiated by the investigator and continue until resolution with further treatment as clinically indicated. To ensure patient safety and comply with regulatory guidance, the investigator is to consult with the Mediti Pharma, Inc. CRP or designee regarding collection of specific recommended clinical information and follow-up laboratory tests (see Appendix 4).

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, only members of the Assessment Committee (see Section 10.3.7) can conduct additional analyses of the safety data. Furthermore, the entire study may be stopped in the event of safety concerns over drug related adverse events.

9.5. Pharmacokinetics

9.5.1. Pharmacokinetic Sampling

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples will be collected from all patients, for a total of 5 scheduled samples per patient, to determine the plasma concentrations of MP-101, and its primary active metabolite LY2812223. The sparse sampling scheme in Table 9.1 will be used.

Table 9.1. Plasma Pharmacokinetic Sampling Scheme

Week	Visit	Sample Collection Time Intervals
2	4	4 to 8 hours postdose
4	5	Predose and 0 to 2 hours postdose
6	6	8 to 12 hours postdose
10	8	2 to 4 hours postdose

The actual sample collection date and time (24-hour clock time) must be recorded, as well as the date and time of the 2 most recent doses. If a patient discontinues early, a sample should be taken at the early termination visit, if possible.

Samples are to be collected at specific time intervals relative to dose administration; therefore, visits that include timed PK testing (Visits 4, 5, 6, and 8 [Weeks 2, 4, 6, and 10, respectively]) must be scheduled relative to the patient's dosing schedule. During Visit 5 (Week 4), the first PK sample will be taken predose; the dose will be administered and another PK sample will be taken up to 2 hours postdose. For all visits that include PK sampling, the approximate start and stop times of food consumption prior to dosing and up to 4 hours postdose will be recorded.

Additional PK samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor.

Instructions for the collection and handling of blood samples will be provided by the sponsor.

9.5.2. Bioassay

Human plasma samples will be analyzed for MP-101 and LY2812223 using a validated liquid chromatography-tandem mass spectrometry method at a laboratory approved by the sponsor. Samples will be collected from all patients, but only samples from patients taking MP-101 are planned to be assayed.

Bioanalytical samples collected to measure investigational product concentrations will be retained for a maximum of 2 years following last patient visit for the study. During this time, samples remaining after the bioanalyses may be used for exploratory analyses such as metabolism and/or protein binding work.

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

9.6. Genetics

9.6.1. Apolipoprotein E and HTR2A Genotyping

Apolipoprotein E and HTR2A genotyping is a mandatory part of this study, unless country-specific laws or regulations prohibit this type of testing. Blood sampling for APOE and HTR2A genotyping will be performed as shown in the Schedule of Activities (Section 2). Sample processing and handling instructions will be provided by the sponsor. Neither patients nor investigators will receive the genotype results unless there is a country-specific law or regulation that requires notification of the results. Failure to collect samples for APOE and HTR2A will not be considered a protocol violation if country-specific regulations prohibit the testing of genetic material or transportation of such material outside of the country.

9.6.2. Whole Blood Sample for Pharmacogenetic Research

A whole blood sample (approximately 10 mL) will be collected for pharmacogenetic analysis as specified in the Schedule of Activities (Section 2), where local regulations allow. Sample processing and handling instructions will be provided by the sponsor. Samples will not be used to conduct unspecified disease or population genetic research, either now or in the future. Samples will be used to investigate variable response to MP-101 and to investigate genetic variants thought to play a role in AD. Assessment of variable response may include evaluation of AEs or differences in efficacy. All samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the investigative site personnel.

Samples will be retained for a maximum of 15 years after the last patient visit, or for a shorter period if local regulations and/or ethical review boards (ERBs)/investigational review boards (IRBs) impose shorter time limits, for the study at a facility selected by Mediti Pharma, Inc. or its

designee. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of MP-101 or after MP-101 is commercially available.

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

9.7. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, PD, mechanism of action, variability of patient response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including DNA, RNA, proteins, lipids, and other cellular elements.

Plasma, serum, and whole blood samples for epigenetic analyses will be collected for non-pharmacogenetic biomarker research at the times specified in the Schedule of Activities (Section 2), where local regulations allow. Sample processing and handling instructions will be provided by the sponsor.

Samples will be used for research on the drug target, disease process, variable response to MP-101, pathways associated with psychosis in AD, mechanism of action of MP-101, and/or research method, or for validating diagnostic tools or assay(s) related to psychosis in AD.

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

Samples will be retained for a maximum of 15 years after the last patient visit, or for a shorter period if local regulations and/or ERBs/IRBs impose shorter time limits, at a facility selected by Mediti Pharma, Inc. or its designee. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of MP-101 or after MP-101 becomes commercially available.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

Approximately 100 patients will be enrolled to enable approximately 80 evaluable patients to complete the study through at least Visit 5 (Week 4). The sample size was chosen so that there is at least an 80% chance the trial will show a statistically significant improvement in the response rate on the NPI-Psychosis scale (hallucinations plus delusions scores) and/or on the NPI-agitation/aggression domain in patients treated with MP-101 compared to placebo. This assumes a true response rate of 65% in the MP-101 treatment group versus 35% in the placebo treatment group, using a one-sided Fisher's exact test with a 5% type 1 error rate.

10.2. Populations for Analyses

For the purposes of analysis, the following populations are defined:

Population	Description
Randomized	All patients who sign informed consent and are randomized.
Safety	All randomized patients who take at least 1 dose of double-blind study treatment. In the event of a treatment error, patients will be analyzed according to the treatment they actually received.
Intent-to-Treat	All randomized patients who take at least 1 dose of double-blind study treatment and have at least 1 postbaseline efficacy assessment. In the event of a treatment error, patients will be analyzed according to the treatment to which they were randomized.
Evaluable	All patients in the Intent-to-Treat population who complete at least Visit 5 (Week 4) with NPI efficacy data. Specifically, patients with a diagnosis of psychosis must have at least one psychosis sub-scale score at Visit 5 or later and patients with a diagnosis of agitation/aggression must have at least one agitation/aggression sub-scale score at Visit 5 or later.

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

Statistical analysis of this study will be the responsibility of Mediti Pharma, Inc. or its designee.

Details of the summarization and analysis of the clinical trial data will be described in the SAP, which will be finalized prior to database lock.

The primary analyses will be performed with patients grouped by treatment arm (i.e., MP-101 or placebo) regardless of their final dose level.

The sample size was calculated assuming a 20% drop-out of patients in each arm, and assuming that early withdrawal is not influenced by the treatment effect. Secondary and supportive analyses may be performed to explore the effect of early withdrawal on the primary endpoint.

Pharmacokinetic analyses will be conducted on data from all patients on MP-101. Safety analyses will be conducted for all treated patients, whether or not they completed all protocol requirements.

Additional exploratory analyses of the data will be conducted as deemed appropriate.

A change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol or SAP, and the justification for making the change, will be described in the clinical study report.

10.3.2. Treatment Group Comparability

10.3.2.1. Patient Disposition

A detailed description of patient disposition will be provided at the end of the study.

10.3.2.2. Patient Characteristics

Patient's baseline age, sex, race, height, body weight, body mass index, MMSE score, other baseline efficacy measures, previous exposure to antipsychotic treatment, and eGFR value will be recorded. Baseline and demographic characteristics will be summarized using descriptive statistics by treatment arm and overall.

10.3.2.3. Concomitant Therapy

Approved medications will be permitted in this study as described in Section 7.7. Patients who begin such treatments during the study will be summarized.

10.3.2.4. Treatment Compliance

The proportion of patients who are significantly noncompliant, as noted in Section 7.6, may be summarized.

10.3.3. Efficacy Analyses

10.3.3.1. Primary Analyses

The primary objective of this study will be assessed in the Evaluable population by analyzing NPI response rates. Response will be defined using two NPI endpoints: 1) the psychosis domain score, calculated as the sum of the delusions and hallucinations domain scores, and 2) the aggression/agitation domain score. Each domain score is the product of the severity and frequency ratings.

A patient with a 30% improvement from baseline on a subscale will be considered a responder for that subscale. At baseline, patients will be given a diagnosis of psychosis and/or agitation/aggression. A patient with a psychosis diagnosis will be considered an overall responder with a response on the psychosis subscale, a patient with a diagnosis of aggression/agitation will be considered an overall responder with a response on the aggression/agitation subscale, and a patient with both diagnoses will be considered an overall responder with a response on either subscale.

The primary analysis will use a one-sided Fisher's exact test with a 5% type 1 error rate.

10.3.3.2. Secondary Analyses

Secondary efficacy outcomes include CGI-I; NPI Total Score; NPI-Core Total (combination of 3 items: hallucinations, delusions, and agitation/aggression); NPI Caregiver Distress; NPI domain of anxiety.

The delusions, hallucinations, and aggression/agitation domain scores will be added together to form a Core Total score. A patient with a 30% improvement from baseline will be considered a responder on the Core Total score. The treatment groups will be compared using a one-sided Fisher's exact test.

The psychosis and aggression/agitation domain scores, and the Core Total score, will be analyzed as continuous measures.

The change from baseline for quantitative endpoints will be analyzed using repeated measures mixed models assuming data are missing at random, with covariates for baseline and the stratification factors.

The CGI-I scores will be analyzed using Cochran-Mantel-Haenszel tests, stratifying by the randomization strata, and using modified Ridit scores (i.e. van Elteren tests).

Details of the analyses of secondary efficacy outcomes will be specified in the SAP.

10.3.3.3. Exploratory Analyses

The exploratory efficacy objectives to determine whether MP-101 is superior to placebo in patient behavior and caregiver burden. Changes in patient behavior will be assessed using NPI domains of depression/dysphoria, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, sleep and nighttime behavior disorders, and appetite and eating disorders; MMSE.

The ZBI-22 is being utilized to assess caregiver burden.

The exposure-response relationships between efficacy and safety endpoints may also be explored, as needed.

Details of the analyses of exploratory efficacy outcomes will be specified in the SAP

10.3.4. Safety Analyses

10.3.4.1. Adverse Events

All investigational product and protocol procedure AEs will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology.

The incidence of symptoms for each treatment will be presented by severity and by association with investigational product as perceived by the investigator. Symptoms reported to occur prior to enrollment will be distinguished from those reported as new or increased in severity during the study. Each symptom will be classified by the most suitable term from the most current version of Medical Dictionary for Regulatory Activities (MedDRA).

The number of investigational product-related SAEs will be reported.

10.3.4.2. Other Evaluations of Safety

Other safety parameters that will be assessed include physical/neurological examinations, safety clinical laboratory parameters, vital signs, and ECG parameters. The parameters will be listed and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data.

10.3.5. Pharmacokinetic Analyses

MP-101 and LY2812223 concentrations will be summarized by treatment and time postdose using summary statistics (number, mean, standard deviation, coefficient of variation [CV], minimum, median, maximum, geometric mean, and geometric CV).

For the final analysis, the PK of LY2812223 will be characterized using population PK methods; the effect of renal function on PK will be evaluated. Data from this study may be pooled with data from previous studies. The relationship of LY2812223 concentrations with efficacy and/or safety measures may be explored. The population PK or PK/PD analyses will be performed separately and reported in a population PK report. Other analyses may be performed as needed.

10.3.6. Other Analyses

10.3.6.1. Pharmacogenetics Exploratory Analyses

To explore the effect of genotype on the response to MP-101 in dementia patients, genotype data for HTR2A SNP rs7330461, HTR2A SNP rs6313 (102T/C), APOE, and other genotypes may be analyzed. The analysis methods may be detailed in the SAP.

10.3.7. Interim Analyses

An interim analysis is planned for this trial which will occur after approximately 20 patients have completed Visit 5 (Week 4) to evaluate safety and LY2812223 PK. A second interim analysis may be performed to evaluate the futility of finding differences in the efficacy endpoints between treatment groups. All interim analysis details, including unblinding plans and stopping rules for the futility analysis, will be documented in the Assessment Committee Charter.

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

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Appendix 1. Abbreviations and Definitions

Term	Definition
5-HT2A/HTR2A	5-hydroxytryptamine (serotonin) 2A (receptor)
AChEI	acetylcholinesterase inhibitors
AD	Alzheimer's disease
ADL	Activity of Daily Living
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
APOE	apolipoprotein E
AST	aspartate aminotransferase
BP	blood pressure
bpm	beats per minute
cAMP	cyclic adenosine monophosphate
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
CI	confidence interval
CKD EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	maximum observed drug concentration
CRF	case report form
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, global safety physician, or other medical officer.
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CT	computed tomography

CTCAE	Common Terminology Criteria for Adverse Events
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
CV	coefficient of variation
DSM-V	Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition
DP	drug product
EC_{50}	half maximal effective concentration
EC_{100}	maximum achievable response concentration
ECG	Electrocardiogram
ERB	ethical review board
eGFR	estimated glomerular filtration rate
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
enter	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
FDA	US Food and Drug Administration
GCP	good clinical practice
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IRB	investigational review board
IWRS	interactive web-response system
mGlu	metabotropic glutamate
MAD	multiple-ascending dose

MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini-Mental State Exam
MRI	magnetic resonance imaging
NPI	Neuropsychiatric Inventory
NPI-D	Neuropsychiatric Inventory-Caregiver Distress
PD	Pharmacodynamics
phMRI	pharmacological magnetic resonance imaging
PK	Pharmacokinetic
PPS	per-protocol set: The set of data generated by the subset of patients/who sufficiently complied with the protocol to ensure that these data would be likely to exhibit the effects of treatment, according to the underlying scientific model.
QD	quaque die (once daily)
QTc	corrected QT interval
QTcF	Fridericia's corrected QT interval
SAD	single-ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SNP	single nucleotide polymorphism
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, which and does not necessarily have to have a causal relationship with this treatment.
t_{max}	time of maximum concentration
TUG	Timed Up and Go
ULN	upper limit of normal
UPDRS	Unified Parkinson's Disease Rating Scale

ZBI-22	Zarit Burden Interview-22

Appendix 2. Clinical Laboratory Tests

Laboratory Tests

Clinical Chemistry[a,b]
- **Serum Concentrations of:**
  - Sodium
  - Potassium
  - Total bilirubin
  - Direct bilirubin
  - Alkaline phosphatase
  - Alanine aminotransferase (ALT)
  - Aspartate aminotransferase (AST)
  - Blood urea nitrogen (BUN)
  - Creatinine[c]
  - Uric acid
  - Calcium
  - Glucose
  - Albumin
  - Total Protein
  - Creatine kinase (CK)
  - Cystatin-C

Complete Blood Count with differential

Urine dipstick[d]

Serology [a,b]
- Hepatitis C Antibody
- HIV
- Hepatitis B Surface Antigen

Other Tests[a]
- FSH[e]

Pharmacokinetic[a]
- MP-101 and LY2812223 plasma concentrations

Abbreviations: CKD-EPI= Chronic Kidney Disease Epidemiology Collaboration; FSH = follicle stimulating hormone; HIV = human immunodeficiency virus.

[a] Assayed by sponsor-designated laboratory

[b] Unscheduled or repeat blood chemistry, hematology, and urinalysis panels may be performed at the discretion of the investigator, as needed.

[c] Estimated glomerular filtration rate will be calculated using serum creatinine values and the CKD-EPI Cystatin C Equation (Grubb et al. 2010; Peralta et al. 2011; Inker et al. 2012).

[d] Microscopic examination of sediment performed only if abnormalities are noted on the routine urinalysis.

[e] To confirm postmenopausal status for women ≥50 and <60 years of age who have had a cessation of menses, an FSH test will be performed. Non-childbearing potential is defined as an FSH ≥40 mIU/mL and a cessation of menses for at least 12 months.

Appendix 3. Study Governance, Regulatory and Ethical Considerations

Informed Consent

The investigator is responsible for:

- ensuring that the patient understands the potential risks and benefits of participating in the study.
- ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the informed consent form (ICF) prior to the performance of any protocol procedures and prior to the administration of investigational product.
- answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the trial.

Ethical Review

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

Documentation of ERB approval of the protocol and the ICF must be provided to Mediti Pharma, Inc. before the study may begin at the investigative site(s). Mediti Pharma, Inc. or its representatives must approve the ICF before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on good clinical practice (GCP).

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

- the current Investigator's Brochure (IB) and updates during the course of the study
- ICF
- relevant curricula vitae

Regulatory Considerations

This study will be conducted in accordance with:

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

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

Protocol Signatures

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

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

Final Report Signature

The sponsor will select a qualified investigator from among participating investigators to serve as the final report coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by the sponsor.

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

Data Quality Assurance

To ensure accurate, complete, and reliable data, Mediti Pharma, Inc. or its representatives will do the following:

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

In addition, Mediti Pharma, Inc. or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Mediti Pharma, Inc. and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

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

Data Collection Tools/Source Data

An electronic data capture system will be used in this study. The site must define and retain all source records and must maintain a record of any data where source data are directly entered into the data capture system.

Study and Site Closure

Discontinuation of Study Sites

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

Discontinuation of the Study

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

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

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

Hepatic Monitoring Tests

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

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

[a] Assayed by Mediti Pharma, Inc.-designated or local laboratory.

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

Appendix 5. Timed Up and Go Test

Name:_____ MR: _____ Date:_____

1. Equipment: arm chair, tape measure, tape, stop watch.
2. Begin the test with the subject sitting correctly (hips all of the way to the back of the seat) in a chair with arm rests. The chair should be stable and positioned such that it will not move when the subject moves from sit to stand. The subject is allowed to use the arm rests during the sit – stand and stand – sit movements.
3. Place a piece of tape or other marker on the floor 3 meters away from the chair so that it is easily seen by the subject.
4. Instructions: "On the word GO you will stand up, walk to the line on the floor, turn around and walk back to the chair and sit down. Walk at your regular pace."
5. Start timing on the word "GO" and stop timing when the subject is seated again correctly in the chair with their back resting on the back of the chair.
6. The subject wears their regular footwear, may use any gait aid that they normally use during ambulation, but may not be assisted by another person. There is no time limit. They may stop and rest (but not sit down) if they need to.
7. Normal healthy elderly usually complete the task in 10 seconds or less. Very frail or weak elderly with poor mobility may take 2 minutes or more.
8. The subject should be given a practice trial that is not timed before testing.
9. Results correlate with gait speed, balance, functional level, the ability to go out, and can follow change over time.

Normative Reference Values by Age	
Age Group	**Time in Seconds (95% Confidence Interval)**
60 – 69 years	8.1 (7.1 – 9.0)
70 – 79 years	9.2 (8.2 – 10.2)
80 – 99 years	11.3 (10.0 – 12.7)

Cut-off Values Predictive of Falls by	
Group	**Time in Seconds**
Community dwelling frail older adults	>14 associated with high fall risk
Postoperative hip fracture patients at time of discharge	>24 predictive of falls within 6 months after hip fracture
Frail older adults	>30 predictive of requiring assistive device for ambulation and being dependent in ADLs

Appendix 6. Protocol Amendment MP-101-01(b) Summary [Tolerability, Pharmacokinetics, and Efficacy of MP-101 in the Treatment of Psychosis in Patients with Alzheimer's Disease]

Overview

Protocol MP-101-01 [Tolerability, Pharmacokinetics, and Efficacy of MP-101 in the Treatment of Psychosis in Patients with Alzheimer's Disease] has been amended. The new protocol is indicated by amendment (b) and will be used to conduct the study in place of any preceding version of the protocol.

The revisions to the protocol detailed below are being implemented to maximize the potential of MP-101 reaching future patients in this difficult-to-treat population. Dementia can be caused by numerous neurodegenerative disorders including (but not limited to) Alzheimer's disease (AD); therefore, to expand patient eligibility, this protocol amendment includes patients with all neurodegeneration-related dementias including Alzheimer's disease, Lewy body dementia, Parkinson's disease dementia, and frontotemporal dementia.

While cognitive impairment is the hallmark symptom of dementia, behavioral and psychological disturbances are almost invariably present at some point during the illness (Steinberg et al. 2008; Lyketsos et al. 2002). Among the most disturbing and burdensome of these symptoms are psychosis (hallucinations and delusions) as well as aggression and agitation. Therefore again, in an effort to expand the patient population, these additional measures are being included in the protocol amendment.

Additionally, an attempt to minimize caregiver and patient burden with the revised protocol has been made by reducing the number of study visits, scales performed at each visit, and excluded concomitant medications.

The overall changes made to this protocol are as follows.

Note: Deletions have been identified by ~~strikethroughs~~ or grayed out for figures. Additions have been identified by the use of underscore. Additional/instructional text is in *italics*.

Revised Protocol Sections

Study Title:

Tolerability, Pharmacokinetics, and Efficacy of MP-101 in the Treatment of Patients with Dementia-Related Psychosis and/or Agitation and Aggression ~~in Patients with Alzheimer's Disease~~

The change in study indication was updated at all relevant places/sections in the protocol.

All edits made to the main body were applied to the synopsis section as well.

Section 2. Schedule of Activities

Following efficacy assessment schedule was revised: Mini-Mental State Examination (MMSE) Visit 6 (Week 6) assessment was removed.

Following efficacy assessments were removed: Cohen Mansfield Agitation Inventory (CMAI), Alzheimer's Disease Cooperative Study Activities of Daily Living (ADCS ADL), Alzheimer's Disease Cooperative Study Clinical Global Impression of Change (ADSC CGIC).

Following efficacy assessments were added: Clinical Global Impression of Improvement (CGI-I) at Visits 5, 8, 9 and ET; Zarit Burden Inverview-22 (ZBI-22) at Visits 2, 5, and 8.

Visit 7 (Week 8) was changed from a site visit to a telephone call, thus cancelling all of the on-site scales and procedures previously associated with that visit. The Visit 7 PK sample draw was moved to Visit 8 (Week 10).

Footnote 'b' meant for Inclusion/Exclusion Criteria Review activity was updated as below:

[b] Patients must have at least one of the following at Visit 1 (screening) and Visit 2 (Week 0) ~~an NPI score of ≥4 on either individual item (delusions or hallucinations) or ≥6 on Psychosis Subscale (combined delusions and hallucinations) at Alternatively, pVisit 1 (screening) and Visit 2 (Week 0):~~

- an NPI score of ≥4 on either delusions or hallucinations individual items
- an NPI score of ≥6 on the Psychosis Subscale (combined delusions and hallucinations)
- an NPI score of ≥4 on agitation/aggression domain

Section 3. Introduction

Introduction section was updated to reflect the change in study indication from Alzheimer's disease and psychosis to dementia-related psychosis and agitation/aggression.

Section 4. Objectives and Endpoints

4.1. Primary Objective and Endpoint

- To test the hypothesis that oral administration of QD MP-101 will improve psychotic symptoms and/or agitation/aggression in patients with dementia ~~AD~~ when compared to placebo

    - Endpoint: Change from baseline to 10-week treatment endpoint in the Neuropsychiatric Inventory (NPI)-Psychosis subscale (combination of 2 items: hallucinations and delusions) and/or in the agitation/aggression domain. ~~(combination of 2 items: hallucinations and delusions).~~

4.2. Secondary Objectives and Endpoints

Secondary objectives and endpoints in patients with dementia related psychosis and/or agitation and aggression are as follows:

- To assess whether MP-101 is superior to placebo in the following: ~~overall psychosis,~~ neuropsychiatric disturbances, caregiver distress, and anxiety~~, agitation/aggression, and function~~

    - Endpoints: Change from baseline to 10-week treatment endpoint in the following: Clinical Global Impression of Improvement~~Severity~~ (CGI-IS~~)~~); NPI Total Score; NPI-Core Total (combination of 3 items: hallucinations, delusions, and agitation/aggression); NPI Caregiver Distress (NPI-D); and NPI domains of anxiety ~~and agitation/aggression; Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (ADCS-ADL); and Cohen-Mansfield Agitation Inventory (CMAI)~~

- To determine if MP-101 is safe and tolerable ~~in AD patients with psychosis~~

    - Endpoints: Treatment-emergent adverse events (TEAEs); Unified Parkinson's Disease Rating Scale (UPDRS) Part III

- To assess the PK of MP-101 and its primary active metabolite, LY2812223

    - Endpoint: Plasma PK data

4.3. Exploratory Objectives and Endpoints

- To assess whether MP-101 is superior to placebo in changes in patient behavior and caregiver burden

    - Endpoints: Change from baseline to 10-week treatment endpoint in the following: ~~Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC);~~ NPI domains of depression/dysphoria, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, sleep and nighttime behavior disorders, and appetite and eating disorders; Mini-Mental State Examination (MMSE); Zarit Burden Interview-22 (ZBI-22)

- To explore the effect of HTR2A and apolipoprotein E (APOE) genotypes on response to treatment

- Endpoints: HTR2A single nucleotide polymorphism (SNP) rs7330461 genotype data; HTR2A SNP rs6313 (102T/C) genotype data; APOE genotype data

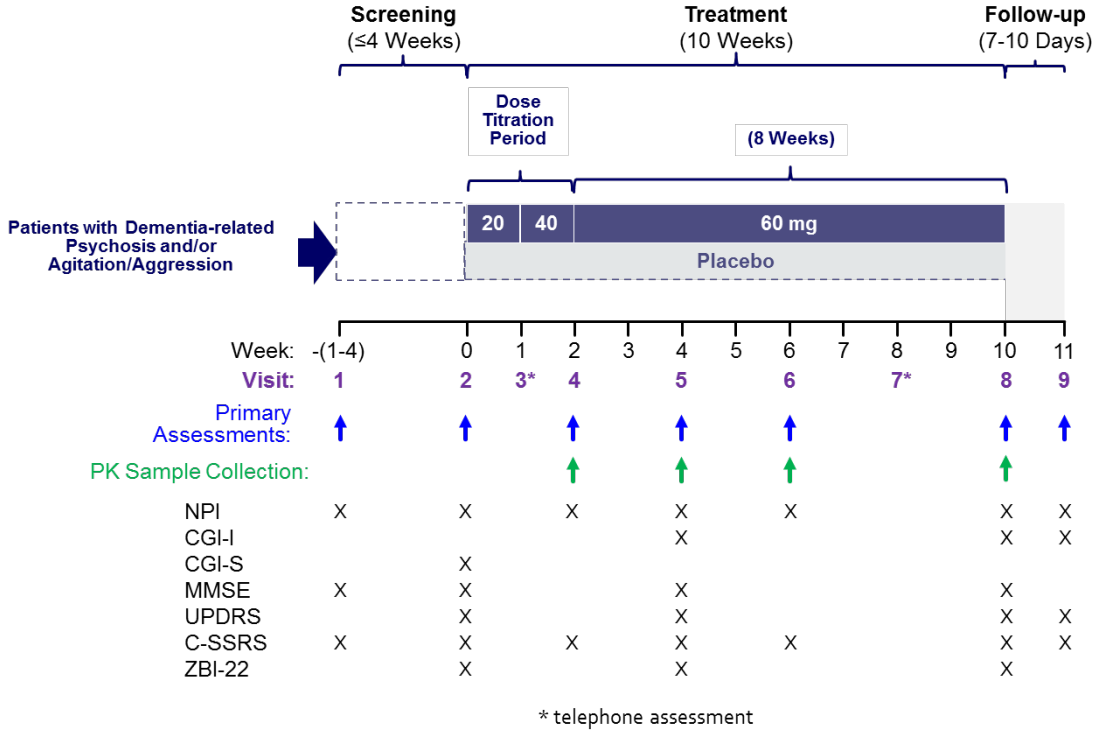
- To explore exposure-response relationships with efficacy and safety clinical endpoints as needed
  - Endpoints: Efficacy and safety clinical endpoints, as needed

Section 5. Study Design

5.1. Overall Design

Study MP-101-01 is a Phase 2, multicenter, double-blind, randomized, parallel, placebo-controlled, 10-week study of MP-101, consisting of screening, treatment, and follow-up periods, in ~~AD~~ patients with dementia related psychosis and/or agitation and aggression. ~~with psychosis.~~ All patients will be randomized 1:1 to receive either placebo or MP-101.

Figure 5.1. Illustrates the study design.



Abbreviations: ~~AD = Alzheimer's disease;~~ CGI-I = Clinical Global Impression of Improvement/Severity; CGI-S = Clinical Global Impression of Severity; C-SSRS= Columbia Suicide Severity Rating Scale; MMSE= Mini-Mental State Examination; NPI ~~P~~ = Neuropsychiatric Inventory ~~Psychosis~~; PK = pharmacokinetic; UPDRS=Unified Parkinson's Disease Rating Scale; Zarit Burden Interview-22.

Figure 5.1. Illustration of study design for protocol MP-101-01.

5.2. Number of Participants

Approximately ~~200~~100 patients will be enrolled to obtained approximately ~~160~~80 patients in the Evaluable population.

Section 6. Study Population

6.1. Inclusion Criteria

Type of Patient – Patient and Disease Characteristics

[2] Ambulatory (with or without walking device) with a stable gait as assessed with a TUG test (Okumiya et al. 1998; Nordin et al. 2006) that must be completed in ≤30 seconds. The test may be repeated once with instruction. Patients in wheelchairs are also eligible and do not need to complete the TUG test.

~~[3] probable AD based on the National Institute on Aging-Alzheimer's Association criteria (McKhann et al, 2011) and~~

[4] Meets clinical criteria for one of the following disorders: dementia associated with Parkinson's disease, dementia with Lewy bodies, possible or probable Alzheimer's disease, frontotemporal degeneration spectrum disorders, vascular dementia

[5] Must be able to communicate verbally.

~~[4] Have psychotic symptoms that developed following the diagnosis of probable AD. The psychotic symptoms must include visual and/or auditory hallucinations, and/or delusions.~~

[5] At Visit 1 (screening) and Visit 2 (Week 0) have at least ONE of the following:

- ~~Have~~ an NPI score of ≥4 on either delusions or hallucinations individual items~~ (delusions or hallucinations)~~
- an NPI score of ≥6 on the Psychosis Subscale (combined delusions and hallucinations)

~~at Visit 1 (screening) and Visit 2 (Week 0)~~

~~or~~

- ~~Have~~ an NPI score of ≥4 on agitation/aggression domain~~at Visit 1 (screening) and Visit 2 (Week 0)~~.

~~[7] Have had an MRI or a computed tomography (CT) scan concurrent with or following the diagnosis of probable AD, to exclude prior stroke or structural brain disease.~~

[8] Must be on a stable dose of cholinesterase inhibitor and/or memantine, if applicable.

[9] ~~Are receiving acetylcholinesterase inhibitors (AChEIs) on a stable doses for ≥13 months prior to the baseline visit and during the study or, in the opinion of the investigator is will be likely to remain on a stable treatment regimen for 6 months. Patients not being treated with AChEIs are also eligible for study enrollment.~~ If taking antipsychotic drugs or any drug intended to treat psychosis, must be on a stable treatment regimen for ≥1 month prior to the baseline visit (Visit 2). Note: If ~~a~~the patient has recently stopped taking antipsychotic drugs or any drugs intended to treat psychosis, he or she must have discontinued treatment at least 4 weeks before Visit 1 (screening). ~~Patients receiving memantine therapy are eligible for study enrollment if there is a washout of memantine treatment (minimum 7 half-lives; approximately 28 days) during the screening period and prior to randomization; such patients must also meet all other eligibility criteria for study entry.~~

6.2. Exclusion Criteria

Diagnostic Assessments

[14] Have a history of significant psychotic disorders ~~prior to or simultaneous with the probable diagnosis of AD~~ (including, but not limited to, schizophrenia, delusional disorder, substance abuse psychosis that lasted over 6 months, major depressive disorder, or bipolar disorder with psychotic episodes).

[15] Had a history of ischemic stroke within the last 12 months or any evidence of hemorrhagic stroke.

~~[16] Have an MRI or CT scan (on file since the onset of symptoms of AD) that is inconsistent with a probable diagnosis of AD~~.

~~[17] Meets National Institute of Neutological Disorders and Stroke/Association International pour la Recherche et l'Eseignement en Neuroscience criteria for vascular dementia (Pohjasvaara et al. 200). Meets Diagnostic and Statistical Manual of Mental Disorder-Fifth Edition (DSM-V) criteria for delirium.~~

Mental Conditions

~~[19] Have psychosis from non-AD-associated etiologies (e.g., substance abuse or a diagnosis of psychosis prior to the development of AD)~~.

~~[24] Uses any antipsychotics or any other drug intended to treat psychosis after Visit 1 (screening). If the patient is taking the medication prior to study entry, there must be a washout period equal to a minimum of 5 half-lives of that medication prior to Visit 2 (Week 0). If the half-life of a medication is unknown (e.g., herbal products), then the patient should have a 28-day medication washout~~.

Section 7. Treatment

7.2 Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomized in a 1:1 ratio (MP-101:placebo) to double-blind treatment at Visit 2 (Week 0). Assignment to treatment arms will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). The IWRS will be used to assign blister packs containing double-blind investigational product to each patient. ~~Two b~~Blister packs ~~(1 for every 2 weeks between visits)~~ will be dispensed at Visits 2, 4, 5, and 6 ~~and 7~~ (Weeks 0, 2, 4, and 6~~, and 8~~, respectively). During the patient's visit, the site will access the IWRS for the correct blister pack numbers to dispense.

7.7 Concomitant Therapy

Patients with worsening psychosis or agitation/aggression requiring rescue therapy will be withdrawn from the study.

Table 7.2. List of Excluded Medications

Drug Class
~~Analgesics (~~Opioids, tramadol, ketorolac except occasional use us as needed
Antiemetics (except occasional use as needed metoclopramide, domperidone, other dopamine receptor blockers)
Antihistamines (except occasional use as needed~~) bromopheneraphine, chlorpheneramine, diphenhydramine)~~
~~Anxiolytics (except lorazepam)~~
~~Buspirone~~
~~Corticosteroids (oral)~~
~~Dopamine agonists~~
~~Eldepryl, selegeline hydrochloride~~
~~Fluorocortisol~~
~~Gastrointestinal antispasmodics (belladonna, dicyclomine, hyoscyamine)~~
~~Herbal supplements with CNS activity~~
~~Including, but not limited to, Ginkgo Biloba, St. John's Wort, Kava, ephedrine, cycloserine, glycine, pregnenolone~~
Hydroxyzine (except occasional use as needed)
Hypnotics
Lithium
Psychostimulants (modafanil)
~~Rimonabant~~
~~Reserpine~~
Skeletal muscle relaxants (except occasional use as needed~~baclofen, carpisopradol~~)
~~Sleeping medications (zolpiden, chloral hydrate)~~
~~Steroids (parenteral)~~
~~Triptans~~

Section 8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

8.1.1. Permanent Discontinuation from Study Treatment

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

- the occurrence of worsening psychosis and/or agitation or aggression requiring rescue therapy

Section 9. Study Assessments and Procedures

9.1.1. Primary Efficacy Assessment

The primary endpoint is the response on the NPI-Psychosis subscale items of delusions and hallucinations and/or the agitation/aggression domain.

9.1.2. Secondary Efficacy Assessment

Following secondary endpoints were removed: Clinical Global Impression of Severity; Cohen Mansfield Agitation Inventory (CMAI); Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (ADCS-ADL).

The following endpoint was added:

Clinical Global Impression of Improvement (CGI-I; Guy et al. 1976)

The CGI-I is a 7-point scale that requires the clinician to assess how much the patient's illness has improved or worsened relative to baseline (Visit 2). The scale ranges from 1 (very much improved) to 7 (very much worse).

9.3. Exploratory Efficacy Assessment

Following exploratory endpoint was removed: Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC).

The following endpoint was added:

Zarit Burden Interview-22 (ZBI-22; Zarit et al. 1980)

Changes in caregiver burden will be assessed using the Zarit Burden Interview-22 (ZBI-22). The ZBI-22 is a 22-point scale used to assess caregiver burden in the dementia patient population (Zari et al. 1980). Each of the 22 items is rated on a scale of 0 to 4, where 0 = never, 1 = rarely, 2 = sometimes, 3 = frequently, 4 = nearly always. The total score of the ZBI-22 is the sum of those 22 items.

9.5.1 Pharmacokinetic Sampling

PK sample collection scheduled at Week 8 (Visit 7) was moved to Week 10, Visit 8 (2 to 4 hours postdose).

Section 10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

Approximately ~~200~~100 patients will be enrolled to enable approximately ~~160~~80 evaluable patients to complete the study through at least Visit 5 (Week 4). The sample size was chosen so that there is at least a ~~76~~ 80% chance the trial will show a ~~65% or greater Bayesian posterior probability of at least a 1 point improvement~~statistically significant improvement in the response rate on the NPI-Psychosis scale (hallucinations plus delusions scores) ~~and/or on the NPI agitation/aggression domain~~ in patients treated with MP-101 compared to placebo ~~at 10 weeks after the start of treatment~~.. This assumes a true response rate of 65% in the MP-101 treatment group versus 35% in the placebo treatment group, using a one-sided Fisher's exact test with a 5% type 1 error rate. ~~The operating characteristics of this analysis were studied through simulations, with non-informative priors for the parameters of the underlying assumed normal distribution of the scores.~~

10.2. Population Analysis

Population	Description
Evaluable	All patients in the Intent-to-Treat population who complete at least Visit 5 (Week 4) with NPI efficacy data. Specifically, patients with a diagnosis of psychosis must have at least one psychosis sub-scale score at Visit 5 or later and patients with a diagnosis of agitation/aggression must have at least one agitation/aggression sub-scale score at Visit 5 or later. ~~All patients in the Intent-to-Treat population who complete Visit 5 (Week 4) with NPI efficacy data.~~

10.3.3. Efficacy Analyses

10.3.3.1. Primary Analyses

The primary objective of this study will be assessed in the Evaluable population by analyzing ~~the change from baseline to the 10-week treatment endpoint of the combined hallucinations and delusions scores from the NPI-Psychosis subscale~~ NPI response rates. Response will be defined using two NPI endpoints: 1) the psychosis domain score, calculated as the sum of the delusions and hallucinations domain scores, and 2) the aggression/agitation domain score. Each domain score is the product of the severity and frequency ratings.

A patient with a 30% improvement from baseline on a subscale will be considered a responder for that subscale. At baseline, patients will be given a diagnosis of psychosis and/or agitation/aggression. A patient with a psychosis diagnosis will be considered an overall responder with a response on the psychosis subscale, a patient with a diagnosis of aggression/agitation will be considered an overall responder with a response on the aggression/agitation subscale, and a patient with both diagnoses will be considered an overall responder with a response on either subscale.

The primary analysis will use a one-sided Fisher's exact test with a 5% type 1 error rate.

~~The change from baseline to the 10-week time point (Visit 8 [Week 10]) will be estimated using repeated measures mixed models assuming data are missing at random, with covariates for baseline and the stratification factors. The Bayesian posterior probability that the mean change from baseline MP-101 score is better than the mean change from baseline placebo score by at~~

~~least 1 point will be calculated. Non-informative priors for the parameters of the normal distribution will be used.~~

~~The precise analysis methods will be detailed in the SAP, which will be completed prior to database lock~~.

10.3.3.2. Secondary Analyses

~~The secondary efficacy endpoints will be assessed by analyzing the change from baseline to the 10-week time point using analysis methods appropriate to the type of measurement~~. ~~These~~ S~~s~~econdary efficacy outcomes include CGI-I~~S~~; NPI Total Score; NPI-Core Total (combination of 3 items: hallucinations, delusions, and agitation/aggression); NPI Caregiver Distress~~-D~~; NPI domain of anxiety, ~~agitation/aggression, and sleep and nighttime behavior disorders; CMAI~~; ~~MMSE; ADCS-ADL; and the UPDRS, Part III~~.

The delusions, hallucinations, and aggression/agitation domain scores will be added together to form a Core Total score. A patient with a 30% improvement from baseline will be considered a responder on the Core Total score. The treatment groups will be compared using a one-sided Fisher's exact test.

The psychosis and aggression/agitation domain scores, and the Core Total score, will be analyzed as continuous measures.

The change from baseline for quantitative endpoints will be analyzed using repeated measures mixed models assuming data are missing at random, with covariates for baseline and the stratification factors.

The CGI-I scores will be analyzed using Cochran-Mantel-Haenszel tests, stratifying by the randomization strata, and using modified Ridit scores (i.e. van Elteren tests).

10.3.3.3. Exploratory Analyses

The exploratory efficacy objectives to determine whether MP-101 is superior to placebo in patient behavior and caregiver burden. Changes in patient behavior will be assessed using ~~ADCS-CGIC and~~ NPI domains of depression/dysphoria, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, sleep and nighttime behavior disorders, and appetite and eating disorders; MMSE. ~~The analysis methods for the exploratory efficacy analyses will be detailed in the SAP.~~

The ZBI-22 is being utilized to assess caregiver burden.

The exposure-response relationships between efficacy and safety endpoints may also be explored, as needed~~, as detailed in the SAP~~.

Details of the analyses of exploratory efficacy outcomes will be detailed in the SAP.

10.3.6. Other Analyses

10.3.6.1. Pharmacogenetics Exploratory Analyses

To explore the effect of genotype on the response to MP-101 in ~~AD~~ dementia patients ~~with psychosis~~, genotype data for HTR2A SNP rs7330461, HTR2A SNP rs6313 (102T/C), APOE, and other genotypes may be analyzed. The analysis methods may be detailed in the SAP.

10.3.7. Interim Analysis

An interim analysis is planned for this trial which will occur after approximately 20 patients have completed Visit 5 (Week 4) to evaluate PK and safety. A second interim analysis may be performed to evaluate the futility of finding differences in the efficacy endpoints between treatment groups. All interim analysis details, including unblinding, plans and stopping rules for the futility analysis, will be documented in the Assessment Committee Charter.

Section 11. References

List of references was updated in line with the edits made in the main body text.