Document Coversheet

Study Title: A Phase 1a, Double-Blind, Randomized, Placebo-Controlled Single Ascending Dose Study to Evaluate the Safety, Tolerability and Pharmacokinetic Profile of MW151 Administered Orally to Healthy Volunteers

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CLINICAL STUDY PROTOCOL NO. MW151-101 AMENDMENT 3

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Full Protocol Title
A Phase 1a, Double-Blind, Randomized, Placebo-Controlled Single Ascending Dose Study to Evaluate the Safety, Tolerability and Pharmacokinetic Profile of MW151 Administered Orally to Healthy Volunteers

Protocol Date: 14 October 2020 (Amendment 3) (V4)

SHORT PROTOCOL TITLE
A Phase 1a SAD Study of MW151

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Version History

Version	Effective Date	Reason for Amendment
Original Protocol (V1)	16 March 2019	N/A
Amendment 1 (V2)	28 August 2019	Inclusion of FDA comments
Amendment 2 (V3)	13 January 2020	Limit enrollment to females only in Cohorts 2-5
Amendment 3 (V4)	14 October 2020	Inclusion of DSMB recommendations

INVESTIGATOR SIGNATURE

I, the undersigned Investigator, have read the following protocol and agree to conduct the study in compliance with the protocol, International Conference on Harmonization (ICH) Good Clinical Practice (GCP), Good Laboratory Practice (GLP) and all applicable regulatory requirements.

I, the undersigned Investigator, agree:

- To assume responsibility for the proper conduct of the study and not to deviate from the procedures described in the protocol.
- I am thoroughly familiar with the investigational product(s) as described in the protocol, Investigator's Brochure and any other relevant information sources provided to me.
- I am aware of and will conduct the study in compliance with the protocol, ICH GCP guidelines and all applicable regulatory requirements.
- I agree to permit monitoring and auditing of the study by the Sponsor and its designates, and inspection by appropriate regulatory authority (ies).
- I agree to ensure that all persons assisting with the conduct of the study are properly qualified for their function.

Investigator Name & Signature:

Investigator Signature Linda J. Van Eldik, PhD	**Date**

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ACRONYMS, ABBREVIATIONS, AND DEFINITIONS OF TERMS

Aβ Amyloid beta

AD Alzheimer's disease

AE Adverse Event

ApoE Apolipoprotein E

AUC Area under the curve

BP Blood pressure

bpm Beats per minute

CCC Clinical Coordination Center

CDE Common Data Elements

CFR Code of Federal Regulations

CIRB Central Institutional Review Board

C_{max} Maximum drug concentration

CNS Central Nervous System

CRF Case report form

CS Clinically Significant

CSF Cerebrospinal fluid

CSS PI Clinical Study Site PI

C-SSRS Columbia Suicide Severity Rating Scale

DCC Data Coordination Center

DM Data Management

DSMB Data Safety Monitoring Board

ECG Electrocardiogram

eCRF Electronic Case Report Form

EDC Electronic data capture

ET Early termination

FDA Food and Drug Administration

GCP Good Clinical Practice

GLP Good Laboratory Practice

HIPAA Health Insurance Portability and Accountability Act

ICF Informed Consent Form

ICH International Conference on Harmonization

IND Investigational New Drug

IRB/IEC Institutional review board/Independent ethics committee iv Intravenous

K_{el} Elimination rate constant

MAD Multiple ascending dose

MedDRA Medical Dictionary for Regulatory Activities

MFD Maximum feasible dose

MW151 The investigational product

NIA National Institute on Aging

NOAEL No adverse events level

PIC Proinflammatory cytokine

PK Pharmacokinetic

PPI Protocol Principal Investigator

PSC Protocol Steering Committee

RBC Red blood cell

SAD Single ascending dose

SAE Serious adverse event

SOA Schedule of Activities

TEAE Treatment emergent adverse event

T_{max} Time at maximum drug concentration

$T_{1/2}$ Half-life

WBC White blood cell

SYNOPSIS

Title	A Phase 1a, Double-Blind, Randomized, Placebo-Controlled Single Ascending Dose Study to Evaluate the Safety, Tolerability and Pharmacokinetic Profile of MW151 Administered Orally to Healthy Volunteers
Short Title	Phase 1a SAD Study of MW151
Indication	Radiation-induced cognitive impairment
Rationale	MW151, a small molecule, is being developed for the treatment of cognitive disorders. The development program is based on nonclinical evidence that MW151 improves neurocognitive outcomes in animal models of radiation-induced cognitive impairment, Alzheimer's disease, and other CNS disorders. The present study will provide safety and PK information on single ascending doses to support decisions for continued clinical development.
Objectives	**Primary Objective:** To assess the safety and tolerability of single ascending doses of MW151 when administered orally to healthy adults **Secondary Objective:** To assess the PK profile of single ascending doses of MW151 when administered orally to healthy adults

Interventions and Duration	Subjects will be screened in the 28 days prior to inpatient admission. Subjects will be admitted to the inpatient clinic on the day prior to dosing (Day -1) and will remain in the unit until discharge on Day 3. A follow-up visit will be done on Day 7. A single dose of study drug or placebo will be administered on Day 1. 40 healthy adult subjects will be assigned to one of 5 dose cohorts (8 subjects each). The starting dose (10 mg) cohort 1 will include male and female subjects; cohorts 2 – 5 will include only female subjects. Within each cohort, 8 subjects will be randomized to receive MW151 or placebo in the ratio 6:2. According to the dosing scheme each subject will receive a single dose of MW151 or placebo under fasted conditions. 1. Starting dose: Dose1 (10 mg) 2. Dose2 (20 mg) 3. Dose3 (40 mg) 4. Dose4 (80 mg) 5. Dose5 (160 mg) As a safety consideration two sentinel subjects in each cohort will be administered MW151 or placebo in a 1:1 ratio.

	Following review of sentinel safety and tolerability data for the first 24 hours of dosing in each cohort (including reported adverse events [AEs], physical examination findings, clinical laboratory results, vital signs, and electrocardiograms [ECGs]), the remaining 6 subjects will be randomized in a 5:1 ratio. Dosing of the remaining subjects in a cohort may proceed after review of sentinel subject safety data collected during the first 24 hours of dosing and determination that no stopping rules are met. The remaining subjects in each cohort will be dosed sequentially, not simultaneously. After the completion of each cohort (Cohorts 1-5), the DSMB will review all available safety data before the dosing of the sentinel subjects of the next cohort. Patients will receive standardized meals during the Inpatient Phase. Data from Cohorts 1-5 will be reviewed in a blinded manner, unless the findings suggest the triggering of a stopping rule, in which case the data for the subjects in question may be unblinded (e.g, if a drug related serious AE [SAE] occurs, identifying whether the subject received MW151 or placebo to determine whether the stopping rule should be triggered). If the data raises questions about safety, the subsequent dose for cohorts may be modified by one of the following: 1) repeating the previous dose, 2) administering an intermediate dose, or 3) terminating dose escalation.
Study Location	1 site located in the United States (US)
Sample Size and Population	40 healthy volunteers who are between the ages of 18-50 years inclusive and weight ≥50kg, with BMI ≤34 kg/m2 inclusive will be enrolled into this study. A complete list of all inclusion/exclusion criteria can be found in section 4 of this protocol.

Statistical Considerations	Six actively treated subjects per cohort of 8 (n = 6 MW151, n = 2 placebo) are considered sufficient to provide information on the PK profile and an estimation of safety and tolerability of MW151. Although the sample size is not based on a statistical power calculation, with 30 actively treated subjects the probability of observing at least 1 AE with true frequencies of 0.1%, 1%, 5% and 10% is as follows: All subjects who receive any study treatment will be included in the safety analysis grouped by treatment received. Statistical analysis of safety data will be descriptive. PK analysis will include, but not be limited to C_{max}, T_{max}, AUC, $T_{½}$ and K_{el}

AE Frequency	N=30
0.1%	0.030
1%	0.260
5%	0.785
10%	0.958

1 STUDY OBJECTIVES

1.1 Primary Objectives

To assess the safety and tolerability of single ascending doses of MW151 when administered orally to healthy adult volunteers.

1.2 Secondary Objectives

To assess the PK profile of single ascending doses of MW151 when administered orally to healthy adult volunteers.

2 BACKGROUND

2.1 Rationale

Rationale for Study and Disease Indication: Cognitive decline and deterioration of long-term cognitive performance are major side effects of CNS cancer treatment. Brain metastases are the most common CNS malignancies and a common cause of morbidity and mortality in up to 40% of all cancer patients with systemic disease, affecting over 170,000 patients in the US annually (Khuntia et al., 2006; Langer & Mehta, 2005). The main treatment modalities for brain metastases include surgery, whole brain radiation therapy (WBRT) and/or stereotactic radiosurgery. Despite the advantages of WBRT for disease control, cognitive impairment can be seen as early as 3 to 6 months after WBRT, and affects approximately 80-90% of patients, with memory and executive function being the major cognitive domains affected (Greene-Schloesser & Robbins, 2012; Khuntia et al., 2006; Langer & Mehta, 2005). Although the mechanisms underlying the treatment-induced cognitive decline are not completely understood, proinflammatory cytokine overproduction by activated glia after radiation therapy has been consistently implicated in the pathogenesis of WBRT-induced cognitive impairment (Greene- Schloesser & Robbins, 2012; Lumniczky et al., 2017; Warrington et al., 2013). Therefore, therapies that reduce the radiation-induced inflammatory response and subsequent neuronal damage should be explored as a potential adjunctive strategy for reducing WBRT-induced cognitive decline in patients with brain metastases.

More broadly, neuroinflammation, or dysregulated inflammation in the brain, is generally accepted as a contributor to disease susceptibility and pathophysiology progression in a wide range of neurodegenerative disorders associated with cognitive impairment such as Alzheimer's disease (AD) and related dementias, traumatic brain injury (TBI), and seizure disorders (Andreasson et al., 2016; Heneka et al., 2015; Heppner et al., 2015; Van Eldik et al., 2007; Van Eldik et al., 2016). A specific aspect of neuroinflammation, proinflammatory cytokine overproduction from abnormally activated glia, is associated with disease progression and is a druggable process for potential disease modification. However, drugs that target this pathological mechanism are severely underrepresented in the portfolio of candidates being advanced for CNS disorders (Cummings et al., 2018; Fillit et al., 2017).

Our clinical candidate **MW01-2-151SRM (=MW151**), was developed as part of ongoing attempts to fill this clinical void. MW151 is a novel, CNS-penetrant, orally bioavailable, small molecule drug candidate that selectively suppresses stressor-induced proinflammatory cytokine overproduction with resultant amelioration of synaptic damage and cognitive impairment (Hu et al., 2007). The efficacy and pharmacodynamics (PD) of MW151 are evident across a dozen diverse animal studies where cytokine overproduction is a contributor to pathophysiology progression. MW151 exhibits efficacy, at low doses. It does not bring about immunosuppression or a non-selective anti-inflammatory action. There is no evidence of suppression of basal cytokine levels characteristic of homeostasis. Function at efficacy doses involves restoration to homeostasis after disease or injury induced increases.

Overall, nonclinical efficacy findings and safety profile from nonclinical safety studies suggest that MW151 holds the potential to be useful clinically in treating multiple CNS disorders with cognitive impairment complications. In addition, based on its mechanism of action, MW151 could have disease-modifying effects not only in dementias, but also in a number of acute CNS injuries where proinflammatory cytokine dysregulation is part of the pathophysiology progression mechanism. Finally, MW151 is attractive for development as a stand-alone disease-modifying therapeutic or as part of an armamentarium of therapeutic approaches to alter disease progression in cognitive disorders.

2.2 Rationale for Dose Selection

To calculate the doses of MW151 to use in this FIH trial, we followed the FDA Guidance for "*Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers.*" We based our dose calculations on NOAEL dose levels from two rat 28- day toxicology studies, as well as the dose with minimal changes in ECG measurement from the dog cardiovascular safety pharmacology study. In one of the rat tox studies the NOAEL was 10 mg/kg in male rats and 30 mg/kg in female rats. In the other rat toxicology study, the NOAEL was 30 mg/kg in both male and female rats. The dog cardiovascular safety pharmacology study revealed only minimal ECG changes at 10 mg/kg. **Table 1** summarizes NOAELs and exposures from the MW151 non-clinical safety program. Based on the human equivalent dose (HED) and AUC, we based our calculations on the most conservative value of 10 mg/kg in male rats. For a 60 kg human subject, this corresponds to a HED of 96 mg. With a 10-fold safety margin, the planned starting dose for FIH clinical studies of MW151 is 10 mg. Therefore, cohort 1 will receive 10 mg, and we plan to double the dose in each subsequent cohort (cohort 2: 20 mg, cohort 3: 40 mg, cohort 4: 80 mg, cohort 5: 160 mg). Cohorts 2 – 5 will consist of female subjects only. These doses may be varied based on the safety review. Efficacious doses of MW151 in mouse models range from 0.5 to 5 mg/kg, which would represent HED ranging from 0.04 to 0.4 mg/kg (=2.4 – 24 mg in a 60 kg human). Thus, the proposed doses in the phase 1a are predicted to be well within the range to provide efficacy in future phase 2 studies.

Table 1: Summary of NOAELs from the MW151 toxicology program

Study Type	Study No.	Strain/Species	NOAEL (mg/kg)	C_{max} (ng/mL)	AUC_{last} (ng x h/mL)	HED (mg/kg)	HED (mg)
28-day	465975	Wistar rat	10 (M)	473	1,480[#]	1.6	96
			30 (F)	937	3,850[#]	4.8	290
28-day	16/301-100P	Sprague-Dawley rat	30	2,790	14,200	4.8	290
28-day	465997	Beagle dog	15	2,220	3,550	8.3	500
28-day	16/301-100K	Beagle dog	25	1,920	12,000	14	840
CV safety pharmacology	1016-2142	Beagle dog	10[&]	n/a	n/a	5.6	340

PK parameters are provided for Day 28 or Week 4. HED conversion factors used were 6.2 and 1.8 for rat and dog, respectively.
For studies with a single NOAEL for both genders, PK parameters are provided as the mean of male and females.
[#] Week 4 AUC values were significantly lower than on Day 1 in this study. Day 1 AUC values in Study 465975 are comparable to Week 4 AUC values in Study 16/301-100P.
[&] A NOAEL was not formally determined in this study. The listed dose level revealed only minimal ECG changes.
CV: cardiovascular

2.3 Supporting Data

Name and Description of Investigational Product: MW01-2-151SRM is the archival ID of the title compound, which is the free base (also referred to by its shortened nickname, MW151), with a molecular weight of 332.40. The MW151 clinical API drug substance (MW151 HCl) is known chemically as 2-(4-(4-methyl-6-phenylpyridazin-3-yl)piperazin-1-yl) pyrimidine dihydrochloride hydrate. It has a molecular formula of $C_{19}H_{20}N_6 \bullet 2HCl \bullet H_2O$ and formula weight of 423.34. MW151 HCl is a white to beige to light yellow powder that is slightly hygroscopic and soluble in water. The

product is available as a capsule filled with the appropriate amount of test substance. In the studies described here, MW151 will refer to the MW151 HCl drug substance unless explicitly stated otherwise.

2.3.1 Nonclinical Studies Pharmacology:

The pharmacological mechanism of action of MW151 is to selectively suppress stressor- induced proinflammatory cytokine overproduction, with resultant amelioration of synaptic damage and cognitive impairment. In *in vitro* based glial activation assays, treatment with MW151 exhibited concentration-dependent suppression of several proinflammatory cytokines typically upregulated by microglia in neurodegenerative disorder, such as IL-1β and TNFα. In addition, in multiple animal models of CNS diseases, MW151 treatment produced histological and biochemical findings consistent with the ability to significantly attenuate glial activation and proinflammatory cytokine overproduction. The inhibition of glial proinflammatory response correlated well with attenuation of synaptic and behavioral deficits. Importantly, this efficacy is achieved in the absence of any signs of general immunosuppression or non-selective anti- inflammatory action, and no suppression of basal cytokine levels in normal animals.

Preclinical Models of Radiation-Induced Impairment: The therapeutic potential of MW151 for radiation induced cognitive impairment was studied in adult, male Fisher 344 rats subjected to whole-brain irradiation (WBI, 10Gy). Twenty-four hours post-WBI, treatment with once daily 5 mg/kg MW151 i.p. or vehicle control was initiated and continued for 28 days. Proinflammatory activated microglia in the dentate gyrus were assayed at 2 and 9 months post-WBI. Cell proliferation and neurogenesis in the dentate gyrus were assayed at 2 months post-WBI. Novel object recognition and long-term potentiation were assayed at 6 and 9 months post-WBI, respectively. MW151 mitigated radiation-induced neuroinflammation at both early and late time points post-WBI, selectively mitigated the deleterious effects of irradiation on hippocampal neurogenesis, and potently mitigated radiation-induced deficits of novel object recognition consolidation ↓ restoring performance to sham-control levels ↓ and of long-term potentiation induction and maintenance (Jenrow et al., 2013).

MW151 was also studied in a model of radiation-induced skin injury in C57BL/6 mice, which received focal irradiation (30Gy) on the right hind leg, followed by 5 mg/kg i.p. administration of MW151 three times per week for 21 days, beginning 3, 7, or 14 days post-irradiation. Infiltrating macrophages were persistently increased in irradiated skin and were reduced by MW151 treatment. Irradiated skin also exhibited persistent increases in cells expressing inflammatory cytokines, TGF-β, TNF-β and MMP9. Relative to radiation alone, MW151 administration initiated on days 7 and 14 dramatically reduced expression of these markers in skin from mice that responded to MW151 therapy when assayed at 60–70 days post-irradiation, with skin injury scores showing improvement starting at Day 28 post-irradiation (Jenrow et al., 2014).

Preclinical Models of Other CNS Disorders/Injury: Complementary pharmacological findings in a variety of nonclinical models of CNS disease and injury indicate that MW151 can effectively limit upregulated glial inflammatory responses and provide neurologic and functional improvements. **Table 2** shows a summary of MW151 efficacy and PD in a variety of preclinical animal models.

Table 2: Summary of MW151 Efficacy and Pharmacodynamics (PD) in Preclinical Animal Models

Experimental System	Efficacy and PD Endpoints
Therapeutic radiation (TR)-induced brain injury model (Jenrow et al., 2013; PMCID:PMC3673739)	Improved novel object recognition performance; Reduced microglial activation; reduced impairments in neurogenesis.
TR-induced skin injury model (Jenrow et al., 2014; PMID:25098729)	Attenuated skin injury; Reduced infiltrating macrophages and proinflammatory cytokine (PIC) up-regulation.
Aβ Infusion model (Hu et al., 2007; PMCID:PMC1868432)	Attenuated cognitive deficits; Suppressed PIC up-regulation; decreased astrocyte and microglial activation; prevented loss of synaptic proteins.
APP/PS1 knock-in model (Bachstetter et al., 2012; PMCID:PMC4396836)	Attenuated LTP deficits in hippocampal slices; Repeat long term daily administration attenuated astrocyte and microglial activation; prevented synaptic protein loss; selectively suppressed PIC up-regulation; no effect on Aβ levels or amyloid plaque burden. Short term daily administration prevented synaptic protein loss; selectively suppressed PIC up-regulation; no effect on Aβ levels or amyloid plaque burden.
TBI mild diffuse CHI model (Bachstetter et al., 2015; PMCID:PMC4396836)	Attenuated cognitive impairments; Suppressed PIC up-regulation dose-dependently; decreased microglia and astrocyte activation.
TBI moderate diffuse CHI model (Lloyd et al., 2008; PMCID:PMC2483713)	Attenuated cognitive impairments; Suppressed PIC up-regulation in hippocampus and cortex; attenuated astrocyte activation; reduced neuronal injury.
TBI midline fluid percussion injury model (Bachstetter et al., 2016; PMCID:PMC4752278)	Dose-dependent suppression of PIC up-regulation; no effect on microglia cell morphology, proliferation, migration, or phagocytosis.
EAE model of multiple sclerosis (Karpus et al., 2008; PMCID:PMC2614915)	Reduced incidence/severity of clinical disease; Reduced spinal cord TNFα levels at peak and CCL2 levels at onset and peak of clinical disease; reduced infiltration of macrophages into the spinal cord at peak clinical disease.
Kainic acid (KA)-induced seizure model (Somera-Molina et al., 2007; PMID:17521344)	Protection after early-life seizures; Attenuated PIC up-regulation in hippocampus; reduced astrocyte activation.
KA KA Two-hit model (Somera-Molina et al., 2009; PMCID:PMC2739829)	Treatment following early-life KA insult reduced seizure susceptibility and cognitive impairment after a 2nd KA insult in adults; Reduced proinflammatory cytokine upregulation, microglial & astrocyte activation, and neuronal injury.

Experimental System	Efficacy and PD Endpoints
INCL disease model (Macauley et al., 2014; PMCID:PMC4172802)	In combination with AAV gene therapy, MW151 improved longevity, motor performance in rotorod, and eradicated seizures (chronic admin, 2.5 mg/kg); MW151 alone decreased seizure frequency; In combination with AAV gene therapy, decreased brain atrophy; reduced astrocyte and microglial activation; small effect on proinflammatory cytokine upregulation.
TBI AD Two-hit model (Webster et al., 2015; PMCID:PMC4405562)	Reduced cognitive impairment when administered after diffuse TBI in AD mice; Reduced PIC up-regulation and astrocyte activation.
TBI ECS Two-Hit Model (Chrzaszcz et al., 2010; PMCID:PMC2942875)	Treatment following TBI (1st insult) reduced seizure severity and cognitive impairment after electroconvulsive shock (2nd insult); Reduced astrocyte and microglial activation, PIC up-regulation and neuronal injury seen after ECS to levels achieved in animals given only TBI insult.

Overall, the nonclinical pharmacology data suggest that MW151 can exert a positive influence on post-injury neurologic outcomes by blunting the brain's intrinsic inflammatory response to CNS insults or disease over a dose range of 0.5 – 10 mg/kg when administered intraperitoneally (i.p.) and 2.5 – 15 mg/kg when administered orally (p.o.). MW151 can suppress the excessive activation of microglia, and their proinflammatory effector responses. The drug is effective at limiting pathophysiological sequelae and secondary neuronal injury in CNS-inflammatory disease relevant animal models, including rodent models of radiation-induced cognitive impairment.

MW151 is moderately well, orally absorbed in rat and dog (F%=23-47%) and distributes into the CNS with brain-plasma ratios > 1. Plasma protein binding of MW151 is high in rat, dog and human with 97.2, 93.9 and 97.1%, respectively.

MW151 appears to be preferentially metabolized by CYP1A2. MW151 has the potential to inhibit CYP2C8 (IC_{50} = 1.6-12 μM) and to induce CYP3A4 at concentrations ≥ 0.4 μM.

ECG measurements in Beagle dogs revealed increases in QT_c prolongation at MW151 doses ≥ 30 mg/kg. These findings appear to be associated with total peak plasma concentrations that are higher than the hERG IC_{50} value for MW151 (9.21 μM) or > 2,400 ng/mL. At the highest proposed clinical dose for the SAD Ph1 Study (160 mg), the corresponding preclinical dose in dog based on BSA conversion (4.8 mg/kg) would be associated with plasma C_{max} values below 2,400 ng/mL.

In 28-day repeat dose toxicity studies in rat and dog, the testes and epididymis were identified as the principal target organs of toxicity of MW151. Macroscopic, organ weight and microscopic findings in testes have been observed in Wistar rats and Beagle dogs. Sprague-Dawley rats did not show the same testicular toxicity effects of MW151 as Wistar rats, and instead showed only slight reduction in the weight of seminal vesicles at comparable dose levels. Increases in liver function enzymes and bilirubin were observed in some studies at the upper part of the evaluated dose spectrum. These findings typically were mild in nature or reversible and had no histopathological correlates in any of the studies performed.

MW151 was found to be non-mutagenic in two GLP Ames assays and negative in in vivo micronucleus studies in mouse and rat. Two out of the three in vitro mammalian cell assays

suggested a genotoxic potential of MW151. MW151 showed mutagenic or weak clastogenic potential in the mouse lymphoma and human lymphocyte mammalian cell genotoxicity assays, respectively, but was negative for clastogenicity in a chromosome aberration assay in V79 Chinese hamster cells. Given the lack of consistent reproducibility of the genotoxic findings, the presence of two negative in vivo micronucleus assays and two negative bacterial reverse mutation assays, and the fact that potential genotoxic findings were only observed with non- GMP batches of MW151, the sponsor concludes that the potential for genotoxity is low and acceptable in the context of a First-in-Human single ascending dose study (Jacobson-Kram & Jacobs, 2005), and that the risk/benefit profile with respect to genotoxicity is acceptable for repeat-dosing in the intended patient population undergoing treatment for brain tumors.

Based on the totality of the data, the Wistar rat was considered the most sensitive species/strain in the context of the MW151 toxicology program. Therefore, the NOAEL for Wistar male rats (10 mg/kg/day) in Study No. 465975 following 28-day dosing with MW151 has been selected for the estimation of the safe starting dose for FIH clinical studies in healthy volunteers. Based on human equivalent dose (HED) conversion and a 10-fold safety factor, a FIH starting dose of 10 mg MW151 (free base equivalent) is being proposed.

Previous Human Experience: None. The phase 1a SAD trial will be a first-in-human study of MW151.

3 STUDY DESIGN

Approximately 40 healthy adult subjects, ages 18-50 years, will be dosed in 1 of 5 dosing cohorts of 8 subjects each (6 MW151, 2 matched placebo). Cohort 1 will consist of males and females; cohorts 2 – 5 will consist of females only. Each subject will receive 1 oral dose level of MW151. Five different doses of MW151 will be evaluated in 5 sequential cohorts. Dosing will start at the lowest dose, then escalate in the 2nd cohort, then escalate sequentially in the 3rd, 4th, and 5th cohorts. Plasma samples drawn at sequential time points for PK analysis; safety parameters monitored. Subjects will be followed in a dedicated inpatient unit at the clinical site, and will receive standardized meals during the Inpatient Phase.

As a safety consideration two sentinel subjects in each cohort will be administered MW151 or placebo in a 1:1 ratio.

Following review of sentinel safety and tolerability data for the first 24 hours of dosing in each cohort (including reported adverse events [AEs], physical examination findings, clinical laboratory results, vital signs, and electrocardiograms [ECGs]), the remaining 6 subjects will be randomized in a 5:1 ratio. Dosing of the remaining subjects in a cohort may proceed after review of sentinel subject safety data collected during the first 24 hours of dosing and determination that no stopping rules are met. The remaining subjects in each cohort will be dosed sequentially, not simultaneously.

After the completion of each cohort (Cohorts 1-5), the DSMB will review all available safety data before the dosing of the sentinel subjects of the next cohort. There will also be an interim PK analysis after the completion of Cohort 2.

Data from Cohorts 1-5 will be reviewed in a blinded manner, unless the findings suggest the triggering of a stopping rule, in which case the data for the subjects in question may be unblinded (e.g, if a drug related serious AE [SAE] occurs, identifying whether the subject received MW151 or placebo to determine whether the stopping rule should be triggered).

Dosing will start in cohort 1 at 10 mg of MW151, then escalate to a planned dose doubling in each subsequent cohort (cohort 2: 20 mg, cohort 3: 40 mg, cohort 4: 80 mg, cohort 5: 160 mg). These doses may be varied based on the safety review, but the maximum dose will not exceed 160mg without amending the protocol. Should the safety data warrant, dose levels may be reduced or additional cohorts added in order to generate a comprehensive understanding of the clinical dose range. Should additional cohorts be required above the planned 5 cohorts or doses within the planned cohorts changed, a protocol amendment will be submitted to the FDA and the Independent Ethics Committee for approval before implementation.

4 SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Inclusion Criteria

A subject will be eligible for inclusion in the study only if **all** of the following criteria are met:

1. Willing and able to provide written informed consent prior to initiation of any study-related procedures.
2. For Cohort 1: Men and women aged 18 to 50 years, inclusive; For Cohorts 2-5: Women aged 18 to 50 years, inclusive.
3. In good health as determined by medical history, physical exam, laboratory examinations, ECG, and vital signs.
4. Weight ≥50kg
5. BMI ≤34 kg/m2.
6. ECG without clinically significant pathologic abnormalities and with QTcF <450 ms at Screening.
7. Systolic BP ≤ 150 mmHg and diastolic BP ≤ 90 mmHg at Screening, measured after 10 to 15 minutes of rest.
8. No suicidal ideation, as demonstrated by a score of "0" on the Columbia Suicide Severity Rating Scale (C-SSRS).
9. Women who are neither pregnant (negative pregnancy test) nor nursing, and are either:
   a) Surgically sterile (bilateral tubal ligation, hysterectomy), or
   b) Postmenopausal with last natural menses greater than 24 months, or
   c) Premenopausal and agrees to use an acceptable form of birth control during the study and for 1 month after dosing. Acceptable forms of birth control include: approved hormonal contraceptives (such as birth control pills, patches, implants, or injections), intrauterine device (IUD), or barrier methods (such as condom or diaphragm) used with a spermicide. All female subjects must have a negative serum pregnancy test at screening and negative urine pregnancy test upon admission to the unit prior to dosing.
10. Men who are surgically sterile or who agree to use a condom with spermicide if sexually active during the study and for 1 month after dosing.
11. Adequate venous access for blood draws.

4.2 Exclusion Criteria

A subject will not be eligible for inclusion in the study if **any** of the following criteria are met:

1. Any unstable chronic medical condition (i.e. hypertension, diabetes mellitus type 2) requiring interventional treatment that might increase the risk to the subject or confound interpretation of safety observations. Subjects who are considered stable and who have been receiving stable treatment for medical condition for ≥ 3 months may be considered with approval of medical monitor.
2. Evidence of active infection requiring antibiotic therapy within 14 days prior to dosing.
3. Medical history of vasculitis or any autoimmune disease excluding seasonal allergic rhinitis and childhood history of atopic dermatitis.
4. History of any treatment for cancer within the past 2 years, other than basal cell or squamous cell carcinoma of the skin.

5. Seropositive for human immunodeficiency virus (HIV).
6. History of acute/chronic hepatitis B or C and/or carriers of hepatitis B (seropositive for Hepatitis B surface antigen [HbsAg] or anti-Hepatitis C [HCV] antibody).
7. Clinically significant abnormalities in screening laboratory tests, including:
    a. Absolute neutrophil count < 1.4 $x10^9$
    b. Alanine transaminase (ALT) or aspartate transaminase (AST) > 1.5 x upper limit of normal (ULN)
    c. Absolute lymphocyte count < 0.6 x 10^9
    d. Total bilirubin level > 1.6 mg/dL
    e. eGFR < 60 mL/min
    f. Any lab abnormalities deemed clinically significant.
8. Over-the-counter and herbal medications are prohibited within 10 days prior to study dosing (with exception of calcium/vitamin D supplements and ocular medications at the discretion of the Investigator). Stable doses (≥ to 3 months of stable dose) of prescription medications are allowed with the approval of the medical monitor (birth control medications are allowed without medical monitor approval). Subjects should not be on non-steroidal anti-inflammatory drugs or immunosuppressive drugs within 10 days prior to dosing.
9. Use of known CYP450 CYP1A2, CYP2D6 or CYP3A4 inhibitors or inducers within 14 days of dosing or planned use during the study.
10. Use of an investigational drug, vaccine, device, or blood product within 3 months prior to dosing in this study.
11. Any disorder that could interfere with the absorption, distribution, metabolism or excretion of drugs (e.g. small bowel disease, Crohn's disease, celiac disease, or liver disease.)
12. Psychiatric history of current or past psychosis, bi-polar disorder, clinical depression, or anxiety disorder requiring chronic medication within the past 2* years.
13. *Short-term (<90 days) use of antidepressants and/or anxiolytics will be assessed by investigator and approved by medical monitor prior to determining eligibility.History of substance abuse including alcohol within the past 5 years.
14. Use of any nicotine containing products within 30 days of screening visit or Day -1 admission.
15. Current substance or drug dependence confirmed by positive urine drug screen at screening visit or Day -1 admission.
16. Current alcohol abuse confirmed by positive breathalyzer at screening visit or Day -1 admission.
17. History of serious head injury as determined by the site investigator or designee.
18. Chronic kidney disease (defined as the presence of any degree of proteinuria on urine analysis and/or an eGFR of <60 ml/min using the MDRD formula).
19. Any reason or opinion of the investigator that would prevent the subject from participation in the study.
20. Inability to follow the instructions or an unwillingness to cooperate with study procedures.
21. Has donated more than 500 mL of blood within the last month prior to dosing.

4.3 Subject Withdrawal Criteria

Subjects may withdraw from the study for any reason at any time. The Investigator may discontinue subjects from the study in order to protect subject safety and/or if the subject is unwilling or unable to comply with required study procedures. Subjects may also be withdrawn from the study if the Sponsor or Regulatory Authorities terminate the study prior to its planned end date.

Should a dosed subject terminate prematurely from the residential phase of the study, the Investigator will make every effort to complete the Early Termination evaluations as scheduled for Day 3 before the subject is discharged.

Subjects discontinuing after randomization but before dosing may be replaced. Subjects discontinuing after dosing may be replaced. If a dosed subject is withdrawn or withdraws due to safety reasons, they will not be replaced. Decisions to replace dosed subjects for other reasons will be made on a case-by-case basis depending on the timing of the discontinuation.

4.4 Study Enrollment Procedures

Subjects will be identified by a unique ID number and initials throughout their participation in the trial. Once randomized, each subject will also have a unique randomization number. Subjects will only be identified numerically in final data tables and listings; no initials will be presented.

Sufficient numbers of subjects will be enrolled into the Screening Phase to ensure at least 8 eligible subjects are available for dosing in each dosing group.

A subject who screen fails at any point pre-dose (Screening through Day 1 pre-dose, inclusive) due to exclusionary findings may **not** be rescreened for the study.

A subject who has been screened but not randomized for non-exclusionary reasons may still qualify for entry into the study as follows:

A subject admitted to the clinical research unit based on acceptable Day -1 findings but who is not randomized on Day 1 (i.e., alternate or logistical/administrative reason) is permitted to remain in the clinical research unit for up to an additional 2 overnight stays to be re-evaluated for dosing. Dosing must occur within 28 days of Screening. Subjects must remain 'residential' during this time and must follow all other restrictions as previously outlined. Day -1 tests need not be repeated, however, any new medical history must be recorded and all Day 1 pre-dose tests must be performed on the 'new' Day 1.

A subject admitted to the clinical research unit based on acceptable Day -1 findings but who is not randomized on Day 1 (i.e. alternate or logistical/administrative reason) and is discharged from the clinic may return once to repeat Day -1 tests and be re-evaluated for dosing. Dosing must occur within 28 days of Screening and all Day -1 procedures must be repeated.

A subject who has been screened but not randomized due to non-exclusionary reasons and is outside the 28 day Screening window may be rescreened once. The subject must repeat the entire Screening visit.

4.4.1 Subject Recruitment and Retention

Participants may be recruited from clinics or existing recruitment registries at the participating site. Postings may be placed on the participating site website. Flyers about the study may be sent to community neurologists. Webinars will be conducted for participant recruitment as needed. Interested participants will be contacted by the investigators or their staff and invited to participate. These recruitment strategies will include a mechanism by which the patients can provide their contact information.

4.4.2 Screening Logs

Screening logs to document reasons for ineligibility and reasons for nonparticipation of eligible subjects will be stored centrally.

4.4.3 Informed Consent

Written informed consent will be obtained from each study participant before any study-specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained. The participant's willingness to participate in the study will be documented in writing in a consent form approved by the Institutional Review Board (IRB), which will be signed by the participant with the date of that signature indicated. The investigator will keep the original consent forms and a copy will be given to the participant. It will also be explained to the participant that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.

Written and/or oral information about the study in a language understandable by the participant will be given to all participants.

4.4.4 Assent

Not Applicable

4.4.5 Randomization/Treatment Assignment

An independent statistician will be responsible for generating the randomization scheme.

The randomization scheme for this study will assign subjects to treatment or placebo in sentinel groups of 2 subjects with a 1:1 ratio (1 drug: 1 placebo), followed by groups of 6 individuals with a 5:1 ratio (5 drug: 1 placebo), so that in each dosing cohort 6 subjects will receive MW151 and 2 subjects will receive placebo (see **Table 3**). Randomization numbers will start at 001.

Table 3: Randomization Scheme

Groups	Subjects per Group (MW151: Placebo)	Dose Level	Subjects per Dose Level (MW151: Placebo)
1 2	2 (1:1) 6 (5:1)	10 mg MW151 or placebo	8 (6:2)
3 4	2 (1:1) 6 (5:1)	20 mg MW151 or placebo	8 (6:2)
5 6	2 (1:1) 6 (5:1)	40 mg MW151 or placebo	8 (6:2)
7 8	2 (1:1) 6 (5:1)	80 mg MW151 or placebo	8 (6:2)
9 10	2 (1:1) 6 (5:1)	160 mg MW151 or placebo	8 (6:2)

After a subject is confirmed eligible for dosing on the afternoon/evening of Day -1 or morning of Day 1, the study staff will allocate the next available randomization number to the subject, starting at the lowest number and continuing in a consecutive manner.

Once a randomization number has been assigned, it cannot be re-assigned to any other subject. To respect treatment allocation and the overall study design, replacement subjects will receive the same treatment assignment as the original subject who is being replaced and their randomization number will be the initial randomization number plus 100 (i.e. a subject replacing ‘009’ will have the number ‘109’).

5 STUDY INTERVENTIONS/STUDY MEDICATION/STUDY DRUG

5.1 Study Medications/Interventions, Administration, and Duration

Drug or placebo will be administered orally in a filled capsule. Subjects will receive a single dose on day 1. Subjects will be dosed in an inpatient facility at the study site.

At the proposed single clinical doses, adverse events related to target organ toxicities observed in non-clinical studies (testicular toxicity, QT interval prolongation) are unlikely to occur, but the investigator should be aware of these findings. There may be other risks, discomforts, or side effects that are currently unknown. These may include rashes, GI upset, or allergic reactions.

After dosing, the Medical Monitor may prescribe any concomitant therapy deemed necessary to provide adequate supportive medical care. More details are given below.

5.2 Handling of Study Medications/Interventions

Drug appearance, packaging and storage: The preparation of the study drug (filling of MW151 drug substance into capsules without any excipients just before use) will be done by a qualified compounding pharmacy, and supplied to the site pharmacy. The study medication will be prepared for the required dose of each cohort.

Study drug must always be stored in a secure location with access limited to designated study staff members. Study drug must be stored in a refrigerator at 2-8^{o}C. Temperature logs will be maintained to verify correct storage conditions throughout the trial.

Blinding and Emergency Code Envelopes: During this study, subjects and all study staff will be blinded to treatment allocation, except as noted below. Sponsor staff will be blinded to treatment allocation. However, Sponsor staff member(s) will be designated as unblinded to enable handling and review of PK data and drug accountability prior to database lock. Safety reviews between dosing cohorts will be performed in a blinded manner unless the data warrants unblinding due to safety concerns.

The site pharmacy staff will be unblinded so that the appropriate test article (MW151 or placebo) can be dispensed appropriately as per the randomization schedule. The unblinded staff will not participate in any other study evaluations.

In an emergency, the blind may be broken and unblinded safety data provided to the Medical Monitor if requested. Should unblinding of the Medical Monitor occur, this must be recorded in the source documents and the study PI should be notified as soon as possible. Breaking of the blind for non-safety reasons will be considered a protocol violation.

Product Preparation: Drug and matched placebo will be provided as an oral capsule(s) containing the appropriate amount of drug required for each cohort. All doses will be administered to the subjects by appropriately qualified personnel.

Product Accountability: The site will use Sponsor-approved product accountability records. The completeness and accuracy of all accountability records will be monitored throughout the course of the study, including study drug receipt, preparation and use, destruction and return.

Upon receipt of a shipment of MW151, site staff will check the condition of the shipping containers and perform a reconciliation of study drug with the shipment logs, notifying the monitor immediately of any problems. In situations where study drug (MW151 or placebo) is dispensed but not used, the dispensed medication should be returned to the pharmacy and segregated until review by the unblinded monitor. After accountability is complete, unused study drug can be discarded according to the study site's normal procedures. All study drug (used/unused) remaining at the completion of the study will either be returned to the pharmacy or will be destroyed at the study site. In case of the latter, the study site will supply destruction records to the investigator.

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of investigational product dispensed and/or administered to study subjects, the amount received from the central pharmacy, and the amount destroyed upon completion of the study. An investigator is responsible for ensuring product accountability records are maintained throughout the course of the study. The inventory will include details of MW151 received and dispensed to subjects, batch, and ID numbers. All unused capsules must be kept until reconciliation of delivery records with accountability logs by the monitor. After the monitor has performed accountability, the site will be instructed to either destroy the remaining study medication or return it to the Central Pharmacy or manufacturer. An accounting must be made of any drug deliberately or accidentally destroyed. Discrepancies between the amount of MW151 received and dispensed drug must be reconciled.

5.3 Concomitant Interventions

After dosing, the site PI or qualified designee may prescribe any concomitant therapy deemed necessary to provide adequate supportive medical care. After discharge the subject should refrain from any medication other than that required for supportive medical care. All medications will be recorded in subject charts.

5.3.1 Required Concomitant Medications/Interventions

Subjects are required to fast for at least 10 hours before all safety laboratory samples. Subjects are allowed water ad libitum. Breakfast may be given on Day 1 before dosing; other meals and snacks may be served at the study site's standard times. The study site will provide subjects with standard meals and snacks while in the Phase 1 unit. The daily menu information will be included in the final clinical report as an appendix.

5.3.2 Prohibited Medications/Interventions

Describe procedure for handling situation(s) when subject uses prohibited intervention during study participation. This may also be detailed in section 8: Criteria for Intervention Discontinuation.

Any antibiotic use within 14 days of Day 1 is prohibited. Subjects are not permitted any prescribed medication (other than birth control or other stable medications previously approved by the medical monitor) or any over-the-counter medication, health/herbal supplement or vitamin by any route of administration within 10 days of Day 1 inclusive other than to manage an adverse event.

Subjects are required to refrain from smoking, using nicotine-based products, alcohol and food or drinks containing caffeine throughout the residential phase. Subjects should refrain from strenuous physical exercise for 48h prior to entry into the Phase 1 unit until the Follow-up visit. Subject should refrain from alcohol consumption after discharge until the Follow-up visit is complete.

Subjects may not donate blood during the study.

5.3.3 Precautionary Medications/Interventions

None anticipated

5.4 Subject compliance

The phase 1a SAD study will be done in an inpatient facility, and therefore compliance of subjects with the study invention will be directly monitored by study personnel.

6 CLINICAL AND LABORATORY EVALUATIONS/STUDY PROCEDURES

6.1 Schedule of Activities

Day/Procedures	Screening (1)	-1 Admission	1	2	3 Discharge (2)	7 FU visit
Informed consent	X					
Inclusion/Exclusion Review	X	X				
Demographics	X					
Medical History	X	X				X
Columbia Suicide Severity Rating Scale	X					
Physical Examination (3)	X	X		X		X
Infection Screen (4)		X				
Body Temperature (5)	X	X	X	X	X	X
Neurological Examination (6)		X		X		
Safety Laboratory Tests (7)	X	X		X		X
Drug Screen (urine)	X	X				
Alcohol Screen (breathalyzer)	X	X				
Hepatitis B & C/ HIV Screen	X					
TB test (blood test)	X					
Pregnancy Test (serum at Screening/urine on D-1)	X	X				
12-lead ECG (8)	X	X	X	X	X	X
Vital signs (BP/HR) (9)	X	X	X	X	X	X
PK blood sampling (10)			X	X		
Admit to Unit/Randomization (11)		X				
Dosing (12)			X			
Apolipoprotein E (blood test) (13)			X			
Adverse Event Assessment			X	X	X	X
Concomitant Medication Review	X	X	X	X	X	X
Discharge from Unit					X	

Footnotes to Schedule of Activities
(1) Screening will occur within 28 days of dosing.

(2) Subjects who discontinue from the study should undergo all Early Termination assessments as per the Day 3 visit.
(3) Weight will be measured during all physical examinations and height will be measured at Screening only. Physical examination will include general appearance; head, eyes, ears, nose, throat (HEENT); cardiovascular; lung; abdominal; musculoskeletal; and skin.
(4) On Day -1, subjects will be screened for the presence of infection as part of physical examination, body temperature, recent/current antibiotic use, recent surgery, evidence of dental abscess, unhealed skin lesions etc. On Day 1 before dosing, subjects will be screened for emergence of acute illness.
(5) Body temperature will be measured at the following time-points:

- Screening
- Day -1
- Day 1 before dosing and again at 12h post-dose
- Day 2 – Day 3 approximately 24h and 48h, respectively, after dosing
- Day 7

(6) Neurological examination will include mental status evaluation, cranial nerves 2-12 testing, motor system and coordination testing, reflex evaluation and sensory system evaluation. The neurological examination should be conducted at the same time as the physical examination when both are scheduled on the same study day.

(7) Safety laboratory samples (Hematology/Coagulation/Biochemistry/Urinalysis) will be taken after the subject has fasted for a minimum of 10 hours as follows:

- Screening (all except creatine kinase, amylase, lipase)
- Day -1
- Day 2
- Day 7

(8) A 12-lead ECG will be performed (after lying quietly for 5 minutes). Triplicate tracings (3x) will be taken at Day -1 only and will serve as the Baseline (pre-dose measurement). ECGs will be performed at the following time points.

- Screening
- Day -1
- Day 1: approximately 1h, 2h, 4h, and 12h post-dose
- Day 2: approximately 24h post-dose
- Day 3
- Day 7

Subjects will be monitored on telemetry from approximately 30 min prior to dosing through the 4 hour post-dose ECG.

(9) Vital signs will include BP and HR. At each time point where vital signs are measured, heart rate and blood pressure will first be checked in the supine position and then in the standing position with at least 2 minutes between the supine and standing measurements. Vitals will be performed at the following time-points:

- Screening
- Day -1
- Day 1: Pre-dose and at 1h, 2h, 4h, and 12h post-dose

- Day 2: approximately 24h and 36h post-dose
- Day 3
- Day 7

(10) PK samples will be taken at the following time-points, anchored to the start of dosing.
- Day 1: Pre-dose, and 0.25h, 0.5h, 1h, 2h, 4h, 8h, 12h post-dose
- Day 2: 24h and 36h post-dose

(11) Randomization is expected to occur on D-1, but if there are delays in receiving prequalification safety labs randomization may occur on D1 prior to dosing.
(12) Dosing will be by oral capsule administration, on day 1.
(13) ApoE will be collected pre-dose on Day 1

6.2 Timing of Study Activities

Order of Tests: When several assessments are required at the same time point, evaluations should be completed in the following order, with **PK sample collection at the required time.** As such, it is understood that ECGs and vital sign measurements may be performed before the actual time point to allow for rest times and procedures:

- Fasting safety laboratory sample
- ECG (supine)
- Vital signs
- PK sample
    - Allowable Windows:
        - PK window for 15min, 30min and 1h post-dose samples: ± 5 minutes
        - PK window for ≥ 2h post-dose samples: ± 10 minutes
- Day 7 Follow-up visit: ± 1 day

6.2.1 Screening/Pre-Randomization Evaluations/procedures

Screening: Having given written informed consent, each subject will be required to undergo a medical screen within 28 days of Day 1. The subject will undergo the following procedures:

- Demographics
- Medical history
- Concomitant medication review
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Body temperature
- 12-lead ECG
- Vital signs (BP, HR)
- Physical examination (must be performed by an Investigator), weight and height
- Safety laboratory tests (fasting, minimum 10 hours). Note: During the phone screen, the subject will be asked to fast prior to her screening visit. After the subject consents at the

screening visit, they will be asked about their fasting status. If the subject states that they have not been fasting for the required time, laboratory samples will still be obtained and the laboratory requisition will be marked accordingly. The investigator will assess the results and if the glucose is within laboratory defined references or deemed not clinically significant by the PI or designee, then the laboratory test does not need to be repeated. In the event that the glucose is abnormal and potentially clinically significant, then the subject may be scheduled to come for an unscheduled visit to have a fasting laboratory glucose drawn.

- Serum pregnancy test (females only)
- Follicle Stimulating Hormone (suspected postmenopausal females only)
- Alcohol screen (breathalyzer)
- Hepatitis B, Hepatitis C, HIV screen
- Urine drug screen
- Quantiferon TB Gold PLUS test

Once complete, the screening evaluations should be reviewed against inclusion/ exclusion criteria to determine the subject's eligibility for continuation. The Sponsor may be involved in the eligibility review and the Medical Monitor may request subject exclusion for safety reasons.

- For those subjects who fail study screening the reason for screen failure will be recorded in the Screening Log. Data for screen failures will not be entered into database for this study.

Infection Screen: On Day -1, subjects will be screened for the presence of infection. This will be evaluated using physical examination findings, body temperature, evaluation of recent/current antibiotic use, any recent surgery, any evidence of dental abscess, unhealed skin lesions etc. Presence of, or the suggestion of infection are exclusionary.

Neurological Examination: The neurological examination will include:

Mental Status: Test for orientation to time, place and person: asking date, current location and what is his/her name. The subject should be able to follow at least one complicated command such as "lift your right shoulder".

Cranial Nerves 2-12: Test visual fields, visual acuity, pupillary reflexes, eye movements, fundoscopy, facial strength (including facial expression and mastication), hearing to finger rub, tongue, palate and head rotation movements, check for dysarthria and shoulder elevation.

Motor System and Coordination: Test strength in upper and lower limbs bilaterally, pronator drift, finger tapping, rapid pronation and supination movements, finger-nose, heel shin, tandem gait, walking on heels.

Reflexes: Test biceps, triceps, knee, ankle and plantar responses (Babinski's reflex).

Sensory System: Test light touch, vibration, Romberg test.

Safety Exclusions: Safety laboratory tests performed as part of Screening and Day -1 assessments **may not be repeated** if any quantitative exclusion criteria are met.

Pre-dose vital signs (Screening, Day -1, Day 1 pre-dose) may be repeated once at each visit to confirm exclusionary findings. In cases where the initial assessment is exclusionary and the repeat assessment is not, the Investigator must evaluate both sets of data and determine whether or not the subject may continue.

Pre-dose ECGs (Screening, Day -1 pre-dose) **may not be repeated** if any quantitative exclusion criteria (QTcF) are met. Other abnormal ECGs may be repeated once at each visit to confirm non-quantitative exclusionary findings. In cases where the initial assessment is exclusionary and the repeat assessment is not, the Investigator must evaluate both sets of data and determine whether or not the subject may continue.

Subjects must not be randomized if there are any clinically significant pre-dose findings on vital signs, ECGs, safety laboratory tests, physical examinations and/or neurological examinations.

Electrocardiogram: A standard 12-lead ECG will be collected at required time points (after lying quietly for 5 minutes). ECG parameters including HR, PR, QT, QTcB, QTcF, QRS, and RR intervals will be collected.

At Day -1, pre-dose triplicate ECG tracings will be obtained and will serve as the Baseline. At all other time points, a single ECG tracing will be obtained.

The tracings may be reviewed and reported both locally by the site PI or qualified designee and by a blinded Medical Monitor. The Day -1 pre-dose ECGs will be evaluated for Inclusion/ Exclusion by the Investigator and the Investigator's evaluation will prevail for any immediate subject safety management purposes. All clinically significant (CS) values should be reported as AEs and recorded into the AE source document/eCRF. All ECG tracings and central reader reports will be filed with each subject's chart.

Vital Signs: Vital signs will include BP and HR.

At each time point where vital signs are measured, heart rate and blood pressure will first be checked in the supine position and then in the standing position with at least 2 minutes between the supine and standing measurements. An appropriately sized cuff (cuff bladder encircling at least 80% of the arm) should be used to ensure accuracy of measurements. The arm used for measurements should be consistent throughout the study.

6.2.2 On-Study/On-Interventions Evaluations/procedures

During the time the subject is in the Phase 1 unit, subjects' observations about the tolerability of the capsule administration will be recorded.

Admission Procedures (Day -1): Subjects will arrive at the Phase 1 unit on Day -1 and will undergo procedures:

- Medical history (to determine any changes since Screening)
- Concomitant medication review
- Infection screen
- Body temperature

- Vital signs (BP, HR)
- ECG (triplicate)
- Physical examination (must be performed by an Investigator), weight
- Neurological exam (must be performed by an Investigator)
- Safety laboratory tests (fasting, minimum 10 hours)
- Urine pregnancy test (females only)
- Breathalyzer
- Urine drug screen
- Randomize the subject. Only subjects whose admission procedures, including safety labs performed on Day -1, meet eligibility criteria will be randomized. Randomization may occur on morning of Day 1 if necessary (e.g., delay in safety laboratory test reporting).

Day 1 – Dosing: A light breakfast will be given prior to dosing.

- Pre-dose vital signs
- Pre-dose body temperature
- Final eligibility review. Only subjects who are confirmed 'eligible' by the Investigator will continue for dosing.
- Start telemetry monitoring approximately 30 min prior to dosing
- Pre-dose PK and ApoE blood sample
- Administer study drug to subject (Time 0)
- 0.25h PK sample
- 0.5h PK sample
- 1h ECG
- 1h vitals
- 1hr PK sample
- 2h ECG
- 2h vitals
- 2h PK sample
- 4h ECG
- 4h vitals
- 4h PK sample
- 8h PK sample
- 12h ECG
- 12h vitals

- 12h body temperature
- 12h PK sample
- Adverse event (AE) assessment (continual throughout Day 1)
- Concomitant medication review (continual throughout Day 1)

PK samples will be taken at the actual required time and the other evaluations should be scheduled around the PK sample.

Day 2: Day 2 times are anchored to the Day 1 dosing time (Time 0). Subjects will fast for a minimum of 10 hours. Water is allowed.

- Fasting safety laboratory tests (blood and urine)
- Light breakfast (subject may decline)
- ECG approximately 24h post-dose
- 24h PK sample
- 24h vital signs
- Physical exam (must be performed by an Investigator), weight
- Neurological exam (must be performed by an Investigator)
- 24h body temperature
- 36h PK sample
- 36h vital signs
- AE assessment (continual throughout Day 2)
- Concomitant medication review (continual throughout Day 2)

PK sample will be taken at the required time and the other evaluations should be scheduled around the PK sample.

Day 3: Discharge. Assessments and Procedures on Day 3 are anchored to the dosing time on Day 1 (Time 0).

- Vital signs
- Body temperature
- ECG
- Light breakfast (subject may decline)
- AE assessment
- Concomitant medication review

Day 7 Follow-up Visit: May be scheduled on Day 6, 7, or 8.

Subjects will fast for a minimum of 10 hours. Water is allowed. Subjects will undergo the following procedures:

- Fasting safety laboratory tests (blood and urine)
- ECG
- Vital signs
- Body temperature
- Physical examination (must be performed by an Investigator), weight
- AE assessment
- Concomitant medication review

Treatment-related AEs ongoing at the Follow-up assessment will be followed until resolution or deemed stable, where feasible. Any Follow-up safety laboratory tests that are deemed clinically significant by the Investigator will be repeated and followed until stabilization at the discretion of the Investigator/Sponsor.

6.2.3 Study Medication/Intervention Discontinuation Evaluations/Procedures

Sufficient numbers of subjects will be enrolled into the Screening Phase to ensure 8 eligible subjects are available for dosing in each dosing group.

Subjects may withdraw from the study for any reason at any time. The Investigator may discontinue subjects from the study in order to protect subject safety and/or if the subject is unwilling or unable to comply with required study procedures. Subjects may also be withdrawn from the study if the Sponsor or Regulatory Authorities terminate the study prior to its planned end date.

Should a dosed subject terminate prematurely from the residential phase of the study, the Investigator will make every effort to complete the Early Termination evaluations, which consist of the procedures scheduled for Day 3 before a subject is discharged and a physical examination. A PK sample may be drawn at the discretion of the Investigator.

Subjects discontinuing after randomization but before dosing may be replaced. Subjects discontinuing after dosing may be replaced. If a dosed subject is withdrawn or withdraws due to safety reasons, they will not be replaced. Decisions to replace dosed subjects will be made on a case-by-case basis depending on the timing of the discontinuation.

6.2.4 Pregnancy

Women who are pregnant at screening or on Day -1 testing will not be allowed to enter into the study. The likelihood of a female subject becoming pregnant while receiving MW151 is highly unlikely because of the requirement for a negative pregnancy test on Day -1 and the requirement that an acceptable barrier form of birth control be used during the study. Therefore, a pregnancy consent form will not be needed and no additional evaluations will take place.

6.3 SPECIAL INSTRUCTIONS AND DEFINITIONS OF EVALUATIONS

6.3.1

6.3.1 Informed Consent

Written informed consent will be obtained from each participant by a study team member authorized to obtained consent. Informed consent will be obtained before any study-specific procedures or assessments are performed and after the aims, methods, anticipated benefits, and potential hazards are explained. The participant's willingness to participate in the study will be documented in writing in a consent form, approved by the IRB, which will be signed by the participant with the date of that signature indicated. The investigator will keep the original consent forms and copies will be given to the participants. It will also be explained to the participants that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. Written and/or oral information about the study in a language understandable by the participant will be given to all participants. HIPAA guidelines for confidentiality and the principles of medical ethics will be adhered to during the study.

6.3.2 Protocol Amendments and Study Termination

All revisions and/or amendments to this protocol must be approved in writing by the Sponsor and the IRB. The Investigator will not make any changes to the conduct of the study or the protocol without first obtaining written approval from the Sponsor and the IRB, except where necessary to eliminate an apparent immediate hazard to a study subject.

The Sponsor reserves the right to discontinue the study at a clinical study site(s) for safety or administrative reasons at any time. Should the study be terminated and/or the clinical study site closed for any reason, all documentation and study medication pertaining to the study must be returned to the Sponsor or its representative.

6.3.3 Pharmacokinetic Studies

Samples will be taken as described in Sections 6.1 and 6.2. Blood samples can be drawn via direct venipuncture or an indwelling catheter may be used. Catheters will be flushed with saline before and after sampling. Heparin flushing is not permitted.

If using a catheter, after the saline flush, withdraw and discard approximately 1.5 mL of blood before obtaining the sample to avoid sample dilution. Next, take 5 mL of blood into a pre-labeled plasma collection tube. Refer to the Laboratory Manual for the specific type of plasma collection tube to be used and for detailed sample processing instructions.

To avoid cross contamination of MW151 and placebo samples, separation of plasma aliquots should be done for one subject at a time, changing gloves between subject samples.

Following processing, plasma will be split into two aliquots. The 1st tube will be sent for PK analysis, and the 2nd tube will be a PK retention sample. Until samples are shipped to the analytical facility they will be frozen at -70°C (+ 10°C). Samples will be sent frozen on sufficient dry ice to maintain frozen conditions for at least 72 hours. The Sponsor will provide direction regarding the timing of sample shipment and sample destruction as applicable.

6.3.4 Laboratory Studies

Laboratory samples will be taken at the time points described in Section 6.1 and Section 6.2.2. Samples will be labelled per laboratory specifications. The parameters listed in **Table 4** will be evaluated:

Table 4: Laboratory Tests

Hematology & Coagulation	Biochemistry	Urinalysis
• Hemoglobin (Hb) • Hematocrit • Red blood cell count (RBC) • White blood cell count (WBC) • Mean cell Hb • Mean cell Hb concentration • Mean cell volume • Platelet count • Red Cell Distribution Width • % Basophils • % Eosinophils • % Lymphocytes • % Monocytes • % Neutrophils • Basophil count • Eosinophil count • Lymphocyte count • Monocyte count • Neutrophil count • Reticulocyte count • Activated partial thromboplastin time	• Pregnancy Test (serum) • Follicle Stimulating Hormone • Sodium • Potassium • Calcium • Chloride • Phosphorus • Glucose • Total protein • Albumin • Creatinine • Amylase • Lipase • BUN • Bilirubin • ALP • AST • ALT • GGT • Creatine kinase • Total cholesterol • High density lipoprotein • Low density lipoprotein • Triglycerides	• pH • Protein • Blood • Ketones • Glucose • Bilirubin • Nitrite • Specific gravity • Leucocytes If ***any abnormal value*** is observed on the urine dipstick test the sample should be further analyzed with urine microscopy: • WBC • RBC • Cellular casts • Granular casts • Hyaline casts

Genetic Testing	Drugs of Abuse (Urine) & Alcohol Testing	Serology Screen & TB Test
Apolipoprotein E	Cannabinoids Amphetamines Barbiturates Cocaine Opiates Benzodiazepines Phencyclidine Methadone Alcohol (ethanol)	Hepatitis B surface antigen Hepatitis C antibody HIV 1 & 2 antibodies Quantiferon TB Gold PLUS test

All values falling outside the laboratory normal range must be assessed for clinical significance.

7 MANAGEMENT OF ADVERSE EXPERIENCES

Adverse Event: An adverse event is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An adverse event can arise from any use of the drug (e.g., off- label use, use in combination with another drug) and from any route of administration, formulation or dose, including an overdose.

Adverse Reaction: An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

Suspected Adverse Reaction: Suspected adverse reaction means any adverse event for which there is a 'reasonable possibility' that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by the drug. The types of evidence that would suggest a casual relationship between the drug and the adverse event include, but are not limited to:

A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)

One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug.

An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

Unexpected Adverse Event: An adverse event or suspected adverse reaction is considered 'unexpected' if it is not listed in the Investigator Brochure or is not listed at the specificity or severity that has been observed.

Serious Adverse Event: An adverse event or suspected adverse reaction is considered 'serious' if, in the view of either the Medical or Safety Monitor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- In-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in subject hospitalization, or the development of drug dependency or drug abuse.

Life Threatening Adverse Event: An adverse event or suspected adverse reaction is considered 'life-threatening' if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Reporting a Serious Adverse Event to the Sponsor: The Investigator is required to inform the Medical Monitor by e-mail/telephone/fax within 24h of his/her becoming aware of any serious adverse event. The notification should be followed by a written report within 1 working day of such an event. The follow up observation period for the subject(s) affected will be jointly decided upon by the Investigator and the Medical Monitor. The Investigator is responsible for notification of serious adverse events to the applicable Institutional Review Board/Independent Ethics Committee (IRB/IEC). The Sponsor is responsible for all IND Safety Reporting to the US Food and Drug Administration (FDA).

Collection of Safety Information: Adverse events (AEs) and serious adverse events (SAEs) will be monitored and reported throughout the study from the time of dosing to the end of study. Each subject will be monitored for AEs throughout the study. Subjects will be asked "how are you feeling?" during each study visit and throughout the day during the residential phase of the study. AEs will be followed to resolution/stabilization, where feasible/possible, regardless of whether the subject is still participating in the study. Follow-up on AEs may include subject referrals to specialists and/or other health care providers. When applicable, the Investigator will obtain reports and/or medical records from non-study providers regarding the AE. In cases of AEs such as rashes, photographs may be taken for the purpose of documentation. Due regard for subject confidentiality will be employed.

The Investigator is not obliged to follow-up with subjects for AEs or SAEs that begin after study completion, however if an SAE is reported to the Investigator after a subject has completed the study, and it is possibly related to the study drug, then the Investigator will report it to the Sponsor.

All abnormal laboratory analytes, ECG results, vital signs and examination findings will be reviewed by the Investigator for clinical significance. If the Investigator deems a post-dose finding to be clinically significant, it will be documented as an AE. Pre-dose clinically significant findings are exclusionary. Pre-dose events will be analyzed separately from treatment emergent AEs in the final analysis.

Assessment of Adverse Events: Investigators will assess each AE based on the following definitions.

7.1 Intensity (Severity)

Mild: The AE is generally transient, does not interfere with usual activities, and is easily tolerated by the subject.

Moderate: The AE causes sufficient discomfort and interferes with usual activities.

Severe: The AE causes considerable interference with usual activities and may be incapacitating.

7.2 Relationship. Unrelated = None, Remote

None (unrelated, not related, no relation):

An unreasonable temporal relationship between administration of the study drug and the onset of the AE (e.g. the event occurred either before, or too long after administration of the study drug for it to be considered drug-related);

A causal relationship between the study drug and the AE is biologically implausible (e.g. death as a passenger in an automobile accident);

A clearly more likely alternative explanation for the AE is present (e.g. typical adverse reaction to a concomitant drug and/or typical disease-related event).

Remote (unlikely, doubtful, improbable):

There is little evidence to suggest there is a causal relationship and there is another reasonable explanation for the event.

7.3 Related = Possible, Probable

- Possible: There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time frame after administration of the study drug); however, the influence of other factors may have contributed to the event (e.g. the subject's clinical condition, other concomitant medications, or concurrent illness).
- Probable: There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

Consider the following when assessing causality:

- Temporal associations between the study drug and the event
- Pre-existing risk factors or concurrent illness
- A plausible mechanism

8 CRITERIA FOR INTERVENTION DISCONTINUATION

8.1 Intolerable Dose

After the safety review, if the Medical Monitor, based on good clinical judgement, considers a dose level to be intolerable, then dose escalation to the next level will not proceed. Depending on the duration and potential seriousness of safety findings, the Sponsor and Investigator will determine whether the current dose level may be repeated, or if a lower dose level may be tested.

If any of the following **sentinel halting criteria** are met the rest of the cohort will not be dosed until review by the Medical and Safety Monitors, Sponsor and Investigator:

- Any subject develops a Grade 3 (severe) AE that is related to the study drug within 24 hours of dosing.
- Any subject develops an SAE related to the study drug.

The following criteria constitute specific **study halting criteria**:

- Two or more subjects experience AEs of severe intensity in the same organ class (Grade 3 according to the “Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials,” Version September 2007) regardless of relatedness to study drug.
- One subject with a reported SAE, unless that SAE is determined to be clearly unrelated to the investigational drug product.
- Occurrence of a life-threatening allergic/hypersensitivity reaction (anaphylaxis) in any subject, manifested by bronchospasm with or without urticaria or angioedema requiring hemodynamic support with pressor medications or mechanical ventilation.
- Death of a dosed subject following dosing and prior to the subject’s last visit that was not the result of trauma or accident, regardless of relatedness to study product.
- Any other event(s) in the good clinical judgment of the responsible physician that is thought to be related to investigational product and comprises a serious risk to subject safety.

If any of the following **dose escalation halting criteria** are met escalation to the next planned dose cohort will not proceed until all available study data have been reviewed by the DSMB:

- Any subject develops an SAE related to the study drug
- Any subject experiences a Grade 3 (severe) AE related to the study drug
- 2 or more subjects in a cohort experience a Grade 2 (moderate) or greater AE that is related to the study drug and is of the same type (preferred term) and occurring in the same SOC.

9 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

Detailed statistical analysis plans will be created for the study and signed off in advance of database lock. One plan will be created for the analysis of PK data and a separate plan will be created for the analysis and presentation of all other study data. General statistical approaches are presented below. Baseline is defined as the last evaluation before dosing.

Safety Analysis: All subjects who receive any study treatment will be included in the safety analysis grouped by treatment received. Statistical analysis of safety data will be descriptive.

For continuous variables, summaries will include sample size, mean, standard deviation, minimum, and maximum. For categorical variables, the summaries will include frequencies and corresponding percentages. No inferential hypothesis testing will be performed on the safety variables. Repeat or unscheduled results will not be included in the summaries, but will be listed. Data from placebo subjects will be pooled for final presentations. Confidence intervals (90%, 95%) may be used in safety summaries.

Adverse Events: AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be listed and summarized by treatment group and dose level. Where applicable, AEs may also be summarized by severity, seriousness, relationship to study treatment and by system organ class and preferred term. The number and percentage of subjects who experience events will be shown in the summaries. Listings for all AEs will be presented.

A treatment-emergent AE is an AE, regardless of relationship to study drug that occurs during or after the first dose of study treatment.

Laboratory Assessments: Summary statistics of observed and change from baseline data will be presented for each treatment group and dose level where applicable. Summary statistics will include number of subjects, mean, standard deviation, minimum, and maximum. Shift tables summarizing the numbers of subjects shifting from normal pre-dose values to abnormal post- dose values will also be presented where applicable. Listings for all laboratory assessments will be presented.

Vital Signs (BP, HR, Body Temperature): Summary statistics for BP and HR and change from baseline (predose) summaries will be presented for each treatment group and dose level where applicable. Summary statistics will include number of subjects, mean, standard deviation, minimum, and maximum. Listings for all vital signs will be presented.

Post-dose clinically notable vital signs will be listed and summarized by treatment and dose. Notable abnormalities are indicated in **Table 5** below:

Table 5: Criteria for Clinically Notable Vital Sign Abnormalities

Parameter	High Threshold	Low Threshold
Systolic BP (supine)	> 30 mmHg increase from baseline	> 30 mmHg decrease from baseline
Diastolic BP (supine)	> 20 mmHg increase from baseline	> 30 mmHg decrease from baseline
Heart Rate	> 120 bpm and an increase in HR of ≥ 15 bpm from baseline	< 40 bpm and a decrease in HR of ≥ 15 bpm from baseline
Body Temperature	> 39.0ºC (> 102.2ºF)	< 35.0ºC (< 95.0ºF)

12-Lead ECG: ECG results from the central reader will be used in the analysis. Shift tables summarizing the numbers of subjects shifting from normal pre-dose values to abnormal post- dose values will also be presented. Numeric ECG data will be summarized by treatment group and dose level and mean summary tables, including change from baseline will be presented.

The ECG results will be listed by treatment group and dose level.

Post-dose clinically notable ECGs will be listed and summarized by treatment and dose. Notable abnormalities are indicated in **Table 6** below:

Table 6: Criteria for Clinically Notable ECG Abnormalities

Parameter	High Threshold	Low Threshold
PR interval	PR ≥ 220 ms	PR ≤ 120 ms
QRS duration	QRS duration ≥ 120 ms and an increase of ≥ 20 ms from baseline	-
QT interval	QT interval > 500 ms	-
QTcF interval	Men: QTcF interval ≥ 450 ms and an increase of ≥ 60 ms from baseline OR QTcF interval > 500 ms Women: QTcF interval ≥ 470 ms and an increase of ≥ 60 ms from baseline OR QTcF interval > 500 ms	-

Pharmacokinetic Analysis: The plasma concentrations of MW151 will be determined, and used to estimate appropriate PK parameters including C_{max}, T_{max}, AUC, $T_{½}$ and K_{el} by non- compartmental analysis. The PK analysis population will include all subjects who received the active study drug and who have sufficient MW151 plasma concentrations to calculate at least 1 PK parameter.

PK parameters will be listed for each individual subject and summarized for each dose level; the summary will consist of number of subjects, arithmetic mean, standard deviation, and geometric mean, coefficient of variation, minimum, median, and maximum. Profiles for each subject will be presented graphically. Additionally, a mean profile will be presented by treatment group and dose level.

The PK analysis will be conducted at a facility selected by the Sponsor. PK data will be provided to the Sponsor for inclusion into the final clinical study report.

9.2 Administrative and Regulatory Considerations

9.2.1 Good Clinical Practice

The study will be conducted in accordance with good clinical practice (ICH GCP) and all applicable regulations including the ethical principles of the Declaration of Helsinki (Edinburgh 2000, with Note of Clarification, Tokyo 2004).

9.2.2 Informed Consent

The Sponsor or designee will provide the Investigator with a template ICF for the study, which may be modified for local use. A study team member authorized to obtain consent will obtain a written ICF from each study subject prior to the performance of any study-related procedures.

Consent will be obtained only after full disclosure of the nature of the study, its risks and benefits, in accordance with local and federal regulations and guidelines. The fact that informed consent was obtained, and the date upon which it was obtained, will be documented in each subject's study records.

If the ICF is amended at any time during the study, the Investigator must follow all applicable regulatory requirements to ensure review and approval of the amended consent form by the IRB/IEC. Subjects must sign the most current IRB/IEC-approved version of the ICF at the time of their participation in the study.

9.2.3 Ethical Review

The Investigator or designee will prepare and submit all required documentation and obtain local IRB/IEC approval to implement the study prior to the conduct of any study procedures. At a minimum, the study protocol, ICF, Investigator's Brochure, and study-related advertisements and promotional materials will be submitted.

If it is necessary to amend the protocol and/or ICF during the course of the study, the Investigator must ensure that the IRB/IEC reviews and approves these amended documents. No amendments to the study protocol should be made without the agreement of the Investigator and Sponsor as well as the IRB/IEC, where applicable.

The Investigator will maintain documentation of the composition of the IRB/IEC as well as all correspondence with the IRB/IEC. The Investigator will comply with local requirements for routine reporting to the IRB/IEC, as well as local and government requirements for notifying the IRB/IEC of SAEs. The Investigator will prepare a final study report and submit it to the IRB/IEC within 3 months of study completion. The Investigator or designee will provide Sponsor or designee with copies of IRB/IEC approval notices, correspondence, annual reports, and final study reports.

9.2.4 Protocol Compliance

The study will be conducted in compliance with the protocol. The Investigator is responsible for ensuring compliance by all study staff members. Deviations from protocol-specified procedures will be documented in subjects' study records.

10 DATA COLLECTION, SITE MONITORING, AND ADVERSE EXPERIENCE REPORTING

10.1 Data Management

Site personnel will collect, transcribe, correct, and transmit the data onto source documents, CRFs, and other forms used to report, track and record clinical research data. The clinical site will be monitored to ensure compliance with data management requirements and Good Clinical Practices. All study data will be collected via systems that comply with all applicable guidelines regarding patient confidentiality and data integrity.

10.1.1 Registration

Registration of participants on this protocol will employ an interactive data system in which the clinical study site will attest to the participant's eligibility as per protocol criteria and obtain appropriate informed consent. IRB approval for the protocol must be on file at the institution before accrual can occur from the clinical study site.

A system of coded identifiers will be used to protect participant confidentiality. When the participant is registered to participate in the study, the system will assign a participant ID number. To confirm the correct participant ID, the data entry system will require a second entry of the unique participant ID and compare for consistency. In this fashion, no personal identifiers would be accessible and the data will be collected on the correctly identified subject.

10.1.2 Documentation of Data

As part of the responsibilities assumed by participating in the study, the Investigator agrees to maintain timely case histories for the subjects treated as part of the research under this protocol, including accurate source documentation. A CFR21, part 11 compliant electronic data capture system for source data will be developed and provided for use in the clinical study. The majority of source data will be recorded directly into data capture system; however some source data, including, but not limited to, AEs, concomitant medications and protocol deviations will be recorded on paper-based source documents. Paper-based data will be entered into a separate clinical database, and will be merged with the electronic data capture system during processing and analysis. ECG readings are printed with a machine interpretation on the ECG. This is then reviewed by the study investigator. If there is a question with the interpretation, the investigator can ask a cardiologist for another read.

ECG data will be forwarded electronically for inclusion in data reporting and analyses. The Investigator will be responsible for ensuring that adequate checks are carried out on all study data.

At the completion of the study, the Sponsor will receive a complete set of data for all subjects.

10.1.3 Source Document Verification

All (100%) subject data (electronic and paper-based source) will be reviewed by the monitors for accuracy and consistency. This will be conducted with due regard to subject confidentiality.

10.2 Data Management

Data collection processes and procedures will be reviewed and validated to ensure completeness, accuracy, reliability, and consistency. A complete audit trail will be maintained of all data changes. Electronic consistency checks and manual review will be used to identify errors or inconsistencies. This information will be provided to the study site by means of electronic or manual queries.

10.2.1 Monitoring the Study Data

The conduct of the study will be monitored by the Sponsor, or designee, to ensure compliance with applicable regulatory requirements and GCP. The study monitor will maintain necessary telephone and letter contact with the Investigative site. The study monitor will verify that the study is conducted in accordance with the currently approved protocol and any amendments and will monitor subject enrolment, completeness and accuracy of subject data and reporting and recording of AEs.

The monitor will maintain current knowledge of the study through observation, review of study records and discussion of the conduct of the study with the Investigator and staff. Monitoring will be conducted according to Good Clinical Practice and applicable government regulations. The investigator agrees to allow monitors access to the clinical supplies, dispensing and storage areas, and to the clinical files of the study subjects, and, if requested, agrees to assist the monitors.

Safety monitoring will include careful assessment and appropriate reporting of adverse events. Medical monitoring will include contemporaneous assessment of serious adverse events.

The DSMB will meet after each cohort is completed or as needed, and will review subject recruitment, AE’s, side effects, withdrawals, protocol violations, and inclusion/exclusion criteria. More frequent meetings will take place if necessary. Roles and responsibilities for the DSMB will be outlined in a separate DSMB charter document.

The Safety Monitor will review all adverse events, in a blinded fashion, on a periodic basis. In addition, the monitor will review all events that meet the regulatory definition of a Serious Adverse Event, upon receipt of notification via the Electronic Data Capture (EDC) system.

An adverse event (AE) is any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with a study, use of a drug product or device whether or not considered related to the drug product or device. FDA, Office of Human Research Protection (OHRP), and IRB requirements for reporting AEs will be followed. Subjects will be monitored for AEs from the time they sign consent until 30 days following permanent discontinuation of study drug. At that point, all ongoing AEs will be followed to resolution, but no new AEs will be recorded. The monitor/DSMB will review cumulative AEs; the frequency of this review will be determined by the monitor/DSMB in conjunction with the Protocol PI.

The Clinical Site Medical Monitor and research team (co-Investigators, research nurse, clinical trial coordinator) are responsible for identifying and reporting AEs and determining the relationship of the event to the study drug/study procedures. Aggregate reports blinded by treatment group, detailed by severity, attribution (expected or unexpected), and relationship to the study drug/study procedures, will be available for review by the monitor. A separate report detailing protocol compliance will also be available monthly for review by the Protocol PI and Safety Monitor, who will provide feedback to the site as needed. The Safety Monitor will advise the Protocol PI as to whether the protocol or informed consent document requires revision based on these reports.

10.3 Inspection of Records

The Investigator and institution involved in the study will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to all study records, medical files, and source data to enable verification of the trial data. In the event of an audit, the Investigator agrees to allow the Sponsor, the FDA, or other Regulatory Agency access to all study records.

The Investigator should promptly notify the Sponsor of any audits scheduled by any Regulatory Authority and promptly forward copies of any audit reports received to the Sponsor.

10.3.1 Records Retention

In accordance with all applicable regulatory requirements, the Investigator will maintain a copy of all site records in a safe and secure location on completion of the study. The location of the Investigator file archive will be made known to the Sponsor at study conclusion and if the archive location changes, the Investigator will notify the Sponsor. Sponsor will archive study data according to their normal practice.

10.3.2 Quality Assurance

The Investigator site, facilities and all data and documentation may be audited by an independent auditor. The Investigator must allow the auditor access to all relevant documents and be available to discuss any findings/issues.

11 HUMAN SUBJECTS

Documented approval from the IRB will be obtained prior to clinical trial start, according to ICH GCP, local laws, regulations and organization. When necessary, an extension, amendment or renewal of the IRB approval must be obtained.

Evidence of training in responsible conduct of research shall be on file for each site PI and co-investigators.

11.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the IRB responsible for oversight of the study. A signed consent form, approved by the IRB, will be obtained from the subject. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the subject, parent, or legal guardian, and this fact will be documented in the subject's record.

11.2 Subject Confidentiality

All laboratory specimens, evaluation forms, reports, video recordings, and other records that leave the clinical study site will be identified only by the study specific Subject Identification Number (SID) to maintain subject confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using study specific SIDs only.

Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, the FDA, the OHRP, the sponsor, or the sponsor's designee.

11.3 Study Modification/Discontinuation

The study may be modified or discontinued at any time by the IRB, the sponsor, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research subjects are protected.

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Statistical Analysis Plan

MW151-101, 28 Aug 2019 V2

IND #143222

DEPRU #: NN09

Clinical Trials.gov #NCT04120233

A Phase 1a, Double-Blind, Randomized, Placebo-Controlled Single Ascending Dose Study to Evaluate the Safety, Tolerability and Pharmacokinetic Profile of MW151 Administered Orally to Healthy Volunteers

Version 1.0

23 October 2019

Sponsor of IND: ImmunoChem Therapeutics, LLC

Sponsor of Clinical Study: University of Kentucky

SIGNATURE PAGE AND APPROVALS

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TABLE OF CONTENTS

1.0 LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AE	Adverse Event
DEPRU	Duke Early Phase Research Unit
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
PK	Pharmacokinetic
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
TEAE	Treatment Emergent Adverse Event

2.0 INTRODUCTION

MW01-2-151SRM (hereafter called MW151) is a CNS-penetrant, orally bioavailable, small molecule drug candidate that selectively suppresses stressor-induced proinflammatory cytokine overproduction with resultant amelioration of synaptic damage and cognitive impairment. The efficacy and pharmacodynamics of MW151 are evident across a dozen diverse animal studies where cytokine overproduction is a contributor to pathophysiology progression. MW151 exhibits efficacy, at low doses. It does not bring about immunosuppression or a non-selective anti-inflammatory action. There is no evidence of suppression of basal cytokine levels characteristic of homeostasis. Function at efficacy doses involves restoration to homeostasis after disease or injury induced increases.

MW151 is being developed for the treatment of cognitive disorders. The development program is based on nonclinical evidence that MW151 improves neurocognitive outcomes in animal models of radiation therapy-induced cognitive impairment, Alzheimer's disease and related dementias, and other cognitive disorders.

The present first-in-human study will provide safety and pharmacokinetic (PK) information on single ascending doses (SAD) of MW151 to support decisions for continued clinical development. This study will assess the safety, tolerability, and PK profile of escalating single doses of MW151 in healthy adult participants. The trial design will be a double-blind, placebo-controlled, SAD study of MW151 in healthy volunteers. Five dosing cohorts are initially planned. All subjects and the study personnel responsible for assessing adverse events (AEs) will be blinded. This statistical analysis plan (SAP) provides a more technical and detailed elaboration of the statistical analyses of safety and tolerability data as outlined in the protocol.

In the study design, 40 healthy male and female volunteers, ages 18-50 years, will be dosed in 1 of 5 dosing cohorts of 8 subjects each. Subjects will be admitted to the inpatient clinic on the day prior to dosing (Day -1) and will remain in the unit until discharge on Day 3. A follow-up visit will be done on Day 7.

A single dose of study drug or placebo will be administered as an oral capsule(s) on Day 1. Five different doses of MW151 will be evaluated in 5 sequential cohorts. Dosing will start at the lowest dose, then escalate in the 2nd cohort, then escalate sequentially in the 3rd, 4th, and 5th cohorts.

Cohort 1: Dose1: MW151/101 10 mg (or matched placebo), 1 x 10 mg capsule administered orally.
Cohort 2: Dose2: MW151/101 20 mg (or matched placebo), 1 x 20 mg capsule administered orally.
Cohort 3: Dose3: MW151/101 40 mg (or matched placebo), 2 x 20 mg capsule administered orally.
Cohort 4: Dose4: MW151/101 80 mg (or matched placebo), 1 x 80 mg capsule administered orally.
Cohort 5: Dose5: MW151/101 160 mg (or matched placebo), 2 x 80 mg capsule administered orally.

As a safety consideration, two sentinel subjects in each cohort will be administered MW151 or placebo in a 1:1 ratio. Dosing of the remaining subjects in a cohort may proceed after review of sentinel subject safety and tolerability data collected during the first 24 hours of dosing and

determination that no stopping rules are met. The remaining 6 subjects will be randomized in a 5:1 ratio. The remaining subjects in each cohort will be dosed sequentially, not simultaneously.

After the completion of each cohort (Cohorts 1-5), the Data Safety Monitoring Board (DSMB) will review all available safety data before the dosing of the sentinel subjects of the next cohort.

Data from Cohorts 1-5 will be reviewed in a blinded manner, unless the findings suggest the triggering of a stopping rule, in which case the data for the subjects in question may be unblinded (e.g., if a drug related serious AE [SAE] occurs, identifying whether the subject received MW151 or placebo to determine whether the stopping rule should be triggered). Doses may be varied based on the safety review, but the maximum dose will not exceed 160mg. Should the safety data warrant, dose levels may be reduced or additional cohorts added in order to generate a comprehensive understanding of the clinical dose range. Should additional cohorts be required above the planned 5 cohorts or doses within the planned cohorts changed, a protocol amendment will be submitted to the FDA and the Independent Ethics Committee for approval before implementation.

Screening will be conducted in the 28 days prior to inpatient admission. After giving written informed consent, each subject will undergo a medical screen consisting of the following procedures: demographics; medical history; concomitant medication review; body temperature; 12-lead ECG; vital signs (BP, HR); physical exam; alcohol and drug screen; Hepatitis B, Hepatitis C, HIV, Columbia Suicide Severity Rating Scale and TB screens; and safety laboratory work and pregnancy testing.

One day prior to dosing (Day -1), subjects will be admitted to the Duke Early Phase Research Unit (DEPRU) Phase 1 unit for final qualification assessments. These assessments will include inclusion/exclusion review, medical history, physical exam, infection screen, body temperature, alcohol and drug screen, vital signs, pregnancy test, neurological exam, and safety laboratory tests.

A single dose of study drug or placebo will be administered as an oral capsule(s) on Day 1. During dosing, subjects will be continuously monitored with 12-lead ECG, blood pressure, and heart rate. Plasma samples will be drawn at sequential time points for PK analysis.

Subjects will remain in the clinical research unit until discharge on Day 3. Follow-up will be done through a clinic visit on Day 7. The follow-up visit will consist of safety lab work, body temperature, ECG, vital signs, concomitant medication review, and assessment of adverse events (AEs).

3.0 OBJECTIVES

Primary Objective

To assess the safety and tolerability of single ascending doses of MW151 when administered orally to healthy adult volunteers.

The hypothesis is that MW151 will be safe in humans when administered in a SAD paradigm, with no severe or serious adverse events.

Secondary Objective

To assess the PK profile of single ascending doses of MW151 when administered orally to healthy adult volunteers.

4.0 SUBJECT POPULATIONS

Any subject who discontinues the study prior to dose administration for reasons other than AEs may be replaced by a different subject. The replacement subject will receive the same treatment as the original subject.

4.1 RANDOMIZED POPULATION

The Randomized Population will consist of all subjects who sign informed consent and who are randomized to a treatment group in the study.

4.2 SAFETY POPULATION

The Safety Population will consist of all subjects in the Randomized Population who receive any double-blind study medication (MW151 or placebo).

4.3 PK POPULATION

The PK Population and analyses will be defined in the PK Analysis Plan.

5.0 STUDY DISPOSITION

The number of subjects included in each study population (i.e., Randomized, Safety) will be summarized by cohort and active drug vs. placebo.

The number and percentage of subjects who completed and prematurely discontinued the study will be presented by study drug and overall vs placebo for the Randomized Population. Reasons for premature discontinuation as recorded on the completion page of the CRF will be summarized, as applicable.

6.0 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographic parameters (e.g. age, race, sex, weight, height, BMI) and other baseline characteristics, such as medical history, will be summarized by treatment group for the Safety Population. In addition, data listings will be generated.

7.0 STATISTICAL ISSUES

7.1 GENERAL ANALYSIS CONVENTIONS

General statistical approaches are presented below.

All subjects in the Safety Population will be included in the safety analysis grouped by cohort and treatment group. Statistical analysis of safety data will be descriptive.

Baseline is defined as the last assessment prior to dosing of study medication.

For continuous variables, summaries will include sample size, mean, median, standard deviation, minimum, and maximum. For categorical variables, the summaries will include frequencies and corresponding percentages. No inferential hypothesis testing will be performed. Repeat or unscheduled results will not be included in the summaries, but will be listed. Data from placebo subjects will be pooled for final presentations.

Missing data results will not be imputed. Data summaries and analyses (e.g. means) will be calculated using all available data. If the start day for an AE is missing, day of study drug administration will be used and AE will be considered treatment emergent. Neither month nor year will be imputed for AE.

Statistical analyses will be performed in SAS, Version 9.4 or newer.

8.0 EXTENT OF EXPOSURE

8.1 STUDY MEDICATION

Exposure to study medication for the Safety Population will be summarized in terms of the amount of dose administered (in mg) for each dose cohort and treatment group. Concomitant medications will be listed. Any instance of a subject receiving a dose other than the assigned dose will be listed. Descriptive statistics will be presented by treatment group.

9.0 PHARMACOKINETIC ANALYSIS

The PK analysis is outside the scope of this SAP and is described in a separate PK statistical analysis plan.

10.0 SAFETY ANALYSES

The safety analysis will be performed using the Safety Population. Safety and tolerability will be assessed on the basis of physical examination, neurological examination, vital signs, clinical laboratory values, ECG readings, and adverse event (AE) reports.

Statistical analysis of safety data will be descriptive.

10.1 ADVERSE EVENT ASSESSMENTS

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) v21.0 – 5 Level or newer. AEs will be listed and summarized by treatment group and dose level. Where applicable, AEs may also be listed by severity, seriousness, relationship to study treatment and by system organ class and preferred term.

A treatment-emergent AE (TEAE) is an AE, regardless of relationship to study drug, which occurs during or after the first dose of study treatment. TEAE will be summarized by MedDRA System Organ Class and Preferred Term.

10.2 CLINICAL LABORATORY TESTING

Summary statistics of observed and change from baseline data will be presented for each treatment group and dose where applicable. Shift tables summarizing the numbers of subjects shifting from normal pre-dose values to abnormal post-dose values will also be presented where applicable. Listings for all safety laboratory assessments will be presented.

Lab tests included will be all in the hematology and coagulation panel, biochemistry panel, and urinalysis panel (as needed lab tests: RBC, WBC, hyaline casts, cellular casts, and granular casts will only be presented as listings).

10.3 VITAL SIGNS

Vital signs (supine systolic and diastolic blood pressure, orthostatic change in systolic and diastolic blood pressure, supine heart rate/pulse, body temperature) and changes from baseline at each time point will be presented by cohort and treatment group. Listings for all vital signs and orthostatic change will be presented.

Clinically notable vital signs will be listed and summarized by treatment group and dose. Criteria for Clinically Notable vital sign abnormalities are indicated in Table 2 below.

Table 2: Criteria for Clinically Notable Vital Sign Abnormalities

Parameter	High Threshold	Low Threshold
Systolic BP (supine)	> 30 mmHg increase from baseline	> 30 mmHg decrease from baseline
Diastolic BP (supine)	> 20 mmHg increase from baseline	> 30 mmHg decrease from baseline
Heart Rate (supine)	> 120 bpm and an increase in HR of ≥ 15 bpm from baseline	< 40 bpm and a decrease in HR of ≥ 15 bpm from baseline
Body Temperature	> 39.0°C (> 102.2°F)	< 35.0°C (< 95.0°F)

10.4 ELECTROCARDIOGRAM MONITORING

ECG parameters (e.g. Ventricular Heart Rate, PR interval, QRS interval, QTc interval, QTcB, QTcF interval, and RR interval) and changes from baseline at each assessment time point will be presented by cohort and treatment group. Listings for ECG parameters will also be presented.

Clinically notable ECGs will be listed and summarized by treatment group and dose. Criteria for Clinically notable ECG abnormalities are indicated in Table 3 below:

Table 3: Criteria for Clinically Notable ECG Abnormalities

Parameter	High Threshold	Low Threshold
PR interval	PR ≥ 220 ms	PR ≤ 120 ms
QRS duration	QRS duration ≥ 120 ms and an increase of ≥ 20 ms from baseline	-
QT interval	QT interval > 500 ms	-
QTcF interval	Men: QTcF interval ≥ 450 ms and an increase of ≥60 ms from baseline OR QTcF interval >500 ms Women: QTcF interval ≥ 470 ms and an increase of ≥60 ms from baseline OR QTcF interval >500 ms	-

10.5 PHYSICAL EXAMINATIONS

Descriptive statistics for weight at baseline and changes from baseline at each assessment time point will be presented by cohort and treatment group. A listing of physical examination data for all subjects will be provided.

10.6 NEUROLOGICAL EXAMINATIONS

Neurological examinations include mental status, cranial nerves 2-12, motor system and coordination, reflexes, and sensory system. Shift tables summarizing the numbers of subjects shifting from normal pre-dose values to abnormal post-dose values will be created. A listing of abnormal neurological examination data for all subjects will be provided.

11.0 DETERMINATION OF SAMPLE SIZE

This trial is designed to investigate the safety, tolerability, and PK properties of the drug MW151 in a dose escalation Phase Ia study. The number of subjects is based upon the need to gain this knowledge in healthy individuals using as few subjects as possible. Since this is the first study of MW151 in humans, there is no prior experience upon which to base estimates of variability for the PK responses to SAD treatment with MW151. No power analysis is conducted but the cohort size is based on accepted standards in similar Phase I studies: 8 subjects per dose with 6 randomly assigned to active drug while the remaining 2 subjects receive placebo. Eight subjects per cohort was deemed sufficient for obtaining an adequate preliminary description of the responses of interest.

Appendix A

Table 1. Schedule of Activities

Day/Procedures	Screening (1)	-1 Admission	1	2	3 Discharge (2)	7 FU visit
Informed consent	X					
Inclusion/Exclusion Review	X	X				
Demographics	X					
Medical History	X	X				X
Columbia Suicide Severity Rating Scale	X					
Physical Examination (3)	X	X		X		X
Infection Screen (4)		X				
Body Temperature (5)	X	X	X	X	X	X
Neurological Examination (6)		X		X		
Safety Laboratory Tests (7)	X	X		X		X
Drug Screen (urine)	X	X				
Alcohol Screen (breathalyzer)	X	X				
Hepatitis B & C/ HIV Screen	X					
TB test (blood test)	X					
Pregnancy Test (serum at Screening/urine on D-1)	X	X				
12-lead ECG (8)	X	X	X	X	X	X
Vital signs (BP/HR) (9)	X	X	X	X	X	X
PK blood sampling (10)			X	X		
Admit to Unit/Randomization (11)		X				
Dosing (12)			X			
Adverse Event Assessment			X	X	X	X
Concomitant Medication Review	X	X	X	X	X	X
Discharge from Unit					X	

Footnotes to Schedule of Activities

(1) Screening will occur within 28 days of dosing.

(2) Subjects who discontinue from the study should undergo all Early Termination assessments as per the Day 3 visit.

(3) Weight will be measured during all physical examinations and height will be measured at Screening only. Physical examination will include general appearance; head, eyes, ears, nose, throat (HEENT); cardiovascular; lung; abdominal; musculoskeletal; and skin.

(4) On Day -1, subjects will be screened for the presence of infection as part of physical examination, body temperature, recent/current antibiotic use, recent surgery, evidence of dental abscess, unhealed skin lesions etc. On Day 1 before dosing, subjects will be screened for emergence of acute illness.

(5) Body temperature will be measured at the following time-points:

- Screening
- Day -1
- Day 1 before dosing and again at 12h post-dose
- Day 2 – Day 3 approximately 24h and 48h, respectively, after dosing
- Day 7

(6) Neurological examination will include mental status evaluation, cranial nerves 2-12 testing, motor system and coordination testing, reflex evaluation and sensory system evaluation. The neurological examination should be conducted at the same time as the physical examination when both are scheduled on the same study day.

- Day -1
- Day 2

(7) Safety laboratory samples (Hematology/Coagulation/Biochemistry/Urinalysis) will be taken after the subject has fasted for a minimum of 10 hours as follows:

- Screening (all except creatine kinase, amylase, lipase, cholesterol, HDL/LDL/triglycerides)
- Day -1
- Day 2
- Day 7

(8) A 12-lead ECG will be performed (after lying quietly for 5 minutes). Triplicate tracings (3x) will be taken at Day -1 only and will serve as the Baseline (pre-dose measurement). ECGs will be performed at the following time points.

- Screening
- Day -1
- Day 1: approximately 1h, 2h, 4h, and 12h post-dose
- Day 2: approximately 24h post-dose
- Day 3
- Day 7

Subjects will be monitored on telemetry from approximately 30 min prior to dosing through the 4 hour post-dose ECG.

(9) Vital signs will include BP and HR. At each time point where vital signs are measured, heart rate and blood pressure will first be checked in the supine position and then in the standing position with at least 2 minutes between the supine and standing measurements. Vitals will be performed at the following time-points:

- Screening
- Day -1
- Day 1: Pre-dose and at 1h, 2h, 4h, and 12h post-dose
- Day 2: approximately 24h and 36h post-dose
- Day 3

- Day 7

(10) PK samples will be taken at the following time-points, anchored to the start of dosing.

- Day 1: Pre-dose, and 0.25h, 0.5h, 1h, 2h, 4h, 8h, 12h post-dose
- Day 2: 24h and 36h post-dose

(11) Randomization is expected to occur on D-1, but if there are delays in receiving prequalification safety labs randomization may occur on D1 prior to dosing.

(12) Dosing will be by oral capsule administration, on day 1.

DUKE UNIVERSITY HEALTH SYSTEM

Consent to Participate in a Research Study
ADULT
A Phase 1a, Double-Blind, Randomized, Placebo-Controlled Single Ascending Dose Study to Evaluate the Safety, Tolerability and Pharmacokinetic Profile of MW151 Administered Orally to Healthy Volunteers
DEPRU #: NN09

CONCISE SUMMARY

The purpose of this study is to find out whether an investigational drug, MW151, is safe and well tolerated.

If enrolled, you will undergo screening procedures to see if you qualify. If you qualify and wish to continue, you will be asked to return to the Duke Early Phase Clinical Research Unit (DEPRU) for a 3-night overnight stay. There is also one follow-up visit which will occur about 3-5 days after discharge. Your participation in the study will last up to 5 weeks. You will have the following procedures performed at various times throughout the study: vital signs, ECGs, blood collection, urine collection, physical exam, and neurological exam. You will receive a single dose of MW151, either 20, 40, 80, or 160 mg. MW151 will be administered as a capsule (orally).

There are risks to this study drug that are described in this document. Common risks include nausea and headache. There could also be additional risks which could be serious that have not yet been identified.

If you are interested in learning more about this study, please continue reading below.

You are being asked to take part in this research study because you are a healthy female individual who does not have known health conditions. Research studies are voluntary and include only people who choose to take part. Please read this consent form carefully and take your time making your decision. As your study doctor or study staff discusses this consent form with you, please ask him/her to explain any words or information that you do not clearly understand. We encourage you to talk with your family and friends before you decide to take part in this research study. The nature of the study, risks, inconveniences, discomforts, and other important information about the study are listed below.

Please tell the study doctor or study staff if you are taking part in another research study.

This study is funded by a grant from the National Institute on Aging, awarded to University of Kentucky. Through this grant, University of Kentucky will pay Duke University Health System (DUHS) and Dr. Jeffrey Guptill to perform this research

WHO WILL BE MY DOCTOR ON THIS STUDY?
If you decide to participate, Dr. Jeffrey Guptill will be your doctor for the study and will be in contact with your regular health care provider throughout the time that you are in the study and afterwards, if needed.

DUKE UNIVERSITY HEALTH SYSTEM

Consent to Participate in a Research Study
ADULT
A Phase 1a, Double-Blind, Randomized, Placebo-Controlled Single Ascending Dose Study to Evaluate the Safety, Tolerability and Pharmacokinetic Profile of MW151 Administered Orally to Healthy Volunteers
DEPRU #: NN09

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to find out whether an investigational drug is safe and well tolerated. "Investigational" in the context of a clinical study means the drug is being tested for safety and effectiveness and has not been approved by the FDA for use in the United States. In this informed consent form, the investigational drug will be referred to as MW151 HCl. The study will also measure how the drug is moved to the bloodstream after administration, and how long it takes for the body to remove the drug from the bloodstream.

MW151 HCl is being studied as a possible treatment for people with brain tumors who suffer from memory loss as a consequence of radiation therapy. Research studies conducted in animals and in test tubes have shown that MW151 HCl can reduce the amount of brain inflammation that occurs in the first few hours to days after the radiation dose. In these research studies, animals that received MW151 HCl were shown to recover better and faster.

MW151 HCl has been given to humans at a single dose of 10 mg. This study will look at the safety and tolerability of MW151 HCl at higher doses (20, 40, 80, 160 mg) and will look at how the amount of drug in the blood changes over time.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Approximately 32 female volunteers (subjects) will take part in this study at Duke (8 subjects at each dose level). It may be necessary to screen as many as 80 subjects to ensure 32 people are able to complete the study. Duke is the only site for this study.

WHAT IS INVOLVED IN THE STUDY?

You will be randomly assigned (like the flip of a coin) to receive either MW151 HCl or placebo. A placebo is an inactive substance given in the same form as the study drug. The first two volunteers dosed will have a 1 in 2 (50%) chance of receiving MW151 HCl or a placebo. Of remaining six subjects you have a 5 in 6 (83%) chance of receiving MW151 HCl and a 1 in 6 (17%) chance of receiving a placebo. Neither you nor the study doctor will know if you are getting MW151 HCl or placebo. However, in an emergency, the study doctor can find out.

You will get one dose of study drug on Day 1. You will receive study drug by mouth in the form of a capsule.

The planned dosing in the study is:
Group 1 (8 volunteers): 10 mg of MW151 HCl or placebo
Group 2 (8 volunteers): 20 mg of MW151 HCl or placebo

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Group 3 (8 volunteers): 40 mg of MW151 HCl or placebo
Group 4 (8 volunteers): 80 mg of MW151 HCl or placebo
Group 5 (8 volunteers): 160 mg of MW151 HCl or placebo

For safety reasons, the first 24 hours of safety data from the first 2 volunteers in each group will be reviewed before the rest of the volunteers may receive study drug. After all 8 volunteers in Group 2 are finished, safety information from Group 2 will be reviewed by the study doctor and the medical and safety monitors before proceeding to the next group. Similar procedures will be followed for the remaining groups.

The study doctor will talk to you about the things you must do or not do to participate. Please tell your regular health care providers and any emergency care providers that you are in this research study.

If you agree to be in this study, you will be asked to sign and date this consent form. You will have the following tests and procedures performed at the Screening Visit to make sure that you are eligible. The Screening Visit will take about 2-3 hours to complete.

Screening Visit
The following will be done during the Screening Visit:

- Before any study procedures are done, you will provide your informed consent.
- You will be asked about your background and medical history. The study staff will also ask you questions about your age and race.
- You will be asked about your history of suicidal ideation and behavior.
- You will be asked about all medicines that you take (including non-prescription medicines, vitamins, herbs and supplements).
- You will be asked about your recent nicotine usage.
- You will have a physical exam, including measuring your height and weight.
- Your vital signs will be measured, including blood pressure, heart rate, and body temperature.
- Blood samples will be collected to check for tuberculosis, hepatitis B, hepatitis C and human immunodeficiency virus (HIV). If you have positive test results for HIV or hepatitis B or C, we will notify you. We are required to notify state health authorities of positive results. If these tests are positive you cannot take part in this research study. If you do not want to be tested, you should not take part in this research study.
- Female subjects will have a pregnancy test.

- Post-menopausal women who have not had a regular period for at least 12 months in a row may need to have a blood sample taken to test for the amount of follicle stimulating hormone (FSH). This test is done to make sure that you can no longer become pregnant.
- Blood samples will be taken in order to check blood cell counts, blood chemistry, and how well your blood clots (these tests are called hematology, serum chemistry, and coagulation panel).
- A urine sample will be taken for testing to check for signs of infection, blood, and protein in the urine.
- A urine sample will be taken to test for any drugs of abuse (illegal or prescription).
- An alcohol breathalyzer will be performed.
- An ECG will be performed. An "ECG" or "electrocardiogram" is a test that measures the electrical activity of the heart. A technician will place patches connected by wires to a machine on your chest. The machine records the electrical activity of your heart.
- The study doctor will determine if you are eligible to continue into the study. If you will not be able to continue in the study, the study doctor will discuss with you.

Study Day -1 (Admission to the Study Clinic)
You will be admitted to the Duke clinic one day before you receive study drug. You will be asked to fast (no food or drink except water) for 10 hours before arriving at the clinic. You will stay at the clinic for 3 nights and 4 days. On Day -1, you will repeat all of the tests and procedures described above for screening to make sure you continue to be eligible. The following procedures will be done on this study day:

- You will be asked about any changes to your health since the screening visit
- You will be asked about any medicines you are taking or have taken since the screening visit
- Your vital signs (blood pressure and pulse) will be measured
- Your temperature will be taken
- Your weight will be measured
- An ECG will be performed
- You will have a physical exam, including an evaluation of any infection you may have (this includes questions about your health, medications, recent surgeries, and examining any skin lesions and inside your mouth for dental infections)
- You will have a neurological exam (to evaluate your nervous system)
- An alcohol breathalyzer will be performed.
- You will give blood and urine for routine lab tests
  - Some of your urine will be tested for drugs of abuse
  - Some of your urine will be tested to check for signs of infection, blood, and protein
  - Women will have a urine pregnancy test

- Your blood will be tested to check your general health, including blood cell counts, blood sugar, and liver function tests

Alternate Subjects
If you are accepted into the study, you may be asked to be an alternate subject (a backup subject). If you are chosen as an alternate, you will be admitted to the Duke clinic on the day before the dosing starts. You will spend one night at the Duke clinic (the night prior to dosing). You will complete all of the planned study activities prior to the dosing. If another subject withdraws from the study prior to dosing, you may take the subject's place and complete the study.

Study Day 1
On the morning of study Day 1, before getting the study drug, the following procedures will be done:

- You will be asked how you are feeling
- Your temperature will be taken
- Your vital signs (blood pressure and pulse) will be measured
- You will be connected to ECG telemetry
- You may have an IV catheter inserted into one arm for blood draws
- You will give a blood sample to measure the level of study drug in your blood
- You will give a blood sample for genetic testing (see details below)
- You will be given a light breakfast prior to dosing
- If you remain eligible and you choose to continue, you will be given a single dose of the study drug (either MW151 HCl or placebo)

After getting the study drug the following procedures will be done:

- You will be asked how you are feeling throughout the day
- You will be asked about any medicine(s) you are taking throughout the day
- You will give blood samples 7 more times throughout the day to measure the level of study drug in your blood
- Your vital signs (blood pressure and pulse) and temperature will be measured throughout the day. You will have ECGs throughout the day

Study Day 2
You will be asked to fast for at least 10 hours before the Day 2 fasting blood samples are taken. The following procedures will be done on this study day:

- You will be asked how you are feeling throughout the day
- You will be asked about any medicine(s) you are taking throughout the day
- You will provide fasting blood samples for routine lab tests
- You will be given a light breakfast
- You will have a physical exam
- You will have a neurological exam
- You will give two blood samples to measure the level of study drug in your blood
- Your vital signs (blood pressure and pulse) will be measured throughout the day
- Your temperature will be taken
- An ECG will be performed

Study Day 3
The following procedures will be done on this study day:

- You will be given a light breakfast
- You will have an ECG
- Your vital signs (blood pressure and pulse) will be measured
- Your temperature will be taken
- You will be asked how you are feeling
- You will be asked about any medicine(s) you are taking

Before you leave the study clinic, the study doctor will confirm that it is safe for you to leave. Additional procedures may be ordered by the study doctor during the study if necessary to check your safety. If it is not safe for you to leave the study doctor may ask for you to remain at the study clinic until it is safe for you to leave.

Study Follow-up Visit: Day 7
You will be asked to fast for at least 10 hours before the Follow-up visit fasting blood samples are taken. The following procedures will be done on this study day:

- You will provide a fasting blood sample for routine lab tests
- Your temperature will be taken
- You will have an ECG
- Your vital signs (blood pressure and pulse) will be measured
- You will have a physical exam

- You will be asked how you are feeling
- You will be asked about any medicine(s) you are taking

Additional procedures may be ordered by the study doctor during the study if necessary to check your safety. In the event of an adverse reaction, such as a rash, photographs of the affected area may be taken for the purpose of documentation.

Early Withdrawal from the Study
You may be withdrawn from the study before completion, even if you want to continue. If you are withdrawn from the study due to safety reasons, you will be discharged from the unit only when the study doctor feels that it is safe to do so. If you stop the study early for any reason, the study doctor will ask you to perform the evaluations that are typically performed on Day 7.

Your participation in the study may be stopped for any of the following reasons:

- Failure to follow the study requirements
- The study doctor decides it is in the best interest of your health and welfare to discontinue
- The sponsor stops development of MW151 HCl
- The FDA stops the study

You may also decide to stop your participation in the study at any time and this will not affect your relationship with Duke or the sponsor.

Genetic Testing
The purpose of the genetic testing described above is to examine your genes (DNA) related to Apolipoprotein E (APOE), which is a protein involved in the metabolism of fats in the body. This testing is for research purposes only. Therefore, you will not receive results from this testing (except in your medical record, as described below). It is not the purpose of this study to look for or provide you with any medical information or diagnoses relating to your present condition or any other disease or illness. The research tests are not being used as diagnostic tests for any disease or illness. Your participation in this study is not a substitute for your regular medical care or check-ups.

HOW LONG WILL I BE IN THIS STUDY?

If you choose to participate in this study, your participation is expected to last up to 5 weeks, including up to 4 weeks for screening and 1 week for dosing and follow-up.

DUKE UNIVERSITY HEALTH SYSTEM

Consent to Participate in a Research Study
ADULT
A Phase 1a, Double-Blind, Randomized, Placebo-Controlled Single Ascending Dose Study to Evaluate the Safety, Tolerability and Pharmacokinetic Profile of MW151 Administered Orally to Healthy Volunteers
DEPRU #: NN09

You can stop participating at any time without penalty or loss of any benefits to which you are entitled. However, if you decide to stop participating in the study, we encourage you to talk to the study doctor first.

WHAT ARE THE RISKS OF THE STUDY?
As a result of your participation in this study, you are at risk for the following side effects. You should discuss these with the study doctor and your regular health care provider if you choose.

Study Drug Risks
Because MW151 HCl is considered "investigational," complete information about the safety of MW151 HCl is not yet available. At this stage of development, there is no evidence that the drug is unsafe or has specific risks when given to people; however, there could be risks, including death, that are as yet unidentified. MW151 HCl is made by chemical synthesis and many precautions have been taken in the making of the MW151 HCl to be used in the study. Group 1 received MW151 HCl at a 10 mg dose level, and there were no problems at that dose level. However, higher doses have not been tested yet.

MW151 HCl may cause some, all or none of the following side-effects including nausea and headache and there could be risks, including death, that are as yet unidentified. You should discuss these with the study doctor and your regular health care provider if you choose.

Animals were given oral doses of MW151 HCl for up to 28 days, at multiple levels higher than those being studied in this clinical study. In rats, at certain doses tested, some changes were seen under the microscope in their testicles and sperm. Some of these changes got worse and did not resolve once the drug was stopped. The doses given to these rats were at least 2 times greater than the comparable dose of drug you could receive. Additionally, you will only be receiving a single dose. However, for maximum safety, Groups 2 – 5 will consist of female subjects only.

In dogs, at doses that are at least 10-times higher than the highest comparable dose you could receive, changes in the electrical signals in the heart (electrocardiogram, ECG) were seen. These electrical changes can potentially cause changes in the heart rhythm and in some severe cases could prevent your heart from pumping sufficient blood and you may be at risk of death. Your heart beat, blood pressure, heart rhythm and ECG will be closely monitored during this study, including continuously for the first 4 hours after you receive the study drug.

In some, but not all studies in petri dishes that tested whether the study drug can damage the chromosomes that carry your genetic material (genes), MW151 HCl appeared to cause some damage to chromosomes. When a similar test was done in rats and in mice, at doses much higher than comparable dose you would be expected to receive, there was no damage to chromosomes seen. Since you receive

only a single dose of MW151 HCl, the risk that your chromosomes become damaged by the study drug, is extremely low. Therefore, we believe the risk that the study drug could cause cancer is also extremely low.

Because of the way the drug is thought to work, there could be a potential for MW151 HCl to affect your immune response (the way your body fights off infection). None of the animals tested so far has shown any bad change in their immune function. Subjects with any present or recent evidence of infection or at risk for infection are not eligible for the study.

If you do not understand what some of these side effects or risks mean, ask the study doctor or the study staff to explain them to you. You will be carefully monitored throughout the study by the study doctor and study staff. Please report any side effects that you may notice.

Co-Occupancy During Confinement

There is an increased risk of COVID-19 with co-occupancy. For this reason, there will also be a need for required additional testing that is explained below.

1. Pre- admission:
    a. Participants are instructed to pay close attention to all COVID precautions, including masking, limiting contact with others, limiting travel, and maintaining social distancing.
    b. Participants will have a COVID test within 72 hours prior to confinement and repeated the day of admission for the confinement period.
    c. Participants will be provided clear instructions regarding confinement expectations.

2. During confinement participants will:
    a. Immediately isolate and report development of new symptoms concerning for COVID
    b. Have a COVID test every 3 days.
    c. Eat and drink only in their assigned rooms.
    d. Wear Duke provided mask unless eating, drinking, or sleeping.
    e. Remain at least 6 feet apart when not wearing a mask.
    f. Remain in their room unless scheduled time in the lounge area and only go there with their roommate. Lounge time will be allocated so that participants remain with the same group during the confinement period in order to minimize exposure to others.
    g. Perform hand hygiene with soap and water or approved hand sanitizer frequently.
    h. Wipe down shared high touch surface areas after use – such as the washing machine, lounge table, remote control, sink handles, etc.

i. Be discharged to home for isolation and close observation should their COVID test become positive.

3. Post-confinement:
   a. Participants will require quarantine and COVID testing day 5-7 post-exposure if they are exposed late during their confinement period.

Allergic Reaction Risks
There is a risk of allergic reaction. If you have a very serious reaction to MW151 HCl or to the placebo you may be at risk of death. Some symptoms of allergic reactions are: rash, difficulty breathing, wheezing, sudden drop in blood pressure, swelling around the mouth, throat or eyes, a fast pulse, and sweating. Please alert the study doctor and study staff immediately if you have any of these symptoms, or any other side effects, during the study.

Injection Risks/Catheter Insertion Risks/Blood Samples
Risks associated with drawing blood from your arm include momentary discomfort and/or bruising. Infection, excess bleeding, clotting, or fainting are also possible, although unlikely.

A temporary needle (catheter) may be placed into your vein during the study to collect blood. This decreases the amount of needle sticks you would receive during these days. The study staff will keep the blood draw area clear and clean. Subjects may feel pain or experience bruising at the site where the blood is drawn or the catheter is inserted. There is a risk of subjects feeling dizzy or may faint. Infection at the site of the blood draw or catheter insertion is possible. Some minor discomfort may be felt when blood is drawn from the veins (or the catheter inserted) in your arm.

You will be required to provide blood samples during the study. Throughout the study up to about 313 mL (about 10.6 oz) of blood will be taken for scheduled tests. This is less than you would give during a regular donation to a blood service agency such as the Red Cross where a typical donation is one pint (about 16 oz or 475 mL). Extra blood samples may be taken, if needed, to check on your safety.

ECGs and Blood Pressure Risks
Electrocardiograms (ECGs) (electrical tracings of the heartbeat or heart rhythm) will be done during this study in which you will have pads placed on different parts of your body. There is no pain or discomfort during an ECG; however, removing the pads may cause some irritation to your skin. You may experience bruising from the blood pressure cuff.

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Reproductive Risks
The effects of the study drug on a developing pregnancy or breastfeeding infant are not known. Women who are pregnant, planning a pregnancy, or breastfeeding are not allowed to participate in studies of the drug.

If you are a woman who could possibly become pregnant (you have not completed menopause, or you have not had a hysterectomy and/or both tubes and/or both ovaries removed) and you have a partner who is able to father children, a blood pregnancy test will be performed at screening, and it must be negative in order to continue. In women 40 years old and older, blood pregnancy tests sometimes give a false positive or indeterminate result and additional testing may be needed. A urine pregnancy test will be performed when you come in for your Study Day 1 visit.

You and your partner must agree to either abstain completely from vaginal intercourse from the time of the screening visit until 1 month after you receive the study drug, or use an effective method of contraception for the same length of time. Effective methods include (a) partner vasectomy, (b) bilateral tubal ligation, (c) intrauterine devices (IUDs), (d) hormonal methods (birth control pills, implants, injections, patches, vaginal rings, or (e) barrier methods (condoms, diaphragm, cervical cap) with a spermicide. If you are not currently using one of these methods and would still like to participate in the study, the study doctor will discuss options with you.

Because no birth control method is 100% effective, you should notify the study doctor immediately if you think there is any chance you are pregnant within 30 days after receiving the study drug.

General Discomfort Risks
You will be asked to fast during parts of this study. This may cause you some discomfort. In addition, study requirements such as overnight stays at the clinic, dietary restrictions and limitations on caffeine, alcohol, and smoking may also cause you some discomfort. You may experience bruising from the blood pressure cuff and/or irritation at the site of the patches applied to the skin for the ECG recordings.

Serious adverse reactions and hospitalization
Although all possible precautions are taken to prevent serious adverse reactions (side effects), if such an event occurs, it may be in your best interest to be admitted to hospital. Depending on the type of reaction, we may contact a medical specialist to be primarily responsible for your treatment. We will provide assistance to the hospital and doctors looking after you, but all hospital records are confidential and for this reason we are asking you to give us, and any emergency medical specialists we contact, consent to visit you and have access to your medical records.

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Drug Interactions
For your safety, you must tell the study doctor or nurse about all the prescribed medical foods and drugs, herbal products, over-the-counter (OTC) drugs, vitamins, natural remedies, and alcohol that you are taking before you start the study and before starting to take any of these products while you are on the study.

There may be risks, discomforts, drug interactions or side effects that are not yet known.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
If you agree to take part in this study, there will be no direct medical benefit to you. We hope the information learned from this study will benefit others in the future.

WILL MY INFORMATION BE KEPT CONFIDENTIAL?
Participation in research involves some loss of privacy. We will do our best to make sure that information about you is kept confidential, but we cannot guarantee total confidentiality. Your personal information may be viewed by individuals involved in this research and may be seen by people including those collaborating, funding, and regulating the study. We will share only the minimum necessary information in order to conduct the research. Your personal information may also be given out if required by law.

As part of the study, results of your study-related laboratory tests, x-rays, and procedures may be reported to University of Kentucky and its affiliates. In addition, your records may be reviewed in order to meet federal or state regulations. Reviewers may include representatives from the Food and Drug Administration, representatives and affiliates of University of Kentucky, the Duke University Health System Institutional Review Board, and others as appropriate. If any of these groups review your research record, they may also need to review your entire medical record.

As part of this study, you will be asked to have certain laboratory tests and/or other procedures performed. These test results will be recorded in your medical record and will be reported to the representatives and affiliates of University of Kentucky.

The Department of Health and Human Services (HHS) has issued a Certificate of Confidentiality to further protect your privacy. With this Certificate, the investigators may not disclose research information that may identify you in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings, unless you have consented for this use. Research information protected by this Certificate cannot be disclosed to anyone else who is not connected with the research unless:

1) there is a law that requires disclosure (such as to report child abuse or communicable diseases but not for legal proceedings);

2) you have consented to the disclosure, including for your medical treatment; or

3) the research information is used for other scientific research, as allowed by federal regulations protecting research subjects.

Disclosure is required, however, for audit or program evaluation requested by the agency that is funding this project or for information that is required by the Food and Drug Administration (FDA).

You should understand that a Confidentiality Certificate does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it. This means that you and your family must also actively protect your own privacy.

Finally, you should understand that the investigator is not prevented from taking steps, including reporting to authorities, to prevent serious harm to yourself or others.

The study results will be retained in your research record for at least six years after the study is completed. At that time either the research information not already in your medical record may be destroyed or information identifying you will be removed from such study results at DUHS. Any research information in your medical record will be kept indefinitely.

Some information collected in research studies is maintained in your medical record. However, for this study that information will be inaccessible until the end of the study, unless your physician(s) decide that it is necessary for your care.

This information may be further disclosed by the sponsor of this study. If disclosed by the sponsor, the information is no longer covered by federal privacy regulations.
If this information is disclosed to outside reviewers for audit purposes, it may be further disclosed by them and may not be covered by federal privacy regulations.

While the information and data resulting from this study may be presented at scientific meetings or published in a scientific journal, your name or other personal information will not be revealed.

Some people or groups who receive your health information might not have to follow the same privacy rules. Once your information is shared outside of DUHS, we cannot guarantee that it will remain private.

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If you decide to share private information with anyone not involved in the study, the federal law designed to protect your health information privacy may no longer apply to the information you have shared. Other laws may or may not protect sharing of private health information.

WHAT ARE THE COSTS TO YOU?
While you are in the study, you may still need to get regular medical care. You (and/or your health care payer) will still have to pay for the costs of your regular medical care that are not part of this study.

There will be no costs to you for being in this study. You will not have to pay to receive the study drug. There are also no costs for the tests or procedures performed as part of the study.

We will monitor your DUHS patient care charges to make sure that costs are directed appropriately. If you have any questions or concerns about appropriate billing, contact your study team coordinator so that he/she can help find a resolution.

WHAT ABOUT COMPENSATION?
You will be reimbursed up to $1050 for your expenses related to your participation (parking, gas, and time). If you withdraw from the study, you will still receive compensation for the parts of the study you completed. If you are an alternate subject, you will be compensated $350.

Visit	**Stipend**
Screening	$100
Day -1 (Admission)	$250
Day 1	$250
Day 2	$250
Day 3 (Discharge)	$100
Day 7	$100
Total	**$1050**

WHAT ABOUT RESEARCH RELATED INJURIES?
Immediate necessary medical care is available at Duke University Medical Center in the event that you are injured as a result of your participation in this research study. However, there is no commitment by Duke University, Duke University Health System, Inc., or your Duke physicians to provide monetary compensation or free medical care to you in the event of a study-related injury.

For questions about the study or research-related injury, contact Dr. Jeffrey Guptill at (919) 684-1672 during regular business hours and at (919) 684-8111 after hours and on weekends and holidays.

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WHAT ABOUT MY RIGHTS TO DECLINE PARTICIPATION OR WITHDRAW FROM THE STUDY?
You may choose not to be in the study, or, if you agree to be in the study, you may withdraw from the study at any time. If you withdraw from the study, no new data about you will be collected for study purposes unless the data concern an adverse event (a bad effect) related to the study. If such an adverse event occurs, we may need to review your entire medical record. All data that have already been collected for study purposes, and any new information about an adverse event related to the study, will be sent to the study sponsor.

Your decision not to participate or to withdraw from the study will not involve any penalty or loss of benefits to which you are entitled, and will not affect your access to health care at Duke. If you do decide to withdraw, we ask that you contact Dr. Guptill in writing and let him know that you are withdrawing from the study. His mailing address is Box 3854, DUMC, Durham, NC 27710.

Dr. Guptill may ask you to complete the tests that would ordinarily occur when a person completes the study.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

Your doctor may decide to take you off this study if you have serious side effects, or if your study doctor determines that it is no longer in your best interest to continue. The sponsor or regulatory agencies may stop this study at any time without your consent. If this occurs, you will be notified and your study doctor will discuss other options with you.

Your samples and/or data may be stored and shared for future research without additional consent if the information that identifies you are removed. If your identifying information is removed from your samples or data, we will no longer be able to identify and destroy them.

The use of your data and samples may result in commercial profit. You will not be compensated for the use of your data and samples other than what is described in this consent form.

A description of this clinical trial will be available on https://clinicaltrials.gov/ as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

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WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?
For questions about the study or a research-related injury, or if you have problems, concerns, questions or suggestions about the research, contact Dr. Jeffrey Guptill at (919) 684-1672 during regular business hours and at (919) 684-8111 after hours and on weekends and holidays.

For questions about your rights as a research participant, or to discuss problems, concerns or suggestions related to the research, or to obtain information or offer input about the research, contact the Duke University Health System Institutional Review Board (IRB) Office at (919) 668-5111.

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STATEMENT OF CONSENT
"The purpose of this study, procedures to be followed, risks and benefits have been explained to me. I have been allowed to ask questions, and my questions have been answered to my satisfaction. I have been told whom to contact if I have questions, to discuss problems, concerns, or suggestions related to the research, or to obtain information or offer input about the research. I have read this consent form and agree to be in this study, with the understanding that I may withdraw at any time. I have been told that I will be given a signed and dated copy of this consent form."

_____	_____	_____
Signature of Subject	Date	Time
_____	_____	_____
Signature of Person Obtaining Consent	Date	Time