Official Protocol Title:	A Single Ascending Dose Clinical Trial to Study the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of MK-7252 in Healthy Subjects
NCT number:	NCT03326986
Document Date:	13-Jul-2018

THIS PROTOCOL AMENDMENT AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC., WHITEHOUSE STATION, NJ, U.S.A.

SPONSOR:
Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or Merck)

One Merck Drive
P.O. Box 100
Whitehouse Station, New Jersey, 08889-0100, U.S.A.

Protocol-specific Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

TITLE:

A Single Ascending Dose Clinical Trial to Study the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of MK-7252 in Healthy Subjects

EudraCT NUMBER: 2017-003407-22

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
1.0	Trial Summary	Panel C was added to the protocol.	Upon review of the interim safety and preliminary PK data of human exposure to date (up to 162 mg), Panel C will be included to study higher MK-7252 doses.
2.1	Trial Design		
2.2	Trial Diagram		
5.2	Trial Treatments		
5.3	Randomization or Treatment Allocation		
6.0	Trial Flow Chart		

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
2.2	Trial Diagram	Added food effect secondary objective and language to all necessary sections to support the food effect evaluation in Panel C.	Food effect was not evaluated in Panel A and B so flexible language has been added to allow for fed period in Panel C.
3.2	Secondary Objectives and Hypothesis		
4.2.3.3	Pharmacokinetic Endpoints		
5.7.1.1	Diet		
7.1.5.2	Treatment Period Visit		
7.1.5.4	Trial Design/Dosing/Procedures Modifications Permitted within Protocol Parameters		
8.0	Statistical Analysis Plan		

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
4.2.2 4.2.3.3 6.0	Rationale for Dose Selection/Regimen/Modification Pharmacokinetic Endpoints Trial Flow Chart	Rationale provided to include a BID dosing option. A separate study flowchart add for the BID dosing procedures.	The flexibility to dose BID at any period has been added and will be based on subject tolerability of previous period. The separate BID flowchart was added to ease operational clarity should the BID dosing be implemented.
4.1.3	Ongoing Clinical Trials	Added PK and safety data from Panels A and B up to 162 mg.	This data supports Panel C dosing and dose selection.
4.2.2	Rationale for Dose Selection/Regimen/Modification	Added justification for Panel C doses.	
4.2.2.3	Maximum Dose/Exposure for this Trial	Added PK projections for the top dose of 540 mg in Panel C.	
4.2.2.4	Rationale for Dose Interval and Trial Design	Updated trial design and PK pauses for Panel C.	Added protocol language to reflect the addition of Panel C.
5.2	Trial Treatments	Add Panel C doses.	
5.3	Randomization or Treatment Allocation	Added Panel C Sample Allocation Schedule.	
12.3	Approximate Blood Volumes Drawn/Collected by Trial Visit by Sample Type	Added Panel C blood volume table.	

1.0 TRIAL SUMMARY

Abbreviated Title	Single Ascending Dose Study of MK-7252 in Healthy Subjects
Sponsor Product Identifiers	MK-7252
Trial Phase	Phase I
Clinical Indication	Oncology
Trial Type	Interventional
Type of control	Placebo
Route of administration	Oral
Trial Blinding	Double-blind
Treatment Groups	Panel A: 1 mg or Placebo/ 6 mg or Placebo/ 24 mg or Placebo/ 72 mg or Placebo/ 108 mg or Placebo Panel B: 3 mg or Placebo/ 12 mg or Placebo/ 48 mg or Placebo/ 72 mg or Placebo/ 162 mg or Placebo Panel C: 120 mg or Placebo/ 240 mg or Placebo/ 360 mg or Placebo/ 540 mg or Placebo/ 120 mg or Placebo fed
Number of trial subjects	Approximately 24 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 1 year and 1 month from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	Each subject will participate in the trial for approximately ~21 weeks in Panels A and B and ~18 weeks in Panel C from the time the subject signs the Informed Consent Form (ICF) through the final contact. After a screening phase of ~4 weeks, each subject will be receiving assigned treatment for approximately 11 weeks in Panels A and B and approximately 16 weeks in Panel C. After the end of treatment, each subject will be followed for 2 weeks.
Randomization Ratio	3:1

2.0 TRIAL DESIGN

2.1 Trial Design

This is a randomized, placebo-controlled, double-blind, single ascending-dose trial to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of MK-7252 in healthy men and women of non-childbearing potential (WONCBP) to be conducted in conformance with Good Clinical Practices.

Three panels (Panels A, B and C) of up to 8 subjects each (n=6 active, n=2 placebo) will be dosed orally. In Panels A and B, subjects will receive a single-rising dose in 5 alternating dosing periods. In Panel C, subjects will receive a single-rising dose in or up to 5 periods. Subjects will be monitored for safety throughout the study by reviewing potential adverse experiences (AEs), laboratory safety tests, vital signs, and electrocardiogram (ECGs).

In all panels, the subjects and investigator will be blinded to the allocation of subjects who receive active or placebo in each treatment period. Treatment will be determined based on a computer-generated randomized allocation schedule. Subjects will only participate in one panel. For each study participant, there will be a minimum of a 7-day washout between each period or dose administration, which will be sufficient to review safety and tolerability data up to 24 hr post dose, including AEs, laboratory safety test, VS and ECGs as outlined in Figure 1. In Panels A and B, following administration of MK-7252 at each dose level, there will be at least 3 days before the administration of the next higher dose in the subsequent panel.

There will be four PK pauses: (1) after Panel B in Period 2, (2) after Panel A in Period 4, (3) after Panel C Period 1 and (4) after Panel C Period 3, to review the interim PK data in addition to the ongoing review of safety data.

Specifically, PK samples up to Panel B Period 2 will be reviewed prior to dosing Panel A Period 3; PK samples up to Panel A Period 4 will be reviewed prior to dosing Panel B Period 4; PK samples up to Panel C Period 1 will be reviewed prior to dosing Panel C Period 2 and PK samples up to Panel C Period 3 will be reviewed prior to dosing Panel C Period 4.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

Because this is a Phase I assessment of MK-7252 in humans, the pharmacokinetic, pharmacodynamic and safety profiles of the compound are still being elucidated. This protocol is therefore written with some flexibility to accommodate the inherent dynamic nature of Phase I clinical trials. Please refer to Section 7.1.5 – Visit Requirements for examples of modifications permitted within the protocol parameters.

2.2 Trial Diagram

The trial design is depicted in Figure 1 and Table 1 below.

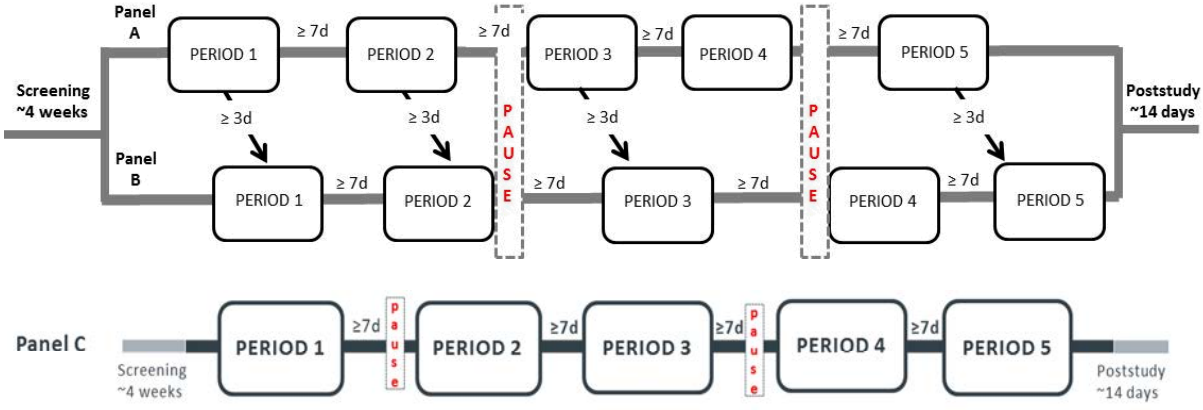

Figure 1 Study Diagram

Table 1 Suggested Dose Escalation Scheme for MK-7252

Panel	Period 1[b]		Period 2[b]			Period 3[b]		Period 4[b]			Period 5[b]	
A[a]	1 mg		6 mg			24 mg		72 mg			108 mg	
B[a]		3 mg		12 mg			48 mg			72 mg		162 mg
C[a]	120 mg[c]		240 mg[d]			360 mg[d]		540 mg[d]			120 mg (fed)[c,d]	

a Within each treatment period, 6 subjects will be randomized to receive MK-7252 and 2 subjects to receive matching placebo according to a computer-generated allocation schedule.

b The suggested doses may be adjusted downward based on evaluation of safety, tolerability, PK and/or PD data observed in previous treatment periods.

c The assigned treatment for Panel C Periods 1 and 5 (fasted/fed) will be the same, such that the same subjects will receive active drug or matching placebo in both treatment periods. Panel C Period 5 may be replaced with a fasting daily dose not exceeding 540 mg.

d Daily dose may be divided into two doses. See study flowcharts (for Panel C only).

The shaded area represents a PK pause after Panel B in Period 2, after Panel A in Period 4 and after Panel C in Period 1 and Period 3; PK samples up to Panel B Period 2 will be reviewed prior to dosing for Panel A Period 3, PK samples up to Panel A Period 4 will be reviewed prior to dosing Panel B Period 4, PK samples up to Panel C Period 1 will be reviewed prior to dosing Panel C Period 2 and PK samples up to Panel C Period 3 will be reviewed prior to dosing in Panel C Period 4.

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

1. **Objective:** To evaluate the safety and tolerability of single ascending dose administration of MK-7252 in healthy men and women of non-childbearing potential (WONCBP).

3.2 Secondary Objective(s) & Hypothesis(es)

1. **Objective:** To obtain preliminary plasma PK data including area under the curve (AUC0-∞, AUC0-24hr, AUC0-12hr, AUClast), maximal concentration (Cmax), C12hr and C24hr postdose, time to reach maximal concentration (Tmax), and apparent terminal half-life (t½) following oral administration of single doses of MK-7252.

   Hypothesis: The geometric mean Ctrough at 12 hr postdose (C12hr) meets or exceeds 100 nM after single dose administration of MK-7252 at a dose that is sufficiently well tolerated to continue development for the treatment of cancer.

2. **Objective**: To evaluate hemodynamic changes of MK-7252 given as single doses on peripheral blood pressure (BP) (systolic and diastolic) and heart rate in healthy men and WONCBP.

3. **Objective (Panel C only)**: To compare the effects of a high-fat breakfast on the plasma PK of MK-7252 to those in the fasted state after administration of a single oral dose of MK-7252 in healthy men and WONCBP.

Estimation: The plasma AUC0-∞, AUC0-12hr and Cmax resulting from a single oral dose of MK-7252 following a standard breakfast will be estimated and compared to that observed with the identical dose level administered in the fasted state.

3.3 Exploratory Objectives

1. [redacted]
2. **Objective:** To explore urinary excretion of MK-7252 following single dose administration in in healthy men and WONCBP.
3. **Objective:** To explore the relationship between genetic variation and response to the treatment administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in this study.

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure (IB) for detailed background information on MK-7252.

4.1.1 Pharmaceutical and Therapeutic Background

MK-7252 is a potent, selective small molecule antagonist of the human adenosine receptor subtype 2A (A2a). [redacted]

Although immunotherapies (including Keytruda) have been shown to be efficacious in treating multiple malignancies, evidence suggests that malignant cells are able to utilize multiple pathways to achieve immune escape, contributing to the lack of response or resistance to T cell immune checkpoint inhibitors. Along with IDO, arginase, TGFβ, etc., adenosine and its receptors represent a key pathway contributing to the immune suppressive environment in tumors, allowing tumors to escape from immune responses [1].

Adenosine is an important natural mediator of immune suppression to avoid collateral tissue damage during inflammatory conditions such as infection and wound healing [2]. Under normal physiologic conditions, extracellular release of adenosine is balanced by rapid cellular uptake thus maintained at very low levels. In contrast, in a tumor microenvironment, aberrant cancer cell growth and hypoxic conditions produce and actively sustain high levels of adenosine levels and extracellular adenosine triphosphate (ATP) [3]. Therefore, an adenosine rich tumor microenvironment (the "adenosine halo") represents a major barrier for effective tumor immunotherapy and needs to be overcome to achieve more effective and broader clinical efficacy.

Adenosine signaling through A2a receptors expressed on a variety of immune cell subsets and endothelial cells has been established as the major pathway in suppressing T cell-mediated cytotoxic activity, proliferation, activation and priming [4]. Levels of extracellular adenosine are also increased by the catabolism of extracellular ATP and adenosine diphosphate by the tandem activity of the ectonucleotidases CD-39 and CD-73. One of the signature features of the solid tumor environment is hypoxia. In response to hypoxia-induced HIF-1 generation in tumors and inflamed tissues, CD-39 and CD-73 are up regulated on endothelial, stromal and some solid tumor cells, and on several subsets of immune cells (including Tregs, CD-8+ T cells, and B cells) [5]. Adenosine/A2aR signaling on endothelial cells upregulates vascular endothelia growth factor (VEGF) production and leads to angiogenesis which directly promotes cancer cell proliferation and tumor metastasis. [redacted]

[redacted]

4.1.2 Pre-clinical and Clinical Trials

Refer to the IB for detailed pre-clinical information on MK-7252. As this is the First-in-Human (FIH) study for MK-7252, there is no clinical trial information related to this molecule besides the initial doses given described in section 4.1.3. Clinical experiences with other A2a Receptor antagonists are summarized in the IB.

4.1.3 Ongoing Clinical Trials

In the current single ascending dose study (Protocol 001), the preliminary plasma exposure of MK-7252 was reviewed, along with safety and tolerability data. The interim PK analysis after oral administration of 1, 3, 6, 12, 24, 48, 72, 108 and 162 mg single doses (shown in Table 2), demonstrated that MK-7252 was rapidly absorbed with a median Tmax of 0.75-1.0 hours. Concentrations declined in a monophasic pattern at lower doses but appear to be exhibiting a biphasic decline at the 162 mg dose. The apparent terminal half-life could not be calculated following the 1 mg and 3 mg doses due to insufficient terminal phase data.

However, the geometric mean t½ ranged from 1.29 to 5.97 hours following the 6 mg to 162 mg doses. All C24hr samples were below the limit of quantitation (BLQ) following 1 to 72 mg doses. The geometric C24hr at 108 and 162 mg was 3.91 and 9.69 nM, respectively and geometric C12hr at 108 mg and 162 mg was 26.1 and 28,2 nM, respectively. Exposure increases were approximately dose proportional.

Table 2 Summary Pharmacokinetic Parameter Values for MK-7252 Following Administration of Single Oral 1 to 162 mg Doses to Healthy Fasted Subjects (Preliminary Results)

Dose (mg)	Tmax[1] (hr)	Cmax[2] (nM)	AUC0-12[2] (nM*hr)	AUC0-24[2] (nM*hr)	t1/2[2] (hr)	AUC0-inf[2] (nM*hr)	C12[2] (nM)	C24[2] (nM)
1	1.0 (0.5-1.0)	20.8 (29.7)	48.4 (45.6)	48.4 (45.6)	--[3]	--[3]	--[4]	--[4]
3	0.75 (0.5-1.0)	50.2 (38.9)	113 (58.8)	113 (58.8)	--[3]	--[3]	--[4]	--[4]
6	0.75 (0.5-1.0)	120 (37.6)	275 (40.4)	275 (40.4)	1.29 (12.2)	273 (47.3)	--[4]	--[4]
12	1.0 (0.5-1.0)	213 (75.7)	541 (83.0)	541 (83.0)	1.34 (15.0)	723 (20.5)	--[4]	--[4]
24	1.0 (0.5-1.0)	474 (39.1)	1250 (37.9)	1260 (38.6)	1.60 (19.9)	1260 (37.9)	2.73 (60.9)[5]	--[4]
48	0.75 (0.5-1.0)	742 (69.1)	1830 (72.7)	1840 (73.5)	1.35 (9.93)	1840 (72.7)	--[6]	--[4]
72 Panel A/B Combined	1.0 (0.5-2.0)	1690 (39.9)	4450 (47.2)	4510 (47.3)	1.67 (41.8)	4480 (47.1)	10.1 (78.5)	--[4]
108	0.75 (0.5-1.0)	2430 (30.4)	6800 (35.8)	7030 (36.7)	3.09 (81.1)	7080 (37.6)	26.1 (132)	3.91 (239)[5]
162	0.75 (0.5-1.0)	3020 (58.5)	8350 (79.8)	8620 (80.0)	5.97 (92.2)	8870 (76.6)	28.2 (138)	9.69 (209)[5]

[1]median (min-max);
[2]geometric mean (%CVGM)
[3]insufficient data to report;
[4]all values were BLQ (2.74nM);
[5]BLQ values replaced with 1/2 LLOQ (1.37nM) to enable GM calculation
[6]greater than half of the values were BLQ;

MK-7252-001 Preliminary Safety and Tolerability

Preliminary interim safety summary revealed that single oral administration of 1, 3, 6, 12, 24, 48, 72, 108 and 162 mg doses of MK-7252 or placebo was generally well tolerated. Orthostatic tachycardia was noted following the 12 mg and 48 mg doses, which was considered to be not drug-related at the time. However, palpitations noted following the 24 mg and 72 mg doses was considered drug-related at the time. Moreover, modest transient increases in systolic blood pressure (5-20 mmHg), diastolic blood pressure (5-12 mmHg), and increases in heart rate (<10 bpm) have been observed at doses up to 162 mg. Of note, one subject at the 72 mg dose, showed across a 2-hr interval, a mean increase in systolic blood pressure of 33 mmHg (semi-recumbent), and a mean increase in heart rate of 49 bpm (semi-recumbent). There were modest elevations of the diastolic BP (mean semi-recumbent DBP increase of 12 mmHg). This subject reported dizziness upon standing at 4 hr post-dose, but otherwise reported no other symptoms. Based on these observations, the subject was discontinued and the 72 mg dose was repeated in the next dosing period. Moreover, upon review of the safety and tolerability data to date, hemodynamic stopping criteria was added (Appendix 12.8) and modification to the original dose escalation plan in Period 5 was made. There were no additional subjects with systolic blood pressure increases of >30 mmHg and/or HR increase of >30 bpm in the repeated 72 mg dose panel, or at the 108 mg and 162 mg dose. Thus no additional subjects were discontinued. No other clinically significant abnormalities were noted in routine blood chemistry, ECG, vital signs, physical exam, and laboratory adverse experiences. There have been no serious adverse events (AEs). Most AEs have been categorized as either mild to moderate intensity, with exception of one AE (headache) categorized as severe. Based on the blinded review of AEs, there were no dose-related increases in the frequency of AEs. Adverse experiences reported to date (April 30, 2018) are provided in Table 3.

Table 3 Subjects with Adverse Events (Incidence >0% in One or More Treatment Group)

	MK-7252 1 mg / PBO		MK-7252 3 mg / PBO		MK-7252 6 mg / PBO		MK-7252 12 mg / PBO		MK-7252 24 mg / PBO		MK-7252 48 mg / PBO		MK-7252 72 mg / PBO	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	8		8		8		8		8		8		16	
With one or more adverse events	3	(37.5)	6	(75.0)	5	(62.5)	7	(87.5)	6	(75.0)	6	(75.0)	10	(62.5)
With no adverse events	5	(62.5)	2	(25.0)	3	(37.5)	1	(12.5)	2	(25.0)	2	(25.0)	6	(37.5)
Cardiac disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(12.5)**	**1**	**(12.5)**	**2**	**(25.0)**	**2**	**(12.5)**
Heart rate increased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Palpitations	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)	2	(12.5)
Postural orthostatic tachycardia syndrome	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)	2	(25.0)	0	(0.0)
Ear and labyrinth disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(12.5)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Cerumen impaction	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Eye disorders	**0**	**(0.0)**	**1**	**(12.5)**	**0**	**(0.0)**	**1**	**(12.5)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(6.3)**
Eye irritation	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.3)
Photophobia	0	(0.0)	1	(12.5)	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)
Visual field defect	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)
Gastrointestinal disorders	**1**	**(12.5)**	**1**	**(12.5)**	**1**	**(12.5)**	**3**	**(37.5)**	**1**	**(12.5)**	**1**	**(12.5)**	**0**	**(0.0)**
Abdominal discomfort	1	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Abdominal pain	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)
Diarrhoea	1	(12.5)	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Epigastric discomfort	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nausea	0	(0.0)	1	(12.5)	0	(0.0)	3	(37.5)	1	(12.5)	0	(0.0)	0	(0.0)
Vomiting	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
General Disorders And Administration Site Conditions	**1**	**(12.5)**	**1**	**(12.5)**	**0**	**(0.0)**	**1**	**(12.5)**	**1**	**(12.5)**	**3**	**(37.5)**	**4**	**(25.0)**
Catheter site hematoma	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Catheter site pain	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)
Chest discomfort	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)
Dermatitis contact	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)
Fatigue	1	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.3)
Feeling of body temperature change	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)	2	(25.0)	1	(6.3)
Pain in extremity	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(12.5)

	MK-7252 108 mg / PBO		MK-7252 162 mg / PBO		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	8		8		16	
With one or more adverse events	6	(75.0)	5	(62.5)	16	(100.0)
With no adverse events	2	(25.0)	3	(37.5)	0	(0.0)
Cardiac disorders	**0**	**(0.0)**	**0**	**(0.0)**	**4**	**(25.0)**
Heart rate increased	0	(0.0)	1	(12.5)	1	(6.3)
Palpitations	0	(0.0)	0	(0.0)	3	(18.8)
Postural orthostatic tachycardia syndrome	0	(0.0)	0	(0.0)	2	(12.5)
Ear and labyrinth disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(6.3)**
Cerumen impaction	0	(0.0)	0	(0.0)	1	(6.3)
Eye disorders	**0**	**(0.0)**	**0**	**(0.0)**	**3**	**(18.8)**
Eye irritation	0	(0.0)	0	(0.0)	1	(6.3)
Photophobia	0	(0.0)	0	(0.0)	2	(12.5)
Visual field defect	0	(0.0)	0	(0.0)	1	(6.3)
Gastrointestinal disorders	**0**	**(0.0)**	**2**	**(25.0)**	**7**	**(43.8)**
Abdominal discomfort	0	(0.0)	0	(0.0)	1	(6.3)
Abdominal pain	0	(0.0)	0	(0.0)	1	(6.3)
Diarrhoea	0	(0.0)	0	(0.0)	2	(12.5)
Epigastric discomfort	0	(0.0)	1	(12.5)	1	(6.3)
Nausea	0	(0.0)	0	(0.0)	5	(31.3)
Vomiting	0	(0.0)	1	(12.5)	1	(6.3)
General Disorders And Administration Site Conditions	**3**	**(37.5)**	**1**	**(12.5)**	**10**	**(62.5)**
Catheter site hematoma	0	(0.0)	0	(0.0)	1	(6.3)
Catheter site pain	0	(0.0)	0	(0.0)	1	(6.3)
Chest discomfort	0	(0.0)	0	(0.0)	1	(6.3)
Dermatitis contact	3	(37.5)	0	(0.0)	5	(31.3)
Fatigue	0	(0.0)	1	(12.5)	2	(12.5)
Feeling of body temperature change	0	(0.0)	0	(0.0)	3	(18.8)
Pain in extremity	0	(0.0)	0	(0.0)	2	(12.5)

	MK-7252 1 mg / PBO		MK-7252 3 mg / PBO		MK-7252 6 mg / PBO		MK-7252 12 mg / PBO		MK-7252 24 mg / PBO		MK-7252 48 mg / PBO		MK-7252 72 mg / PBO	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Infections And Infestations	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(12.5)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(12.5)**	**2**	**(12.5)**
Cystitis	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nasopharyngitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)
Oral herpes	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.3)
Sinusitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.3)
Vulvovaginitis	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Injury, poisoning and procedural complications	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(6.3)**
Ligament sprain	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.3)
Musculoskeletal and connective tissue disorders	**0**	**(0.0)**	**1**	**(12.5)**	**1**	**(12.5)**	**1**	**(12.5)**	**1**	**(12.5)**	**2**	**(25.0)**	**7**	**(43.8)**
Arthralgia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)
Back pain	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(12.5)
Muscle contusion	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Muscle spasms	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)	2	(12.5)
Muscle twitching	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.3)
Musculoskeletal pain	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)	2	(12.5)
Musculoskeletal stiffness	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.3)
Myofascial pain syndrome	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.3)
Neck pain	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)	1	(6.3)
Trismus	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.3)
Nervous system disorders	**1**	**(12.5)**	**5**	**(62.5)**	**3**	**(37.5)**	**7**	**(87.5)**	**2**	**(25.0)**	**1**	**(12.5)**	**1**	**(6.3)**
Dizziness	0	(0.0)	0	(0.0)	1	(12.5)	2	(25.0)	0	(0.0)	1	(12.5)	0	(0.0)
Dizziness postural	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.3)
Dysgeusia	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)
Headache	1	(12.5)	4	(50.0)	3	(37.5)	3	(37.5)	2	(25.0)	0	(0.0)	1	(6.3)
Paresthesia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.3)
Presyncope	0	(0.0)	1	(12.5)	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)
Sensory loss	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)
Psychiatric disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Irritability	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

	MK-7252 108 mg / PBO		MK-7252 162 mg / PBO		Total	
	n	(%)	n	(%)	n	(%)
Infections And Infestations	**0**	**(0.0)**	**0**	**(0.0)**	**4**	**(25.0)**
Cystitis	0	(0.0)	0	(0.0)	1	(6.3)
Nasopharyngitis	0	(0.0)	0	(0.0)	1	(6.3)
Oral herpes	0	(0.0)	0	(0.0)	1	(6.3)
Sinusitis	0	(0.0)	0	(0.0)	1	(6.3)
Vulvovaginitis	0	(0.0)	0	(0.0)	1	(6.3)
Injury, poisoning and procedural complications	**0**	**(0.0)**	**0**	**(0.0)**	**1**	(6.3)
Ligament sprain	0	(0.0)	0	(0.0)	1	(6.3)
Musculoskeletal and connective tissue disorders	**0**	**(0.0)**	**1**	**(12.5)**	**11**	**(68.8)**
Arthralgia	0	(0.0)	1	(12.5)	2	(12.5)
Back pain	0	(0.0)	0	(0.0)	2	(12.5)
Muscle contusion	0	(0.0)	0	(0.0)	1	(6.3)
Muscle spasms	0	(0.0)	0	(0.0)	3	(18.8)
Muscle twitching	0	(0.0)	0	(0.0)	1	(6.3)
Musculoskeletal pain	0	(0.0)	0	(0.0)	3	(18.8)
Musculoskeletal stiffness	0	(0.0)	0	(0.0)	1	(6.3)
Myofascial pain syndrome	0	(0.0)	0	(0.0)	1	(6.3)
Neck pain	0	(0.0)	0	(0.0)	2	(12.5)
Trismus	0	(0.0)	0	(0.0)	1	(6.3)
Nervous system disorders	**2**	**(25.0)**	**5**	**(62.5)**	**12**	**(75.0)**
Dizziness	0	(0.0)	0	(0.0)	4	(6.3)
Dizziness postural	0	(0.0)	1	(12.5)	2	(12.5)
Dysgeusia	0	(0.0)	1	(12.5)	1	(6.3)
Headache	2	(25.0)	3	(37.5)	11	(68.8)
Paresthesia	0	(0.0)	1	(12.5)	2	(12.5)
Presyncope	0	(0.0)	0	(0.0)	2	(12.5)
Sensory loss	0	(0.0)	0	(0.0)	1	(6.3)
Psychiatric disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(12.5)**
Irritability	0	(0.0)	1	(12.5)	1	(12.5)

	MK-7252 1 mg / PBO		MK-7252 3 mg / PBO		MK-7252 6 mg / PBO		MK-7252 12 mg / PBO		MK-7252 24 mg / PBO		MK-7252 48 mg / PBO		MK-7252 72 mg / PBO	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Respiratory, thoracic and mediastinal disorders	**2**	**(25.0)**	**0**	**(0.0)**	**2**	**(25.0)**	**1**	**(12.5)**	**4**	**(50.0)**	**0**	**(0.0)**	**2**	**(12.5)**
Cough	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.3)
Mouth swelling	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.3)
Mucosal pain	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nasal congestion	0	(0.0)	0	(0.0)	2	(12.5)	1	(12.5)	1	(25.0)	0	(0.0)	0	(0.0)
Oropharyngeal pain	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)
Throat irritation	2	(25.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Throat tightness	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)
Skin and subcutaneous tissue disorders	**0**	**(0.0)**	**1**	**(12.5)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(12.5)**
Cold sweat	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Dry skin	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.3)
Ecchymosis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Erythema	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.3)
Vascular Disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(6.3)**
Peripheral coldness	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(6.3)

	MK-7252 108 mg / PBO		MK-7252 162 mg / PBO		Total	
	n	(%)	n	(%)	n	(%)
Respiratory, thoracic and mediastinal disorders	**1**	**(12.5)**	**1**	**(12.5)**	**9**	**(56.3)**
Cough	0	(0.0)	0	(0.0)	1	(6.3)
Mouth swelling	0	(0.0)	0	(0.0)	1	(6.3)
Mucosal pain	0	(0.0)	1	(12.5)	1	(6.3)
Nasal congestion	1	(12.5)	0	(0.0)	5	(31.3)
Oropharyngeal pain	0	(0.0)	0	(0.0)	2	(12.5)
Throat irritation	0	(0.0)	0	(0.0)	2	(12.5)
Throat tightness	0	(0.0)	0	(0.0)	1	(6.3)
Skin and subcutaneous tissue disorders	**1**	**(12.5)**	**1**	**(12.5)**	**5**	**(31.3)**
Cold sweat	0	(0.0)	0	(0.0)	1	(6.3)
Dry skin	1	(12.5)	0	(0.0)	2	(12.5)
Ecchymosis	0	(0.0)	1	(12.5)	1	(6.3)
Erythema	0	(0.0)	0	(0.0)	1	(6.3)
Vascular Disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(6.3)**
Peripheral coldness	0	(0.0)	0	(0.0)	1	(6.3)

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

This First-in-Human (FIH) study is being conducted to evaluate safety, tolerability, PK and PD of MK-7252 after administration of single oral doses in healthy men and WONCBP subjects. Reproductive toxicity studies have yet to be conducted thus WONCBP subjects will be included in this study.

4.2.2 Rationale for Dose Selection/Regimen/Modification

As this is a Phase I assessment of MK-7252 in humans, and the PK, PD and safety profiles of the compound are still being evaluated, modifications to the dose or dosing regimen may be required to achieve the scientific goals of the trial objectives and/or to ensure appropriate safety monitoring of the trial subjects. Details of allowed modifications are provided in Section 7.1.5.6 - Trial Design/Dosing/Procedures Modifications Permitted within Protocol Parameter.

The primary objective of this study is to assess the safety and tolerability profile of MK-7252 after single dose administration in healthy subjects to support the current clinical development of MK-7252. [redacted]

[redacted]

Dosing with food (Panel C Period 5) may be replaced with a fasting dose and will not exceed the maximum daily dose of 540 mg.

4.2.2.1 Rationale for the Use of Placebo

The primary objective of this study is to evaluate the safety and tolerability of MK-7252. A matching placebo control trial will facilitate an unbiased assessment of safety and tolerability. Because subjects are healthy adults and will not receive clinical benefit from MK-7252, an A2a receptor antagonist, an active comparator, is not justified.

4.2.2.2 Starting Dose for This Trial

As recommended by the ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals (2009), the calculation of the first starting dose in human subjects is based on no-observed adverse effect level (NOAEL) determined in nonclinical safety studies performed in the most sensitive and relevant animal species adjusted with allometric factors to calculate the Human Equivalent Dose (HED).

The administration of MK-7252 to humans is supported by preclinical toxicology studies outlined in the IB. One-month good laboratory practice (GLP) repeat dose toxicity studies were conducted in both rats and dogs. The NOAEL of the sensitive species was the mid-dose tested at 20mg/kg in the dog (with AUC0-24hr of 64.7 µM*hr and Cmax of 13.6 µM).

For MK-7252, a dog NOAEL of 20 mg/kg/day supports the first starting dose of 66 mg (with default safety factor of $1/10^{th}$), assuming 60 kg human using the following calculation, where 1.8 is the conversion factor from the dog dose in mg/kg to HED in mg/kg:

HED = 20 mg/kg/day ÷ 1.8 = 11.11 mg/kg ÷ 10 = 1.11mg/kg x 60kg = 66 mg.

[redacted]
adenosine is associated with multiple signaling pathways that are ubiquitously expressed in immune system and is a known vasodilator. [redacted]

A starting dose of 1 mg is proposed for this study (with a predicted human AUC0-24hr of approximately 0.24 µM*hr). [redacted]

4.2.2.3 Maximum Dose/Exposure for This Trial

As described above, the initial target dose for efficacy was projected to be 128 mg MK-7252 BID, which was expected to achieve steady state human exposure of AUC0-12hr: 32.1 (28.7 – 35.8) µM.hr, and Cmax: 5.39 (4.72 – 6.10) µM. However, review of interim human PK data up to 162 mg, suggested that human exposures were considerably lower than initial projections because the rate of elimination seems to be faster than anticipated. Therefore, in order to achieve exposures closer to the target exposure for efficacy, the maximum dose proposed for Panel C is 540 mg in this amendment.

[redacted]

As recommended by the EMA Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products (2017), the maximum exposure in humans should be predefined and justified based on all available non-clinical and clinical data, including PD, PK and findings in toxicity studies and exposures at the expected therapeutic dose range.

Current projections of exposure are based on population modeling of measurable PK data up to 162 mg. However, uncertainty exists about the characterization of a relatively flat terminal phase, since it was seen only at the highest doses tested to date (108 mg and 162 mg). To better characterize the terminal elimination rate at higher doses, the maximum dose (in this amendment) has been increased to 540 mg and two additional PK sampling time points (at 14 hr and 32 hr postdose) have been added. At the maximum single dose proposed (540 mg), the currently projected AUC0-24hr of ~29.4 µM*hr, and Cmax ~8.7 µM, are expected to be approximately 2-fold and 1.5-fold below for AUC and Cmax of the dog NOAEL levels (at 20mg/kg) AUC0-24hr and Cmax of 64.7µM*hr and 13.6 µM, respectively.

Four (4) interim PK pauses are included in this trial: (1) following Panel B Period 2; (2) following Panel A Period 4 and two PK pauses in Panel C: (3) following Period 1 and (4) following Period 3. The first PK pause, after Panel C Period 1, will confirm that exposures in Panel C subjects are consistent with interim PK data from Panels A and B. Available PK data will be reviewed to ensure that subsequent doses administered are not projected to exceed the NOAEL AUC and Cmax levels determined from preclinical toxicology studies.

The ascending-dose study design and interim available PK data ensure that human exposure levels will be reviewed along with safety and tolerability from previous dose levels before escalating to dose levels that would approach dog NOAEL dose. If the interim PK data reveals that subsequent doses may produce exposures that would exceed the dog NOAEL exposure, then doses will be adjusted downward or subsequent dosing periods may be

eliminated. Dose escalation decisions will be communicated to the site via an administrative letter, and safety will be monitored throughout the study by repeated clinical and laboratory evaluations.

4.2.2.4 Rationale for Dose Interval and Trial Design

MK-7252, an adenosine 2a receptor antagonist, is not considered a compound with a high degree of uncertainty to the potential for risk of harm to volunteers according to the publication "Guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products" (European Medicine Agency guidance released July 2017). The degree of uncertainty was determined by careful evaluation of the following: mode of action of MK-7252, presence or absence of biomarkers, the nature of the target, the relevance of available animal models and/or findings in non-clinical safety studies, and the study population. Furthermore, MK-7252 acts via a well-established mechanism. Safety assessment toxicity trials and ancillary pharmacology trials with MK-7252 provide no contraindications to the initiation of clinical trials in people with this compound via the oral route. Monitorable dose-limiting toxicities were observed (hemodynamic changes) in a 7-day rat and ascending-dose dog toxicity trials and substantial preclinical safety margins were obtained over initial human doses.

The trial design includes 2 alternating ascending dose panels (Panels A and B) and one ascending dose Panel C, of 8 subjects each, 6 subjects randomized to active treatment and 2 to placebo in a balanced design across periods. For each panel in each period, all 8 subjects are planned to be administered MK-7252 or matching placebo on the same day in spaced time intervals by Phase I Clinical Research standards for compounds not considered to have a high degree of uncertainty related to the potential of harm to participants. The dosing regimen was determined based on the following: the presence of preclinical safety margins for MK-7252, the inclusion of extensive safety monitoring in the clinic, and the fact that MK-7252 is not considered a compound with a high potential for risk of harm. There will be frequent, careful assessments of adverse events throughout the postdose period prior to administering the next dose level. This recommendation is in keeping with the projected safety profile and the ability of the Phase I unit to monitor each subject closely. Other modifications to the dosing and/or clinical procedure, currently outlined in the protocol, may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study subjects.

There will be a 7-day washout between doses for any given subject. Based on initial PK results with a terminal t1/2 of 1.3 to 6 hours, this 7-day washout is sufficient to ensure appropriate elimination of MK-7252 before the following dose period.

The study will also include four pre-specified PK breaks (after Panel B Period 2; after Panel A Period 4 and after Panel C Periods 1 and 3. This will provide an estimation of exposure/concentration during the study and further guide subsequent conduct of the study.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

No efficacy endpoints will be obtained in this study.

4.2.3.2 Safety Endpoints

This will be the first introduction of MK-7252 into humans. It is anticipated that oral administration of MK-7252 will be well-tolerated in humans based on preclinical safety and toxicology testing in rats and dogs; and based on experience with another A2aR antagonist, preladenant.

The safety and tolerability of MK-7252 will be monitored by standard means including clinical assessments of AEs, repeated physical examinations, targeted neurologic examination, monitoring vital signs, 12-lead ECGs, and standard laboratory safety tests (including hematology, chemistry, and urinalysis). The time points for safety data collection are based on the projected PK of MK-7252.

Adenosine is known to be a vasodilator, and antagonism of the A2a receptor by MK-7252 is expected to affect hemodynamic changes (e.g., BP changes observed in both in clinical trials with another A2aR antagonist, preladenant and in dog studies with MK-7252). [redacted] Thus blood pressure will be monitored throughout study as outlined in the protocol.

4.2.3.3 Pharmacokinetic Endpoints

The systemic pharmacokinetics of MK-7252 will be characterized following single dose administration of MK-7252. The primary PK endpoints will include AUC0-12hr, AUC0-24hr, AUC0-∞, Cmax, C12hr and C24hr, Tmax, and apparent terminal t½ following single oral dose administration of MK-7252. Plasma samples will be analyzed at specified times for the determination of MK-7252 as specified in the Study Flow Chart (Section 6.0). These procedures may also be performed at various unscheduled time points, if deemed clinically appropriate. This study is planned to include an assessment of plasma PK of MK-7252 in fasted and fed conditions in Panel C; to evaluate the potential for a food effect (high fat) on exposure.

To evaluate the renal excretion of MK-7252, urine will also be collected for determination of MK-7252 concentrations following single dose administration. If data permits, urinary PK

values (amount recovered [Ae], fraction of dose recovered [fe], and renal clearance [Clr]) will be calculated.

4.2.3.4 Pharmacodynamic Endpoints

[redacted]

4.2.3.5 Planned Exploratory Biomarker Research

[redacted]

Planned Genetic Analysis

Understanding genetic determinants of drug response and the molecular basis of disease is an important endeavor during medical research. This research will evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation and/or disease. If genetic variation is found to predict efficacy or adverse events, the data might inform optimal use of therapies in the patient population. Knowledge of the molecular basis of disease contributes to the development of novel biomarkers and the identification of new drug targets. This research contributes to understanding molecular basis of disease and the genetic determinants of efficacy and safety associated with the treatments in this study.

4.2.3.6 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on specimens consented for future biomedical research during this clinical trial. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma) and/or the measurement of other analytes, depending on which specimens are consented for future biomedical research.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting/retaining specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that subjects receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research sub-trial are presented in Section 12.2 – Collection and Management of Specimens for Future Biomedical Research.

4.3 Benefit/Risk

Subjects in early clinical trials generally cannot expect to receive direct benefit from treatment during participation as these clinical trials are designed to provide information about the safety and pharmacokinetics of an investigational medicine.

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying IB and Informed Consent documents.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Healthy men and women of non-childbearing potential between the ages of 18 and 50 years (inclusive) will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Provide written informed consent for the trial, including for Future Biomedical Research.
2. Be male or female of non-childbearing potential 18 to 50 years of age at the pre-trial (screening) visit; further:
    a. If postmenopausal female: subject is without menses for at least 1 year and has a documented follicle stimulating hormone (FSH) level in the postmenopausal range at pre-trial (screening) - OR -

b. If surgically sterile female: subject is status post hysterectomy, oophorectomy or tubal ligation.

NOTE: These procedures must be confirmed with medical records. In the absence of documentation, hysterectomy may be confirmed by pelvic exam or if necessary by ultrasound; oophorectomy may be confirmed by hormone levels, particularly FSH in the post-menopausal range, but tubal ligation subjects without records should be excluded. Information must be captured appropriately within the site's source documents.

3. Have a Body Mass Index (BMI) between 18.5 and 32 kg/m^2, inclusive. BMI = weight (kg)/height $(m)^2$.
4. While in semi-recumbent position, have a systolic blood pressure (SBP) ≤ 140 mmHg and diastolic blood pressure (DBP) ≤ 90 mm Hg and a respiratory rate (RR) ≤20 breath/min at the pre-trial (screening) visit and prior to randomization in triplicate; mean values from triplicate measurements will be used; if mean value is out of range, repeat triplicate measurement may be taken and mean value of subsequent triplicate may be used.
5. Be judged to be in good health based on medical history, physical examination, vital sign measurements and ECG performed prior to randomization. Appendix section 12.5 provides a table of 12-Lead Electrocardiogram Abnormality Criteria.
6. Be judged to be in good health based on laboratory safety tests (Section 7.1.3.1) obtained at the screening visit and at screening 2. Appendix section 12.4 provides an algorithm for the assessment of out-of-range laboratory values.
   a. Liver Function Tests including aspartate aminotransferase (AST), alanine aminotransferase (ALT) direct bilirubin, and alkaline phosphatase must be equal to or below the upper limit of normal before the subject can considered eligible for randomization.
7. Be a non-smoker and/or has not used nicotine or nicotine-containing products (e.g., nicotine patch) for at least approximately 3 months.
8. Be willing to comply with the trial restrictions (see Section 5.7 for a complete summary of trial restrictions).

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Is under the age of legal consent.
2. Is mentally or legally incapacitated, has significant emotional problems at the time of pretrial (screening) visit or expected during the conduct of the trial or has a history of clinically significant psychiatric disorder of the last 5 years. Subjects who have had situational depression may be enrolled in the trial at the discretion of the investigator.

3. Has a history of clinically significant endocrine, gastrointestinal, cardiovascular, hematological, hepatic, immunological, renal, respiratory, genitourinary or major neurological (including stroke and chronic seizures) abnormalities or diseases. Subjects with a history of uncomplicated kidney stones, as defined as spontaneous passage and no recurrence in the last 5 years, or childhood asthma may be enrolled in the trial at the discretion of the investigator.
4. Has a history of liver disease (chronic hepatitis, cirrhosis, etc.).
5. Has a history of cancer (malignancy).

   Exceptions: (1) Subjects with adequately treated non-melanomatous skin carcinoma or carcinoma in situ of the cervix may participate in the trial; (2) Subjects with other malignancies which have been successfully treated ≥10 years prior to the pretrial (screening) visit where, in the judgment of both the investigator and treating physician, appropriate follow-up has revealed no evidence of recurrence from the time of treatment through the time of the pretrial (screening) visit (except those cancers identified at the beginning of exclusion criterion 5); or, (3) Subjects, who, in the opinion of the trial investigator, are highly unlikely to sustain a recurrence for the duration of the trial.
6. Has a history of significant multiple and/or severe allergies (e.g. food, drug, latex allergy), or has had an anaphylactic reaction or significant intolerability (i.e. systemic allergic reaction) to prescription or non-prescription drugs or food.
7. Is positive for hepatitis B surface antigen, hepatitis C antibodies or HIV.
8. Had major surgery, donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to the pretrial (screening) visit.
9. Has participated in another investigational trial within 4 weeks (or 5 half-lives), whichever is greater, prior to the pretrial (screening) visit. The window will be derived from the date of the last visit in the previous trial.
10. Has QTc interval ≥470 msec (for males) and ≥480 msec (for females).
11. Has taken during the 5 days prior to start of study treatment a Proton Pump Inhibitor (PPI).
12. Is unable to refrain from or anticipates the use of any medication, including prescription and non-prescription drugs or herbal remedies beginning approximately 2 weeks (or 5 half-lives) prior to administration of the initial dose of trial drug, throughout the trial (including washout intervals between treatment periods), until the post-trial visit. There may be certain medications that are permitted, see Section 5.5.
13. Consumes greater than 3 glasses of alcoholic beverages (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day. Subjects that consume 4 glasses of alcoholic beverages per day may be enrolled at the discretion of the investigator.

14. Consumes excessive amounts, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, energy-drinks, or other caffeinated beverages per day.
15. Is a regular user of cannabis, any illicit drugs or has a history of drug (including alcohol) abuse within approximately 1 year. Subjects must have a negative UDS prior to randomization.
16. Is any concern by the investigator regarding the safe participation of the subject in the trial or for any other reasons the investigator considers the subject inappropriate for participation in the trial.
17. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or Sponsor staff directly involved with this trial.

5.2 Trial Treatment(s)

The treatments to be used in this trial are outlined below in Table 4.

Table 4 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen /Treatment Period	Use
MK-7252	Panel A or B: 1, 3, 6, 12, 24, 48, 72, 108, and 162 mg Panel C: 120 (fasted and fed), 240, 360 and 540 (doses in all panels may be adjusted downward) Potencies: 1mg/mL and 20 mg/mL	Single dose in each period	Oral	Day 1 in Periods 1, 2, 3, 4 or 5	Experimental
Placebo	N/A	Single dose in each period	Oral	Day 1 in Periods 1, 2, 3, 4 or 5	Placebo-control

Trial treatment should begin on the day of treatment allocation/randomization or as close as possible to the date on which the subject is allocated/assigned.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of trial treatments in accordance with the protocol and any applicable laws and regulations.

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection (Preparation)

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background & Rationale. Specific calculations or evaluations required to be performed in order to administer the proper dose to each subject are outlined in a separate document provided by the Sponsor.

5.2.1.2 Dose Modification (Escalation)

All dose escalation decisions will be made jointly by the investigator and the Sponsor. Each dose escalation decision will occur after at least 6 evaluable participants have completed the previous dose level (subjects will be randomized to receive MK-7252 or placebo in a 3:1 ratio, respectively. Given that the compound has no significant toxicology findings in the dose range to be studied, dose escalation decisions can be made based on 6 evaluable subjects (minimum of 4 subjects on active study drug). Dose escalation decisions will be based on key safety variables including vital signs, 12-lead ECG, laboratory safety tests, targeted neurological examination and adverse events from the previous dose levels up to at least 24 hours (or longer depending on the compound). Pharmacokinetic and pharmacodynamic data may be included in the dose escalation decisions. See Background & Rationale - Section 4.0.

If, as judged by the Sponsor and investigator, the safety and tolerability data do not justify dose escalation, the dose will not be increased as planned. Instead, subjects may:

- receive the same dose level to further explore safety and tolerability at that level;
- receive a lower dose of the trial drug;
- receive the same or lower dose as a divided dose; or
- receive a lower dose with or without food.

Or, dosing may be stopped. Subject discontinuation criteria are outlined in Section 5.8.

Prior to each treatment, the clinical and laboratory safety parameters from the previous dose level will be reviewed by the investigator and discussed with the Sponsor to permit a decision on whether to advance to the next higher dose level. No dose escalation will occur without the joint agreement of the investigator and the Sponsor.

5.2.2 Timing of Dose Administration

All doses of MK-7252 or matching placebo will be prepared and dosed per the instructions outlined in the Method of Preparation Document.

In each treatment period, subjects will receive a single dose (or divided doses without exceeding the maximum daily dose as indicated per period in Panel C only) of MK-7252 or matching placebo as an oral suspension. Each on-site formulation (OSF) oral suspension dose should be administered with a water volume that brings the total ingested volume to approximately 240 mL (approximate to the nearest 10 mL). For example, if the OSF suspension volume dosed is 10 mL, the water volume to follow dosing would be 230 mL.

5.2.3 Trial Blinding

A double-blinding technique will be used. MK-7252 and placebo will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified trial site personnel. The subject and the investigator who is involved in the MK-7252 and placebo administration or clinical evaluation of the subjects are unaware of the group assignments.

See Section 7.1.4.2, Blinding/Unblinding, for a description of the method of unblinding a subject during the trial, should such action be warranted.

5.3 Randomization or Treatment Allocation

Subjects will be assigned randomly according to a computer-generated allocation schedule.

The sample allocation schedules are shown below in Table 5. In Panels A and B, the allocation schedule from the original protocol (001-00) will be used for active or placebo assignment, however the protocol clarification letter (PCL) issued after each dose escalation meeting will provide the dose.

Table 5 Sample Allocation Schedule

Subjects [a]	Period 1[b]	Period 2[b]	Period 3[b]	Period 4[b]	Period 5[b]
Panel A					
n=2	Placebo	6 mg	24 mg	72 mg	108 mg
n=2	1 mg	Placebo	24 mg	72 mg	108 mg
n=2	1 mg	6 mg	Placebo	72 mg	Placebo
n=2	1 mg	6 mg	24 mg	Placebo	108 mg
Panel B					
n=2	Placebo	12 mg	48 mg	72 mg	162 mg
n=2	3 mg	Placebo	48 mg	72 mg	162 mg
n=2	3 mg	12 mg	Placebo	72 mg	Placebo
n=2	3 mg	12 mg	48 mg	Placebo	162 mg
Panel C					
n=2	Placebo[c]	240 mg [d]	360 mg [d]	540 mg [d]	Placebo[c,d]
n=2	120 mg[c]	Placebo [d]	360 mg [d]	540 mg [d]	120 mg fed[c,d]
n=2	120 mg[c]	240 mg [d]	Placebo[d]	540 mg [d]	120 mg fed[c,d]
n=2	120 mg[c]	240 mg [d]	360 mg [d]	Placebo [d]	120 mg fed[c,d]

[a] Within each treatment period, 6 subjects will be randomized to receive MK-7252 and 2 subjects to receive matching placebo according to a computer-generated allocation schedule.

[b] The suggested doses may be adjusted downward based on evaluation of safety, tolerability, PK and/or PD data observed in previous treatment periods.

c The assigned treatment for Panel C Periods 1 and 5 (fasted/fed) will be the same, such that the same subjects will receive active drug or matching placebo in both treatment periods. Panel C Period 5 may be replaced with a fasting daily dose not exceeding 540 mg.

d Daily dose may be divided into two doses. See study flowcharts (for Panel C only).

The shaded area represents a PK pause after Panel B Period 2, after Panel A Period 4 and after Panel C Period 1 and after Panel C Period 3; PK samples up to Panel B Period 2 will be reviewed prior to dosing for Panel A Period 3, PK samples up to Panel A Period 4 will be reviewed prior to dosing Panel B Period 4, PK samples up to Panel C Period 1 will be reviewed prior to dosing for Panel C Period 2 and PK samples up to Panel C Period 3 will be reviewed prior to dosing for Panel C Period 4.

5.4 Stratification

No stratification based on age, sex or other characteristics will be used in this trial.

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

If a subject does not discontinue all prior medications within 14 days or 5 half-lives of the first dose of trial medication, he/she may be included in the study if the investigator can rationalize that the specific use of a prior medication is not clinically relevant within the context of the trial.

Concurrent use of any prescription or non-prescription medication, or concurrent vaccination, during the course of the trial (i.e., after randomization or treatment allocation) must first be discussed between the investigator and Sponsor prior to administration, unless appropriate

medical care necessitates that therapy or vaccination should begin before the investigator and Sponsor can consult. The subject will be allowed to continue in the trial if both the Sponsor and the investigator agree.

Paracetamol/acetaminophen may be used for minor ailments without prior consultation with the Sponsor.

5.6 Rescue Medications & Supportive Care

No rescue or supportive medications are specified to be used in this trial.

5.7 Diet/Activity/Other Considerations

5.7.1 Diet and Fruit Juice Restrictions

5.7.1.1 Diet

Fasting requirements for trial procedures, such as but not limited to laboratory safety evaluations, are specified in Section 7.1.

In each treatment period (except the fed panel), subjects will fast from all food and drinks, except water, for at least 8 hours prior to the dose administration. Subjects will fast from all food and drinks except water between trial drug administration and the first scheduled meal. Meals and snack(s) will be provided by the investigator at time points indicated in the trial flowchart. Subjects will fast from all food and drinks except water between meals and snacks. The caloric content and composition of meals will be the same in each treatment period, with the exception that a standard high-fat breakfast will be provided prior to trial drug administration for the fed panel. After the 24-hour postdose procedures have been completed, subsequent meals and snacks will be unrestricted in caloric content, composition and timing.

Water will be provided during trial drug administration. Water will be restricted 1 hour prior to and 1 hour after trial drug administration. Each OSF oral suspension dose should be administered with a water volume that brings the total ingested volume to approximately 240 mL (approximate to the nearest 10 mL). For example, if the OSF volume dosed is 100 mL, the water volume to follow dosing would be 140 mL.

In treatment Period 5 of Panel C, approximately 30 minutes prior to trial drug administration, subjects will begin to consume a standard high-fat breakfast. The contents of the standard high-fat breakfast are listed in Table 6.

Table 6 Contents of the Standard, High-Fat Breakfast

2 fried or scrambled eggs
2 strips bacon or 60 g feta cheese (for vegetarian)
2 slices toast with 2 pats of butter
4 oz (113 g) hash browns (fried potato)
240 mL whole milk

The nutritional content of the high-fat breakfast is as follows:

Total fat = 55.6 g

Total carbohydrates = 55 g

Total protein = 31.1 g

Total calories (for non-vegetarian, i.e. bacon) = 500.4 in fat, 220 in carbohydrates, and 124.4 in protein.

Total calories (for vegetarian, i.e. feta cheese) = ~513 in fat, ~236 in carbohydrates, and ~148 in protein.

The exact meal contents may be substituted with agreement between Sponsor and investigator, and must be documented in an administrative letter.

This breakfast should be consumed in its entirety within approximately 20 minutes. The start and stop time of the breakfast will be recorded. Within approximately 10 minutes after consuming the breakfast, subjects will be administered trial drug as indicated in Section 5.2.

Instructions on whether to take MK-7252 with or without food and/or drink may be modified during the trial based on newly available data.

5.7.1.2 Fruit Juice Restrictions

Subjects will refrain from the consumption of grapefruit juice, grapefruits and grapefruit products beginning approximately 2 weeks prior to administration of the initial dose of trial drug, throughout the trial (including the washout interval between treatment periods) and until the post-trial visit.

Subject also will refrain from the consumption of all fruit juices 24 hours prior to and after trial drug administration. All other days during the trial, consumption of fruits and fruit juices (except for grapefruit, grapefruit juices, and grapefruit products) is allowed.

5.7.2 Alcohol, Caffeine, Tobacco, Activity

5.7.2.1 Alcohol Restrictions

Subjects will refrain from consumption of alcohol 24 hours prior to the pre- and post-trial visits and from 24 hours prior to and after trial drug administration in each treatment period. At all other times, alcohol consumption is limited to no more than approximately 3 alcoholic beverages or equivalent (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day.

5.7.2.2 Caffeine Restrictions

Subjects will refrain from consumption of caffeinated beverages or xanthine containing products from 12 hours prior to the pre- and post-trial visits and from 12 hours prior to and after trial drug administration and prior to the 48 hour and 72 hour postdose procedures in each treatment period. At all other times, caffeinated beverages or xanthine-containing products will be limited to no more than 6 units per day amounts (>6 units: 1 unit=120 mg of caffeine).

5.7.2.3 Smoking Restrictions

Smoking and/or the use of nicotine/nicotine containing products is not permitted during the trial.

5.7.2.4 Activity Restrictions

Subjects will avoid unaccustomed strenuous physical activity (i.e., weight lifting, running, bicycling, etc.) from the pre-trial (screening) visit until administration of the initial dose of trial drug, throughout the trial (including washout intervals between treatment periods) and until the post-trial visit.

5.7.3 Contraception

Male subjects with female partner(s) of child-bearing potential must agree to use a medically acceptable method of contraception during the trial and for 90 days after the last dose of trial drug. Males should use a condom. Female partners must additionally use one of the following methods if they are not pregnant: hormonal contraception, intra-uterine device, diaphragm, or cervical cap. If their partner is pregnant, males must agree to use a condom and no additional method of contraception is required for the pregnant partner. Male subjects must also agree to not donate sperm during the study and for a period of 90 days after the last dose of study drug.

5.7.4 Other: Sun Exposure

MK-7252 absorbs light in the UV-VIS range, and phototoxicity testing for MK-7252 has not yet been conducted. Therefore prolonged exposure to sunlight should be avoided. Subject must minimize sunlight exposure on the skin from 24hr prior to first dosing until the post-

trial visit. Subjects should also refrain from activities, including doing sports in the sun, tanning lamp exposure, or any other occupational, recreational or incidental sunlight exposure. Subjects should apply a sunscreen with minimum SPF 50 or wear a long-sleeve shirt, long pants, and hats to block sunlight. All subjects should use the same sunscreen. Subjects will also be instructed to not change any of their other personal care products including cosmetics, cleansers or lotion during the course of the study.

5.7.5 Stopping rules:

The following stopping rules will be employed during the conduct of this trial.

If any of the below stopping rules are met, the trial will be paused and no further dosing will occur until the Sponsor has reviewed the totality of data available. In order to continue the trial (upon joint agreement with the Sponsor and investigator), a substantial amendment will be submitted for approval.

1. An individual participant reports a Serious Adverse Event considered related to the study drug by the investigator.
2. Two (2) or more participants within a Panel (at the same dose level) report Severe Non-Serious Adverse Events considered related to the study drug by the investigator.

If any of the below stopping rules are met, subsequent higher doses will be lowered based upon joint agreement of the Sponsor and investigator in order for the trial to continue.

Panel Wide: Should the emerging PK (mean) data indicate that the maximum clinical exposure (Cmax or AUC), as defined in Section 4.2 will be exceeded, subsequent higher doses will be adjusted based upon joint agreement of the Sponsor and investigator.

Individual: Hemodynamic changes that exceed the pre-specified limitations (see Appendix 12.8)

5.8 Subject Withdrawal/Discontinuation Criteria

5.8.1 Discontinuation of Treatment

Discontinuation of treatment does not represent withdrawal from the trial.

As certain data on clinical events beyond treatment discontinuation may be important to the study, they must be collected through the subject's last scheduled follow-up, even if the subject has discontinued treatment. Therefore, all subjects who discontinue trial treatment prior to completion of the treatment period will still continue to participate in the trial as specified in Section 6.0 - Trial Flow Chart and Section 7.1.4.1 – Withdrawal/Discontinuation, or if available, Protocol Clarification Letter.

Subjects may discontinue treatment at any time for any reason or be dropped from treatment at the discretion of the investigator should any untoward effect occur. In addition, a subject may be discontinued from treatment by the investigator or the Sponsor if treatment is

inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at treatment discontinuation are provided in Section 7.1.4 – Other Procedures.

A subject must be discontinued from treatment but continue to be monitored in the trial for any of the following reasons:

- The subject or subject's legally acceptable representative requests to discontinue treatment.
- The subject's treatment assignment has been unblinded by the investigator or Merck subsidiary.
- The subject has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the subject at unnecessary risk from continued administration of study drug.
- The subject has findings on targeted neurologic examination (including assessment of mental status, motor function (muscle strength, coordination and gait) that in the opinion of the investigator and/or Sponsor, places the subject at unnecessary risk with continued administration of study drug.
- The subject has a positive urine drug screen at any time during the course of the trial, confirmed upon rechecks.
- The subject meets hemodynamic stopping criteria per Appendix 12.8.

For subjects who are discontinued from treatment, all applicable discontinuation activities will be performed according to Section 7.1.4.1 – Withdrawal/Discontinuation, or if available, Protocol Clarification Letter.

Discontinuation from treatment is "permanent." Once a subject is discontinued, he/she shall not be allowed to restart treatment.

5.8.2 Withdrawal from the Trial

A subject must be withdrawn from the trial if the subject or subject's legally acceptable representative withdraws consent from the trial.

If a subject withdraws from the study, they will no longer receive treatment or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the trial including the procedures to be performed should a subject repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the subject, as well as specific details regarding withdrawal from Future Biomedical Research are outlined in Section 7.1.4 – Other Procedures.

5.9 Subject Replacement Strategy

If a subject discontinues from trial treatment or withdraws from the trial, a replacement subject may be enrolled if deemed appropriate by the investigator and Sponsor. The replacement subject will generally receive the same treatment or treatment sequence (as appropriate) as the subject being replaced. The replacement subject will be assigned a unique treatment/randomization number. The trial site should contact the Sponsor for the replacement subject's treatment/randomization number.

The replacement subject may begin dosing at the subsequent dose level for that panel, based on investigator and Sponsor review and discussion.

5.10 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form. The overall trial ends when the last subject completes the last study-related phone-call or visit, withdraws from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator).

A trial may be paused during review of newly available preclinical/clinical safety, pharmacokinetic, pharmacodynamic, efficacy or biologic data or other items of interest, prior to a final decision on continuation or termination of the trial. It may be necessary to keep the trial open for gathering/reviewing of additional supportive data to optimally complete the objective(s) of the trial. If necessary, the appropriate amendment(s) to the protocol and/or appropriate communication(s) will be generated. If the decision has been made to end the study following this review period, the study end will be defined as the date of the Sponsor decision and this end of study date supersedes the definitions outlined above. The Competent Authority(ies) and Institutional Review Board(s)/Independent Ethics Committee(s) [IRB(s)/IEC(s)] will be apprised of the maximum duration of the trial beyond the last subject out and the justification for keeping the trial open.

5.11 Clinical Criteria for Early Trial Termination

There are no pre-specified criteria for terminating the trial early.

A primary objective of this early Phase I trial is to identify the maximum safe and well-tolerated dose and/or dosing regimen that achieve pharmacokinetic, pharmacodynamic and/or biologic targets in humans based on preclinical or early clinical data. Therefore, it is possible that trial subjects may not receive all doses specified in the protocol if this objective is achieved at lesser dose levels in this trial. This would not be defined as early termination of the trial, but rather an earlier than anticipated achievement of the trial objective(s). If a finding (e.g., pharmacokinetic, pharmacodynamic, efficacy, biologic targets, etc.) from another preclinical or clinical trial using the trial treatment(s), comparator(s), drug(s) of the same class, or methodology(ies) used in this trial, results in the trial(s) or program being stopped for non-safety reasons, this also does not meet the definition of early trial termination.

Early trial termination is defined as a permanent discontinuation of the trial due to unanticipated concerns of safety to the trial subjects arising from clinical or preclinical trials with the trial treatment(s), comparator(s), drug(s) of the same class or methodology(ies) used in this trial.

6.0 TRIAL FLOW CHART

Procedures for Panels A and B																
	Scheduled Time															
			Hours/Days – All Periods													
				D1									D2	D3	D4	
	Screening 1	Screening 2[a]	Predose	0	0.25	0.5	1	2	4	8	10	12	24	48	72	Post-trial[r]
Administrative Procedures																
Informed Consent	X															
Informed Consent for Future Biomedical Research	X															
Inclusion/Exclusion Criteria[b]	X	X	X[c]													
Subject Identification Card	X		X[c]													
Medical History	X	X	X													
Concomitant Medication Review	X----------X															
Assignment of Screening Number	X															
Assignment of Randomization Number			X[c]													
Clinic Procedures/Assessments																
Full Physical Examination	X		X[d]										X			X
Targeted Neurological Examination	X		X[d]						X				X			
Height	X															
Weight[e]	X		X													X
12-Lead Electrocardiogram[f]	X		X				X	X	X	X		X	X	X	X	X
Vital Signs (heart rate, blood pressure)[g]	X		X				X	X	X	X		X	X	X	X	X
Orthostatic Vital Signs (heart rate, blood pressure)[g]	X		X						X				X			
Vital Signs (respiratory rate, oral/tympanic temperature)[h]	X		X						X				X			
Standard Meals[i]									X--------X							
MK-7252/Placebo Administration[j]				X												
Taste Assessment Questionnaire[k]				X												

Procedures for Panels A and B																
	Scheduled Time															
			Hours/Days – All Periods													
				D1									D2	D3	D4	
	Screening 1	Screening 2[a]	Predose	0	0.25	0.5	1	2	4	8	10	12	24	48	72	Post-trial[r]
Adverse Events Monitoring	X----------															----------X
Laboratory Procedures/Assessments																
Laboratory Safety Tests[l] (Hematology, Urinalysis and Serum Chemistry)	X	X	X[d]										X			X
FSH (if applicable)	X															
Urine/Blood Drug Screen[m]	X		X													
HIV/Hepatitis Screen (per site SOP)	X															
Blood for Genetic Analysis[n]													X			
Pharmacokinetics Evaluations																
Blood for Plasma MK-7252 Assay[o]			X		X	X	X	X	X	X	X	X	X	X	X	
Urine for Urinary MK-7252 Assay[p]			X	X----------									----------X			
Pharmacodynamic Evaluations																
[redacted]																

a	If screening 1 occurs within 72hrs prior to the initial dose of trial drug, screening 2 is not required.
b	Review of inclusion/exclusion criteria will occur at Screening and after predose procedures (if applicable) in Period 1 only.
c	These predose procedures are only applicable to Period 1.
d	Physical examination, targeted neurological exam and safety labs can be conducted/collected on admission within 24 hours prior to dosing.
e	Weight will be measured after 8 hours of fasting, with shoes and jacket off.
f	In all treatment periods, all ECGs will be obtained in triplicate and the mean of QTcF will be calculated. There should be ~1-2 minute intervals between ECG measurements. Predose ECGs will be obtained in triplicate at least 1-2 minutes apart within 3 hours prior to dosing of trial drug.
g	All semi-recumbent HR and BP measurements will be done in triplicate at least a 1-2 minutes interval between measurements. Predose measurements can be performed within 3 hours prior to dosing. Subjects should be resting in the semi-recumbent position for at least 10 minutes prior to obtaining HR and BP. At pre-specified time points, following measurements of the semi-recumbent HR and BP, subjects assume a standing position for approximately 2 minutes and then orthostatic HR and BP will be obtained. Refer to Appendix 12.8, which provides guidance on hemodynamic monitoring and stopping criteria should a subject have an increase in HR or BP.
h	RR taken at screening and predose will be done in triplicate with at least a 1-2 minute interval between measurements. Predose measurements will be performed within 3 hours prior to dosing. For all other time points, a single measurement will be obtained.
i	Standardized meals will be provided at ~ 4 hours (lunch) and ~10 hours (dinner) postdose. A snack will be offered at ~ 7 and ~13 hours postdose. After the 24 hr. postdose procedures have completed, subsequent meal and snacks will be unrestricted in terms of caloric content, composition, and timing.
j	MK-7252 or placebo will be administered fasted unless otherwise specified in the protocol
k	The taste assessment questionnaire should to be administered immediately after dosing and 10 min postdose at the dose level/panel anticipated to receive the highest dose only.
l	Safety laboratory samples will be collected after at least an 8-hour fast.
m	The drug screen at Screening is mandatory; any additional drug screens are conducted per site SOP. Predose drug screen can be conducted within 24 hours prior to dosing.
n	This sample should be drawn once only after randomization for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.
o	Leftover main study plasma will be stored for future biomedical research.
p	Urine for Urinary MK-7252 Assay will be collected only in Panel B Period 2 and Panel B Period 5 at predose and at the following intervals postdose: 0-4, 4-8, 8-12, and 12-24 hrs.
q	[redacted]
r	Post-trial visit should occur approximately 14 days postdose. If the visit occurs prior to 14 days postdose, a phone call should be made to follow up on potential AEs.

Procedures for Panel C (QD Dosing)																		
	Scheduled Time																	
			Hours/Days – All Periods															
				D1										D2		D3	D4	
	Screening 1	Screening 2[a]	Pre-dose	0	0.25	0.5	1	2	4	8	10	12	14	24	32	48	72	Post-trial[r]
Administrative Procedures																		
Informed Consent	X																	
Informed Consent for Future Biomedical Research	X																	
Inclusion/Exclusion Criteria[b]	X	X	X[c]															
Subject Identification Card	X		X[c]															
Medical History	X	X	X															
Concomitant Medication Review	X----------																	----------X
Assignment of Screening Number	X																	
Assignment of Randomization Number			X[c]															
Clinic Procedures/Assessments																		
Full Physical Examination	X		X[d]											X				X
Targeted Neurological Examination	X		X[d]						X					X				
Height	X																	
Weight[e]	X		X															X
12-Lead Electrocardiogram[f]	X		X				X	X	X	X		X		X		X	X	X
Vital Signs (heart rate, blood pressure)[g]	X		X				X	X	X	X		X		X		X	X	X
Orthostatic Vital Signs (heart rate, blood pressure)[g]	X		X						X					X				
Vital Signs (respiratory rate, oral/tympanic temperature)[h]	X		X						X					X				
Standard Meals[i]									X----------									----------X
Standard High-Fat Meal for Fed Period[j]			X															
MK-7252/Placebo Administration[k]				X														
Adverse Events Monitoring	X----------																	----------X

Procedures for Panel C (QD Dosing)																		
	Scheduled Time																	
			Hours/Days – All Periods															
				D1										D2		D3	D4	
	Screening 1	Screening 2[a]	Pre-dose	0	0.25	0.5	1	2	4	8	10	12	14	24	32	48	72	Post-trial[r]
Laboratory Procedures/Assessments																		
Laboratory Safety Tests[l] (Hematology, Urinalysis and Serum Chemistry)	X	X	X[d]											X				X
FSH (if applicable)	X																	
Urine/Blood Drug Screen[m]	X		X															
HIV/Hepatitis Screen (per site SOP)	X																	
Blood for Genetic Analysis[n]														X				
Pharmacokinetics Evaluations																		
Blood for Plasma MK-7252 Assay[o]			X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine for Urinary MK-7252 Assay[p]			X	X----------										----------X				
[redacted]																		

a. If screening 1 occurs within 72hrs prior to the initial dose of trial drug, screening 2 is not required.
b. Review of inclusion/exclusion criteria will occur at Screening and after predose procedures (if applicable) in Period 1 only.
c. These pre-dose procedures are only applicable to Period 1.
d. Physical examination, targeted neurological exam and safety labs can be conducted/collected on admission within 24 hours prior to dosing.
e. Weight will be measured after 8 hours of fasting, with shoes and jacket off.
f. In all treatment periods, all ECGs will be obtained in triplicate and the mean of QTcF will be calculated. There should be ~1-2 minute intervals between ECG measurements. Predose ECGs will be obtained in triplicate at least 1-2 minutes apart within 3 hours prior to dosing of trial drug..
g. All semi-recumbent HR and BP measurements will be done in triplicate at least a 1-2 minutes interval between measurements. Predose measurements can be performed within 3 hours prior to dosing. Subjects should be resting in the semi-recumbent position for at least 10 minutes prior to obtaining HR and BP. At pre-specified time points, following measurements of the semi-recumbent HR and BP, subjects assume a standing position for approximately 2 minutes and then orthostatic HR and BP will be obtained.
   Refer to Appendix 12.8, which provides guidance on hemodynamic monitoring and stopping criteria should a subject have an increase in HR or BP.
h. RR taken at screening and predose will be done in triplicate with at least a 1-2 minute interval between measurements. Predose measurements will be performed within 3 hours prior to dosing. For all other timepoints, a single measurement will be obtained.
i. Standardized meals will be provided at ~ 4 hours (lunch) and ~10 hours (dinner) post dose. A snack will be offered at ~ 7 and ~13 hours post dose. After the 24 h post dose procedures have completed, subsequent meal and snacks will be unrestricted in terms of caloric content, composition, and timing.
j. A standard high-fat breakfast is to be administered 30 minutes prior to dosing for the fed period.
k. MK-7252 or placebo will be administered fasted unless otherwise specified in the protocol
l. Safety laboratory samples will be collected after at least an 8-hour fast.
m. The drug screen at Screening is mandatory; any additional drug screens are conducted per site SOP. Predose drug screen can be conducted within 24 hours prior to dosing.
n. This sample should be drawn once only after randomization for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.
o. Leftover main study plasma will be stored for future biomedical research.
p. Urine for Urinary MK-7252 Assay will be collected only in Period 2 and Period 4 at pre-dose and at the following intervals post-dose: 0-4, 4-8, 8-12, and 12-24 hrs.
q. [redacted]
r. Post-trial visit should occur approximately 14 days postdose. If the visit occurs prior to 14 days postdose, a phone call should be made to follow up on potential AEs.

Procedures for Panel C (BID Dosing)																	
	Scheduled Time																
	Hours/Days – All Applicable Periods																
		D1												D2		D3	
	Pre-dose	0	0.5	1	2	3	4	4.5	5	6	8	12	14	24	32	48	Post-trial[m]
Administrative Procedures																	
Medical History	X																
Concomitant Medication Review	X----------																----------X
Clinic Procedures/Assessments																	
Full Physical Examination	X[a]													X			X
Targeted Neurological Examination	X[a]						X							X			
Weight[b]	X																X
12-Lead Electrocardiogram[c]	X			X	X		X	X	X	X	X	X	X	X	X	X	X
Vital Signs (heart rate, blood pressure)[d]	X			X	X		X	X	X	X	X	X	X	X	X	X	X
Orthostatic Vital Signs (heart rate, blood pressure)[d]	X						X							X			
Vital Signs (respiratory rate, oral/tympanic temperature)[e]	X						X							X			
Standard Meals[f]						X----------							----------X				
MK-7252/Placebo Administration[g]		X					X										
Adverse Events Monitoring	X----------																----------X
Laboratory Procedures/Assessments																	
Laboratory Safety Tests[h] (Hematology, Urinalysis and Serum Chemistry)	X[a]													X			X
Urine/Blood Drug Screen	X[a]																
Blood for Genetic Analysis[i] (only applicable if sample not drawn in Period 1)														X			

Procedures for Panel C (BID Dosing)																	
	Scheduled Time																
	Hours/Days – All Applicable Periods																
		D1												D2		D3	
	Pre-dose	0	0.5	1	2	3	4	4.5	5	6	8	12	14	24	32	48	Post-trial[m]
Pharmacokinetics Evaluations																	
Blood for Plasma MK-7252 Assay[j]	X		X	X	X		X	X	X	X	X	X	X	X	X	X	
Urine for Urinary MK-7252 Assay[k]	X	X----------X															
[ccf] [redacted]																	

a. Physical examination, targeted neurological exam, safety labs and drug screen can be conducted/collected on admission within 24 hours prior to dosing.
b. Weight will be measured after 8 hours of fasting, with shoes and jacket off.
c. In all treatment periods, all ECGs will be obtained in triplicate and the mean of QTcF will be calculated. There should be ~1-2 minute intervals between ECG measurements. Predose ECGs will be obtained in triplicate at least 1-2 minutes apart within 3 hours prior to dosing of trial drug..
d. All semi-recumbent HR and BP measurements will be done in triplicate at least a 1-2 minutes interval between measurements. Predose measurements can be performed within 3 hours prior to dosing. Subjects should be resting in the semi-recumbent position for at least 10 minutes prior to obtaining HR and BP. At pre-specified time points, following measurements of the semi-recumbent HR and BP, subjects assume a standing position for approximately 2 minutes and then orthostatic HR and BP will be obtained.
   Refer to Appendix 12.8, which provides guidance on hemodynamic monitoring and stopping criteria should a subject have an increase in HR or BP.
e. RR taken predose will be done in triplicate with at least a 1-2 minute interval between measurements and within 3 hours prior to dosing. For all other timepoints, a single measurement will be obtained.
f. Standardized meals will be provided at ~ 3 hours (lunch) and ~10 hours (dinner) post dose. A snack will be offered at ~ 7 and ~13 hours post dose. After the 24 h post dose procedures have completed, subsequent meal and snacks will be unrestricted in terms of caloric content, composition, and timing.
g. MK-7252 or placebo will be administered fasted unless otherwise specified in the protocol
h. Safety laboratory samples will be collected after at least an 8-hour fast.
i. This sample should be drawn once only after randomization for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.
j. Leftover main study plasma will be stored for future biomedical research.
k. Urine for Urinary MK-7252 Assay will be collected only in Period 2 and Period 4 at pre-dose and at the following intervals post-dose: 0-4, 4-8, 8-12, and 12-24 hrs.
l. [ccf] [redacted]
m. Post-trial visit should occur approximately 14 days postdose. If the visit occurs prior to 14 days postdose, a phone call should be made to follow up on potential AEs.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial or Future Biomedical Research. If there are changes to the subject's status during the trial (e.g., health or age of majority requirements), the investigator or qualified designee must ensure the appropriate consent is in place.

7.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/IEC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent to the subject, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the Future Biomedical Research sub-trial. A copy of the informed consent will be given to the subject.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.3 Subject Identification Card

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card immediately after the subject provides written informed consent. At the time of treatment allocation/randomization, site personnel will add the treatment/randomization number to the Subject Identification Card.

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee.

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within14 days (or 5 half-lives) before first dose of trial medication.

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial.

7.1.1.6 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to randomization or treatment allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 7.1.5.1.

7.1.1.7 Assignment of Treatment/Randomization Number

All eligible subjects will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the subject for all procedures occurring after randomization. Once a treatment/randomization number is assigned to a subject, it can never be re-assigned to another subject.

A single subject cannot be assigned more than 1 treatment/randomization number.

7.1.1.8 Trial Compliance (Medication)

Administration of trial medication will be witnessed by the investigator and/or trial staff. The date and time of administration as well as volume will also be recorded. Please refer to the Method of Preparation Document regarding study drug preparation and administration.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Physical Examination

The physical exam assessments will be defined and conducted per the site SOP.

7.1.2.2 Targeted Neurological Examination

Please refer to the Appendix section 12.7 for details about the targeted neurological examination. When applicable, targeted neurological examination assessments should be performed after all other pre-specified 4hr and 24hr procedures at the same time point (including vital sign measurements).

7.1.2.3 Body Weight and Height

Body height and weight will be obtained with the subjects shoes off, jacket or coat removed.

7.1.2.4 Body Mass Index (BMI)

Body mass index equals a person's weight in kilograms divided by height in meters squared. (BMI=kg/m^2). Body weight and height will be obtained with the subjects shoes off, jacket or coat removed.

7.1.2.5 12-Lead ECG

Special care must be taken for proper lead placement by qualified personnel. Skin should be clean and dry prior to lead placement. Subjects may need to be shaved to ensure proper lead placement. Female subjects may need to remove their bra.

Lead placement should be rechecked in cases where unexpected ECG findings are noted.

Subjects should be resting in the semi-recumbent position for at least 10 minutes prior to each ECG measurement. Subject position during safety ECG collection should be consistent throughout the study.

The correction formula to be used for QTc is Fridericia.

If repeat ECGs are required the clinical site will decide whether to leave the electrodes in place or mark the position of the electrodes for subsequent ECGs. To mark the position of the electrodes, 12-lead electrode sites will be marked on the skin of each subject with an ECG skin marker pen to ensure reproducible electrode placement.

In all treatment periods, all ECGs will be obtained in triplicate and the mean of QTcF will be calculated. There should be ~1-2 minute intervals between ECG measurements. Predose ECGs will be obtained in triplicate at least 1-2 minutes apart within 3 hours prior to dosing of trial drug. The mean of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed). The investigator may perform additional ECGs for safety at other times if deemed necessary.

During each treatment period, if a subject demonstrates an increase in mean QTcF interval ≥60 msec compared with mean predose baseline measurement, the ECG will be repeated twice within 5 minutes. The mean value of the QTcF interval from the 5 ECGs will represent the value at that time point. If the mean QTcF interval increase from baseline for any postdose time point is ≥60 msec, the subject will continue to be monitored by repeat safety 12-lead ECGs every 15 minutes for at least 1 hour or until the QTcF is within 60 msec of baseline. If prolongation of the QTcF interval ≥60 msec persists, a consultation with a study cardiologist may be appropriate and the Sponsor should be notified.

If the QTcF interval is ≥500 msec, the Sponsor should be notified and the safety ECGs should be reviewed by a cardiologist. The subject should be telemetry-monitored (until the QTcF is <500 msec) or should be considered for transfer to a location where closer monitoring and definitive care (e.g., a Cardiac or Intensive Care Unit) is available.

If the subject has unstable hemodynamics, or has any clinically significant dysrhythmias noted on telemetry, the subject should be immediately transferred to an acute care setting for definitive therapy.

If prolongation of the QTcF is noted, concomitant medications that prolong QTcF should be held until the QTcF is within 60 msec of baseline and the QTcF is <500 msec.

A study cardiologist should be arranged by the Principal Investigator to be available as needed to review safety ECG tracings with abnormalities.

7.1.2.6 Vital Sign Measurements (Heart Rate and Blood Pressure)

Subjects should be resting in a semi-recumbent position for at least 10 minutes prior to having vital sign measurements obtained. Semi-recumbent vital signs will include HR and BP. The correct size of the blood pressure cuff and the correct positioning on the subjects' arm is essential to increase the accuracy of BP measurements.

All HR and BP measurements are to be obtained using a validated, semi-automated oscillometric device supplied by the investigator. The same type of device (model) is to be used for all subjects throughout the study. Preferentially, the same machine is to be used on the same subject throughout the study. The oscillometric device model name and assigned number should be recorded in the source document for each subject. Additionally, the arm used to obtain the BP measurements should be recorded in the source documents. Ideally, the same arm will be used for these measurements for each subject throughout the study.

At all predose and postdose timepoints in each period, HR and BP triplicate measurements will be obtained at least ~1-2 minutes apart. The mean predose measurements in each period, taken 3 hours before dosing, will be used as the baseline for the purpose of safety monitoring by the site during the trial.

Orthostatic vital signs (HR and BP) will also be obtained. Subjects should be semi-recumbent for at least 10 minutes and then stand upright for 2 minutes prior to measurement of orthostatic vital signs.

Subjects will continue to rest semi-recumbent from dosing until 4 hours postdose except to stand for the measurement of orthostatic vital signs or other trial related procedure (if needed).

Refer to Appendix 12.8, which provides guidance on hemodynamic monitoring and stopping criteria should a subject have an increase in HR or BP.

7.1.2.7 Respiratory Rate Assessment

Respiratory rate will be counted as per site's SOP. Respiratory rate taken at screening and predose will be done in triplicate with at least 1 to 2 minute interval between measurements and predose measurements will be performed within 3 hours prior to dosing. Subject should be resting in a semi-recumbent position for at least 10 minutes prior to measurement. All other measurements will be single measurements.

7.1.2.8 Body Temperature

The same method must be used for all body temperature measurements for each individual subject and should be the same for all subjects.

7.1.2.9 Taste Assessment Questionnaire

A taste assessment questionnaire will be implemented in this trial to assist with the development of future formulations of MK-7252. A panel of subjects (anticipated to be Panel B) will be given this questionnaire immediately after dosing and at 10 minutes postdose in Period 5 or the highest dose period.

In order to prevent potential study unblinding, the questionnaire will be administered and reviewed by clinical staff members not involved with safety evaluations. Subjects will be asked to individually complete their questionnaires and not discuss/share their responses with one another. An example of the taste questionnaire is in Appendix section 12.6 and additional information is provided in the Study Operations Manual.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in Section 12.3.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry and urinalysis are specified in Table 7.

Table 7 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood (RBC, WBC)	Follicle Stimulating Hormone (FSH) in WONCBP*
Hemoglobin	Alkaline phosphatase	Glucose	Hepatitis B surface antigen
Platelet count	Alanine aminotransferase (ALT)	Protein	Hepatitis C antibodies
WBC: total and differentials including: Absolute Neutrophils Absolute Lymphocytes Absolute Monocytes Absolute Eosinophils Absolute Basophils	Aspartate aminotransferase (AST)	Specific gravity	HIV
RBC	Bicarbonate	Microscopic exam, if abnormal results are noted	Urine Drug Screen
	Calcium		
	Chloride		
	Creatinine		
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal		
	Total protein		
	Ureum		
*Only collected at prestudy			

Laboratory safety tests will be performed after at least an 8-hour fast. Predose laboratory procedures can be conducted up to 24 hours prior to dosing.

7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations

The decision as to which plasma and/or urine samples collected will be assayed for evaluation of PK/PD will be collaboratively determined by the Department of Quantitative Pharmacology and Pharmacometrics (QP2) and the appropriate department within Early-Stage Development, (e.g., samples at lower doses may not be assayed if samples at higher doses reveal undetectable drug concentrations). If indicated, these samples may also be assayed and/or pooled for assay in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

7.1.3.3 Blood Collection for Plasma MK-7252

Sample collection, storage and shipment instructions for plasma samples will be provided in the Study Operations Manual.

7.1.3.4 Urine Collection for Urinary MK-7252

Sample collection, storage and shipment instructions for urine samples will be provided in the Study Operations Manual.

[redacted]

7.1.3.6 Planned Genetic Analysis Sample Collection

Sample collection, storage and shipment instructions for Planned Genetic Analysis samples will be provided in the Study Operations Manual.

7.1.3.7 Future Biomedical Research Samples

The following specimens are to be obtained as part of Future Biomedical Research:

- DNA for future research
- Leftover main study plasma samples from MK-7252 stored for future research

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

The investigator or trial coordinator must notify the Sponsor when a subject has been discontinued/withdrawn from the trial and/or treatment. If a subject discontinues for any reason at any time during the course of the trial and/or treatment, the subject may be asked to return to the clinic (or be contacted) for a post-trial visit (approximately 14 days after the last dose of trial drug is given) to have the applicable procedures conducted. However, the investigator may decide to perform the post-trial procedures at the time of discontinuation or as soon as possible after discontinuation. If the post-trial visit occurs prior to 14 days after the last dose of trial drug is given, the investigator should perform a follow-up phone call 14 days after the last dose of trial drug to determine if any adverse events have occurred since the post-trial clinic visit. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events.

7.1.4.1.1 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the subject's consent for Future Biomedical Research will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the subject of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject’s personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

7.1.4.1.2 Lost to Follow-up

If a subject fails to return to the clinic for a required study visit and/or if the site is unable to contact the subject, the following procedures are to be performed:

- The site must attempt to contact the subject and reschedule the missed visit. If the subject is contacted, the subject should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the subject at each missed visit (e.g. phone calls and/or a certified letter to the subject's last known mailing address or locally equivalent methods). These contact attempts should be documented in the subject's medical record.
- Note: A subject is not considered lost to follow up until the last scheduled visit for the individual subject. The amount of missing data for the subject will be managed via the pre-specified statistical data handling and analysis guidelines.

7.1.4.2 Subject Blinding/Unblinding

Supplies will be provided with random code/disclosure envelopes or lists containing drug disclosure information. The Sponsor will provide one sealed envelope to the investigator for each treatment/randomization number and for each interval identifier (e.g., treatment period or visit).

Random code/disclosure envelopes or lists must be received by a designated person at the trial site and kept in a secured location to which only the investigator and delegate(s) have access. The random code/disclosure envelopes or lists should be opened only in the case of an emergency. Drug identification information is to be unblinded ONLY in the event that this is required for subject safety. Subjects whose treatment assignment has been unblinded by the investigator/delegate and/or non-study treating physician must be discontinued from study drug, but should continue to be monitored in the trial.

Treatment identification information is to be unmasked ONLY if necessary for the welfare of the subject. Every effort should be made not to unblind the subject unless necessary.

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date, reason and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Only the principal investigator or delegate and the respective subject's code should be unblinded. Other trial site personnel and Sponsor personnel directly associated with the conduct of the trial should not be unblinded.

At the end of the trial, random code/disclosure envelopes or lists and unblinding logs are to be returned to the Sponsor or designee.

7.1.4.3 Domiciling

Subjects will report to the clinical research unit (CRU) the evening prior to the scheduled day of trial drug administration in each treatment period remain in the unit until 24 hours postdose. At the discretion of the investigator, subjects may be requested to remain in the CRU longer.

7.1.4.4 Calibration of Critical Equipment

The investigator or qualified designee has the responsibility to ensure that any critical device or instrument used for a clinical evaluation/test during a clinical trial that provides important

information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the trial site.

Critical Equipment for this trial includes:

- Equipment for taking vital signs
- 12-Lead ECG
- Freezers used for PK and PD assay samples

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Screening

Approximately 4 weeks prior to treatment allocation/randomization, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1.

Subjects may be rescreened after consultation with the Sponsor. Rescreening should include all screening procedures listed in the protocol flow chart, including consent review. Rescreen procedures cannot be conducted the day prior to treatment allocation/randomization if there are Day -1 procedures planned per protocol.

7.1.5.2 Treatment Period Visit

In each treatment period, subjects will report to the CRU prior to the scheduled day of dosing or time as specified by the investigator. Subjects will fast from all food and drink, except for water, for at least 8 hours prior to trial drug administration. Subjects in the designated fed cohort (e.g. Period 5 of Panel C) will consume a standard high-fat meal (refer to Section 5.7) 30 minutes prior to trial drug administration. At all other visits, subjects will report to the CRU the evening prior to or the morning of the scheduled procedure. Subjects are not required to have fasted prior to the scheduled visits following 24 hours postdose.

7.1.5.3 Critical Procedures Based on Trial Objectives: Timing of Procedure

For this trial, the blood sample for MK-7252 is the critical procedure.

At any postdose timepoint, the blood sample for MK-7252 needs to be collected as close to the exact timepoint as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible. Trial procedures can be performed prior or after the prescribed/scheduled time.

The order of priority can be changed during the trial with joint agreement of the investigator and the Sponsor Clinical Director.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

The following variance in procedure collection times will be permitted.

- PK Collection as outlined in Table 8 and Table 9 below.

Table 8 PK (Blood) Collection Windows (QD Dosing)

PK/PD collection	**PK /PD Collection Window**
0 to <1 hr	5 min
1 to <24 hr	15 min
24 to <48 hr	60 min
≥48 hr	2 hr

Table 9 PK (Blood) Collection Windows (BID Dosing)

PK/PD collection	**PK /PD Collection Window**
0 to <5 hr	5 min
5 to <24 hr	15 min
24 to <48 hr	60 min
≥48 hr	2 hr

- Urine PK Collection as outlined in Table 10 below.

Table 10 PK (Urine) Collection Windows

Urine PK collection	**Urine PK Collection Window**
0 to <24 hr	15 min
≥24 hr	60 min

- Predose standard safety evaluations:
  - Vital signs (including weight) and ECG 3 hrs. prior to dosing;
  - Laboratory safety tests (including drug screen) and physical and targeted neurological exam 24 hrs. prior to dosing.
- Postdose standard safety evaluations (vital signs including weight, ECG, blood laboratory safety tests, physical exam, targeted neurological exam) as outlined in Table 11 below.
- Postdose urine laboratory safety tests: 3 hrs.

Table 11 Scheduled Time Collection Windows

Scheduled Time	Collection Window
0 to <1 hr	15 min
1 to <24 hr	30 min
24 to <48 hr	60 min
≥48 hr	2 hrs

7.1.5.4 Trial Design/Dosing/Procedures Modifications Permitted within Protocol Parameters

This is a Phase I assessment of MK-7252 in humans, and the PK, PD and safety profiles of the compound is still being elucidated. This protocol is written with some flexibility to accommodate the inherent dynamic nature of Phase I clinical trials. Modifications to the dose, dosing regimen and/or clinical or laboratory procedures currently outlined below may be required to achieve the scientific goals of the trial objectives and/or to ensure appropriate safety monitoring of the trial subjects.

As such, some alterations from the currently outlined dose and/or dosing regimen may be permitted based on newly available data, but the maximum daily dose may not exceed those currently outlined in the protocol.

- Repeat of or decrease in the dose of the trial drug administered in any given period/panel
- Interchange of doses between panels
- Entire period(s) or panel(s) may be omitted
- Adjustment of the dosing interval (e.g., divided doses [BID to QD, QD to BID, TID or vice versa])

- Lengthening of the wash-out period between doses
- Remove a planned pharmacokinetic pause if agreed by Sponsor and investigator if no further increases in total daily dose
- Addition of pharmacokinetic pause
- Instructions to take trial drug with or without food or drink may also be modified based on newly available data
- Modification of the fed period to dosing in the fasted state or elimination of the fed period.
- Taste assessment questionnaire may be administered in an earlier treatment period in the event that the highest planned dose level is not reached (e.g. due to safety signals etc.)
- Modification of the PK/PD sample processing and shipping details based on newly available data
- Modification of urine sample collection to another panel or period.
- [redacted]

The pharmacokinetic/pharmacodynamic sampling scheme currently outlined in the protocol may be modified during the trial based on newly available pharmacokinetic or pharmacodynamic data (e.g., to obtain data closer to the time of peak plasma concentrations). If indicated, these collected samples may also be assayed in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

Up to additional 50 mL (NOTE: Never more than 50 mL) of blood may be drawn for safety, pharmacokinetic, and/or pharmacodynamic analyses. The total blood volume withdrawn from any single subject will not exceed the maximum allowable volume during his/her participation in the entire trial (Appendix section 12.3).

The timing of procedures for assessment of safety procedures (e.g., vital signs, ECG, safety laboratory tests, etc.) currently outlined in the protocol may be modified during the trial based on newly available safety, tolerability, pharmacokinetic or pharmacodynamic data (e.g., to obtain data closer to the time of peak plasma concentrations). Additional laboratory safety tests may be added to blood samples previously drawn to obtain additional safety information (e.g., adding creatinine kinase to serum chemistry panel that was already drawn. These changes will not increase the number of trial procedures for a given subject during his/her participation in the entire trial.

It is understood that the current trial may employ some or none of the alterations described above. Any alteration made to this protocol to meet the trial objectives must be detailed by the Sponsor in a letter to the Trial File and forwarded to the investigator for retention. The letter may be forwarded to the IRB/IEC at the discretion of the investigator.

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

Adverse events may occur during clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

For randomized subjects only, all adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by investigator if they are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of treatment allocation/randomization through 14 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Electronic reporting procedures can be found in the Electronic Data Capture (EDC) data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

The subject has taken (accidentally or intentionally) any drug administered as part of the protocol and exceeding the dose as prescribed by the protocol. It is up to the investigator or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the Sponsor.

If an adverse event(s) is associated with ("results from") the overdose of Sponsor's product or vaccine, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Sponsor's product or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations that occur from the time of treatment allocation/randomization through 14 days following cessation of Sponsor's product must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event.

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

- Is a cancer;
- Is associated with an overdose.

Refer to Table 12 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 14 days following cessation of treatment, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

All subjects with serious adverse events must be followed up for outcome.

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 14 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

   *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that must trigger an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

   It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline phosphatase that do not meet the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study investigators and the Sponsor Clinical Director. However, abnormalities of liver blood tests that do not meet the criteria noted above are not ECIs for this trial.

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in Table 12. The investigator's assessment of causality is required for each adverse event. Refer to Table 12 for instructions in evaluating adverse events.

Table 12 Evaluating Adverse Events

Maximum Intensity	**Mild**	awareness of sign or symptom, but easily tolerated (for pediatric trials, awareness of symptom, but easily tolerated)
	Moderate	discomfort enough to cause interference with usual activity (for pediatric trials, definitely acting like something is wrong)
	Severe	incapacitating with inability to work or do usual activity (for pediatric trials, extremely distressed or unable to do usual activities)
Seriousness	A serious adverse event (AE) is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred [Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.]; or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect (**in offspring of subject taking the product regardless of time to diagnosis); or	
	Is a cancer (although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or**	
	Is associated with an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Sponsor's product to be discontinued?	

Relationship to Sponsor's Product	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event:	
	Exposure	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors
	Dechallenge	Was the Sponsor's product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Sponsor's product in this trial? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time.) NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		

Record one of the following:	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).**
Yes, there is a reasonable possibility of Sponsor's product relationship.	There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.
No, there is not a reasonable possibility of Sponsor's product relationship	Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a subject with overdose without an associated AE.)

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this trial. Full detail is in the Statistical Analysis Plan (SAP) (Section 8.2).

8.1.1 Statistical Methods

Safety

Summary statistics and plots will be generated for raw laboratory safety tests, ECGs, and vital signs as well as for change from baseline, as deemed clinically appropriate. Depending on the safety parameter, the difference from baseline will either be computed on the original scale (raw change from baseline) or on the log scale and back-transformed for reporting (percent change from baseline).

Pharmacokinetics

Model-based PK summary: Separately for each PK parameter, individual values of [AUC0-∞, AUC0-24hr, AUC0-12hr, AUClast, Cmax , C12hr and C24hr postdose, Tmax and t½] at each fasted and fed dose level will be natural log-transformed and evaluated with a linear mixed effects model containing a fixed effect for treatment and a random effect for subject. Kenward and Roger's method will be used to calculate the denominator degrees of freedom for the fixed effects. Ninety-five percent confidence intervals for the least squares means for each treatment will be constructed on the natural log scale and will reference a t-distribution. Exponentiating the least-squares means and lower and upper limits of these confidence intervals will yield estimates for the population geometric means and confidence intervals about the geometric means on the original scale.

Food effect: The effect of food on MK-7252 will be estimated by obtaining the geometric mean ratio (fed/fasted) and 90% confidence interval for [AUC0-∞, AUC0-12hr and Cmax] at the dose level administered in both the fasted and fed state, using the previously-defined model.

Target PK level: The secondary hypothesis that the geometric mean C12hr of MK-7252 exceeds 100 nM at 1 or more well-tolerated fasted doses will be tested using the previously-defined linear mixed effects model and the following stepwise procedure. At the highest safe and well-tolerated fasted dose, a 2-sided 90% confidence interval for the geometric mean of C12hr will be constructed. The hypothesis will be supported (i.e., the true geometric mean C12hr exceeds 100 nM at this dose level) if the lower limit of this 90% confidence interval (equivalent to the lower limit of a one-sided 95% confidence interval) is greater than 100 nM.

If the hypothesis is supported in the previous step, then the same procedure will be applied to the next lowest safe and well-tolerated fasted dose. The procedure continues in this stepwise fashion until the lower limit of the 90% confidence interval at a particular dose fails to exceed 100 nM (i.e. the true geometric mean C12hr fails to exceed 100 nM at this, and all lower doses). For estimation purposes, 90% confidence intervals will also be constructed for all doses at which the true geometric mean C12hr fails to exceed 100 nM.

8.1.2 Power

Pharmacokinetics: Since this will be the first administration of MK-7252 to humans, no variability estimates for PK are available from which to estimate power or precision.

A sample size of 6 subjects on active dose and 2 on placebo per panel per treatment period is considered to be adequate to address the primary objectives of the study.

8.2 Responsibility for Analyses/In-House Blinding

The statistical analysis of the data obtained from this study will be conducted by, or under the direct auspices of the Early Clinical Development Statistics Department in collaboration with the Quantitative Pharmacology and Pharmacometrics Department and Translational Pharmacology Department of the Sponsor.

If, after the study has begun, changes are made to the statistical analysis plan stated below, then these deviations to the plan will be listed, along with an explanation as to why they occurred, in the Clinical Study Report.

8.3 Objective(s) & Hypotheses/Estimation

Primary

1. **Objective:** To evaluate the safety and tolerability of single ascending dose administration of MK-7252 in healthy men and women of non-childbearing potential (WONCBP).

Secondary

1. **Objective:** To obtain preliminary plasma pharmacokinetic data including area under the curve (AUC0-∞, AUC0-24hr, AUC0-12hr, AUClast), maximal concentration (Cmax), C12hr and C24hr postdose, time to reach maximal concentration (Tmax), and apparent terminal half-life (t½) following oral administration of single doses of MK-7252.

   Hypothesis: The geometric mean Ctrough at 12 hr postdose (C12hr) meets or exceeds 100 nM after single dose administration of MK-7252 at a dose that is sufficiently well tolerated to continue development for the treatment of cancer.

2. **Objective:** To evaluate the hemodynamic changes of MK-7252 given as single doses on peripheral BP (systolic and diastolic) and heart rate in healthy men and WONCBP.

3. **Objective (Panel C only)**: To compare the effects of a high-fat breakfast on the plasma pharmacokinetics of MK-7252 to those in the fasted state after administration of a single oral dose of MK-7252 in in healthy males and WONCBP.

   Estimation: The plasma AUC0-∞, AUC0-12hr and Cmax resulting from a single oral dose of MK-7252 following a standard breakfast will be estimated and compared to that observed with the identical dose level administered in the fasted state.

Exploratory

1. [redacted]

2. **Objective:** To explore urinary excretion of MK-7252 following single dose administration in in healthy men and WONCBP.

3. **Objective**: To explore the relationship between genetic variation and response to the treatment administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in this study.

8.4 Analysis Endpoints

Primary Endpoints

Safety: Primary safety endpoints will include all types of adverse experiences, in addition to laboratory safety tests, ECGs, and vital signs. [For changes from baseline analyses, baseline is defined as Day 1 Predose]

Secondary Endpoints (Pharmacokinetic)

1. Pharmacokinetics: The pharmacokinetic variables of interest for MK-7252 are AUC0-∞, AUC0-24hr, AUC0-12hr, AUClast, Cmax, Ctrough (12 hrs. and 24 hrs. postdose), Tmax and $t_{1/2}$.

2. Peripheral BP (systolic and diastolic)

Exploratory Endpoints:

1. [redacted]

2. Urine excretion of MK-7252 is of secondary interest.

8.5 Analysis Populations

The following populations are defined for the analysis and reporting of data. All subjects will be reported, and their data analyzed, according to the treatment(s) they actually received.

All Subjects as Treated (AST): The All Subjects as Treated Population consists of all subjects who received at least one dose of treatment. This population will be used for assessments of safety and tolerability.

Per-Protocol (PP): The Per-Protocol Population consists of the set of data generated by the subset of subjects who comply with the protocol sufficiently to ensure that these data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of major protocol deviations. Major protocol deviations will be identified to the extent possible prior to unblinding by individuals responsible for data collection/compliance, and its analysis and interpretation. Any subjects or data values excluded from analysis will be identified, along with their reason for exclusion, in the CSR. At the end of the study, all subjects who are compliant with the study procedure as aforementioned and have available data from at least one treatment will be included in the Per-Protocol dataset. This population will be used for the PK and PD analyses.

8.6 Statistical Methods

Safety

Summary statistics and plots will be generated for raw laboratory safety tests, ECGs, and/or vital signs as well as for change from baseline, as deemed clinically appropriate. Depending on the safety parameter, the difference from baseline will either be computed on the original scale (raw change from baseline) or on the log scale and back-transformed for reporting (percent change from baseline).

Pharmacokinetics

Model-Based PK Summary

Separately for each PK parameter, individual values of [AUC0-∞, AUC0-24hr, AUC0-12hr, AUClast, Cmax, Ctrough (12 hrs. and 24 hrs. postdose), Tmax and t½] at each fasted and fed dose level will be natural log-transformed and evaluated with a linear mixed effects model containing a fixed effect for treatment and a random effect for subject. Kenward and Roger's method will be used to calculate the denominator degrees of freedom for the fixed effects. Ninety-five percent confidence intervals for the least squares means for each treatment will be constructed on the natural log scale and will reference the t-distribution. Exponentiating the least-squares means and lower and upper limits of these confidence intervals will yield estimates for the population geometric means and confidence intervals about the geometric means on the original scale.

If BID dosing is implemented in Panel C, a slightly different model than described above for selected PK parameters may be utilized.

Food Effect

The effect of food on MK-7252 will be estimated by obtaining the geometric mean ratio (fed/fasted) and 90% confidence interval for [AUC0-∞, AUC0-12hr and Cmax] at the dose level administered in both the fasted and fed state, using the previously-described linear mixed effects model.

Target PK Level

The secondary hypothesis that the geometric mean Ctrough at 12 hr. postdose (C12hr) of MK-7252 exceeds 100 nM at one or more well-tolerated fasted doses will be tested using the previously-described linear mixed effects model and the following stepwise procedure. At the highest safe and well-tolerated fasted dose, a 2-sided 90% confidence interval for the geometric mean of C12hr will be constructed. The hypothesis will be supported (i.e., the true geometric mean C12hr exceeds 100 nM at this dose level) if the lower limit of this 90% confidence interval (equivalent to the lower bound of a one-sided 95% confidence interval) is greater than 100 nM. If the hypothesis is supported in the previous step, then the same procedure will be applied to the next lowest safe and well-tolerated fasted dose. The procedure continues in this stepwise fashion until the lower limit of the 90% confidence interval at a particular dose fails to exceed 100 nM (i.e. the true geometric mean C12hr fails to exceed 100 nM at this, and all lower doses). For estimation purposes, 90% confidence intervals will also be constructed for all doses at which the true geometric mean C12hr fails to exceed 100 nM.

Dose Proportionality

An exploratory analysis will be conducted to preliminarily assess dose proportionality of MK-7252 [AUC0-∞, Cmax, Ctrough (12 hrs. and 24 hrs. postdose)] in the fasted state. Separately for each PK parameter, the potential effects of panel will be first explored using a linear mixed effect model with ln(dose), panel, and ln(dose) by panel interaction as fixed effects and subject within panel as a random effect. If the ln(dose) by panel interaction is found to be statistically significant at the 0.05 significance level, the slope will be estimated separately for each panel, and a plot containing observed PK data vs. dose and an estimated regression line on the raw scale will be provided separately for each panel, together with a 95% Schéffe confidence band for the regression line. If the interaction term is not statistically significant, then it will be dropped from the above full model, and the main panel effect will be tested for statistical significance at the 0.05 level. If the panel effect is statistically significant, then the final model will include ln(dose) as a covariate, panel as a fixed effect and subject within panel as a random effect; otherwise, the final model will include ln(dose) as a covariate and subject within panel as a random effect. In both cases, an overall slope will be estimated across both panels. In the former case, a plot containing observed PK data vs. dose and an estimated regression line on the raw scale will be provided separately for each panel, together with a 95% Schéffe confidence band for the regression line. In the latter case, a plot of the observed PK data versus dose will be provided along with an overall estimated regression line on the raw scale and a 95% Schéffe confidence band.

Descriptive Statistics

Individual values will be listed for each PK parameter by treatment, and the following (non-model-based) descriptive statistics will be provided: N (number of subjects with non-missing data), arithmetic mean, standard deviation, arithmetic percent CV (calculated as 100 x standard deviation/arithmetic mean), median, minimum, maximum, geometric mean, and geometric percent CV (calculated as 100 x sqrt(exp(s^2) - 1), where s^2 is the observed variance on the natural log-scale).

Pharmacodynamics

[redacted]

PK-PD

The relationship between plasma concentrations [redacted] peripheral BP (systolic and diastolic) and HR will be explored graphically. Upon visual inspection, additional model-based analysis may be employed to further explore the PK/PD relationship.

QTc Analysis

If multiple QT measurements are taken at a single time point, then the average of the multiple measurements will be calculated prior to any further analysis. Fridericia's correction to QT (QTcF = QT^(RR1/3)) will be made in order to correct for HR. The appropriateness of the correction factor (i.e., 1/3) will be assessed via a linear mixed effects model with QTcF as the response variable and RR interval as a covariate and subject as a random effect, using data from the placebo treatment and the predose measurements of the active treatments. A slope estimate close to zero would indicate that Fridericia's correction provides an adequate correction to the original QT data; otherwise, an appropriate transformation on RR will be further explored.

The predose value in each treatment period will serve as baseline for calculating individual change from baseline at each time point in that period. Observed plasma concentrations and observed QTcF change from baseline will be used to investigate the relationship between QTcF and plasma MK-7252 concentrations (placebo data will also be used in this assessment, with the plasma concentration of MK-7252 set to 0). Scatter plots of QTcF change from baseline versus corresponding time-matched MK-7252 concentration will be provided.

The QTcF change from baseline will be further evaluated using a linear mixed effects model with fixed effects for treatment and time point and continuous effects for QTcF baseline and plasma concentration. A double compound symmetry covariance structure will be assumed. The highest 'safe' drug concentration (C_safe), defined as the highest drug concentration whose upper limit of 2-sided 90% confidence interval (equivalent to a 1-sided upper 95% confidence limit) of ΔΔQTcF (placebo- baseline- adjusted) less than 10 milliseconds (ms), will be reported. An estimate of the expected mean effect and 90% confidence interval of

ΔΔQTcF will also be computed at the observed geometric mean Cmax for each MK-7252 dose of interest.

The adequacy of the above models and covariance structure will be assessed, and other models (e.g., nonlinear, delayed effect, additional random effect on slope) may be explored if needed.

Additionally, a bootstrap based 2-sided 90% confidence interval for the ΔΔQTcF at the observed geometric mean Cmax for each MK-7252 dose of interest will be obtained using a bias corrected nonparametric bootstrap procedure with 3000 replicates and subject as unit of resampling. The geometric mean Cmax for each MK-7252 dose of interest will be determined for each replicate. The estimated ΔΔQTcF at the observed geometric mean Cmax will be determined from each of the replicates using the above linear mixed effects model. The bootstrap-based 2-sided 90% confidence interval at the observed geometric mean Cmax will be obtained as the 5% quartile and 95% quartile of the distribution of estimated ΔΔQTcF at the observed geometric mean Cmax from 3000 replicates.

General

For all analyses, data will be examined for departures from the assumptions of the statistical model(s) as appropriate; e.g., heteroscedasticity, non-normality of the error terms. Distribution-free methods may be used if a serious departure from the assumptions of the models(s) is observed, or suitable data transformations may be applied.

8.7 Multiplicity

No multiplicity adjustment is needed given the estimation purpose of this trial.

8.8 Sample Size and Power Calculations

Pharmacokinetics: Since this will be the first administration of MK-7252 to humans, no variability estimates for PK are available from which to estimate power or precision.

A sample size of 6 subjects on active dose and 2 on placebo per panel in each treatment period is considered to be adequate to address the primary objectives of the study.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by the Sponsor as summarized in Table 13. The on-site formulation of MK-7252 and an identically appearing placebo will be prepared and packaged at the clinical study site.

Clinical supplies will be packaged to support enrollment and replacement subjects as required. When a replacement subject is required, the Sponsor or designee needs to be contacted prior to dosing the replacement supplies.

Table 13 Product Descriptions

Product Name & Potency	Dosage Form
MK-7252 (1 mg/mL)	Powder for oral suspension (1 mg/mL)
MK-7252 (20 mg/mL)	Powder for oral suspension (20 mg/mL)

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

Subjects will receive doses of MK-7252 provided in syringes covered with blinding label, dispensed by an unblinded pharmacist from clinical supplies. No kitting is required. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

9.3 Clinical Supplies Disclosure

This trial is blinded but supplies are provided open label; therefore, an unblinded pharmacist or qualified trial site personnel will be used to blind supplies. Treatment identity (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are provided.

Supplies will be provided with random code/disclosure envelopes or lists containing drug disclosure information. The Sponsor will provide one sealed envelope to the investigator for each treatment/randomization number per treatment period.

See Section 7.1.4.2, Blinding/Unblinding, for a description of the method of unblinding a subject during the trial, should such action be warranted.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Discard/Destruction/Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. name, address, telephone number and e-mail address;

2. hospital or clinic address and telephone number;

3. curriculum vitae or other summary of qualifications and credentials; and

4. other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

10.1.4 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this trial. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and

all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in Section 12.1 - Merck Code of Conduct for Clinical Trials.

The investigator also agrees to allow monitoring, audits, IRB/IEC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the trial reimbursed to the investigator by the Sponsor.

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The Sponsor also recognizes that documents may need to be retained for

a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [Clinical Study Report (CSR) CI]. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the Protocol/CSR CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this trial or its results to those registries.

10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

10.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. Merck will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will

allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

For multicenter trials, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single trial site data prior to the main paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

11.0 LIST OF REFERENCES

[1] Smyth MJ, Ngiow SF, Ribas A, Teng MW. Combination cancer immunotherapies tailored to the tumour microenvironment. Nat Rev Clin Oncol. 2016 Mar;13(3):143-58.

[2] Bours MJ, Swennen EL, Di Virgilio F, Cronstein BN, Dagnelie PC. Adenosine 5'-triphosphate and adenosine as endogenous signaling molecules in immunity and inflammation. Pharmacol Ther. 2006 Nov;112(2):358-404.

[3] Hatfield SM, Sitkovsky M. A2A adenosine receptor antagonists to weaken the hypoxia-HIF-1α driven immunosuppression and improve immunotherapies of cancer. Curr Opin Pharmacol. 2016 Aug;29:90-6.

[4] Linnemann C, Schildberg FA, Schurich A, Diehl L, Hegenbarth SI, Endl E, et al. Adenosine regulates CD8 T-cell priming by inhibition of membrane-proximal T-cell receptor signalling. Immunology. 2009 Sep;128(1 Suppl):e728-37.

[5] Leone RD, Lo YC, Powell JD. A2aR antagonists: Next generation checkpoint blockade for cancer immunotherapy. Comput Struct Biotechnol J. 2015 Apr 8;13:265-72.

[6] Mittal D, Young A, Stannard K, Yong M, Teng MW, Allard B, et al. Antimetastatic effects of blocking PD-1 and the adenosine A2A receptor. Cancer Res. 2014 Jul 15;74(14):3652-8.

[7] Willingham S, Ho P, Leone R, Piccione E, Choy C, Hotson A, et al. The adenosine A2A receptor antagonist CPI-444 blocks adenosine-mediated T-cell suppression and exhibits antitumor activity alone and in combination with anti-PD-1 and anti-PD-L1. Poster session presented at: 107th Annual Meeting of the American Association for Cancer Research; 2016 Apr 16-20; New Orleans, LA.

[8] Hotson A, Willingham S, Ho P, Choy C, Laport G, McCaffery I, et al. CPI-444: a potent and selective inhibitor of adenosine 2A receptor (A2AR) induces anti-tumor responses alone and in combination with anti-PD-L1 [abstract]. Journal for ImmunoTherapy of Cancer. 2016 Nov; 04(1):120. Abstract no. P-212.

12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*

Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of subject safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials which are not under the control of Merck.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine subject preferences, etc.

The design (i.e., subject population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research subjects must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

Merck selects investigative sites based on medical expertise, access to appropriate subjects, adequacy of facilities and staff, previous performance in Merck trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. Merck funding of a trial will be acknowledged in publications.

III. Subject Protection

A. IRB/ERC review

All clinical trials will be reviewed and approved by an independent IRB/ERC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/ERC prior to implementation, except that changes required urgently to protect subject safety and well-being may be enacted in anticipation of IRB/ERC approval. For each site, the IRB/ERC and Merck will approve the subject informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that subject welfare is of primary importance. Potential subjects will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care. Subjects are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Subjects are enrolled only after providing informed consent for participation. Subjects may withdraw from a Merck trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

Merck is committed to safeguarding subject confidentiality, to the greatest extent possible. Unless required by law, only the investigator, Sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research subject by name.

D. Genomic Research

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck trials. Merck does not pay incentives to enroll subjects in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

Merck does not pay for subject referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible subjects.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local IRB/ERC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck trials will indicate Merck as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

Investigators will be expected to review Merck's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens consented and/or collected in this trial as outlined in Section 7.1.3.7 – Future Biomedical Research Samples will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways drugs/vaccines may interact with
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

All subjects enrolled in the clinical trial will be considered for enrollment in the Future Biomedical Research sub-trial.

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on the visit designated in the

trial flow chart. If delayed, present consent at next possible Subject Visit. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons.

A template of each trial site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of subject consent for Future Biomedical Research will be captured in the electronic Case Report Forms (eCRFs). Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

Collection of specimens for Future Biomedical Research will be performed as outlined in the trial flow chart. In general, if additional blood specimens are being collected for Future Biomedical Research, these will usually be obtained at a time when the subject is having blood drawn for other trial purposes.

4. Confidential Subject Information for Future Biomedical Research

In order to optimize the research that can be conducted with Future Biomedical Research specimens, it is critical to link subject' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical trial data to the specimen. The clinical data allow specific analyses to be conducted. Knowing subject characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for Future Biomedical Research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical trial site, unique codes will be placed on the Future Biomedical Research specimens. This code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between subject identifiers and this unique code will be held at the trial site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses utilizing the Future Biomedical Research specimens may be performed by the Sponsor, or an additional third party (e.g., a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in this sub-trial. Future Biomedical Research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and ask that their biospecimens not be used for Future Biomedical Research. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the subject's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for Future Biomedical Research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the subject of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject’s personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens

Future Biomedical Research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the trial site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular trial, the trial site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated trial administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Subjects

No information obtained from exploratory laboratory studies will be reported to the subject, family, or physicians. Principle reasons not to inform or return results to the subject include: Lack of relevance to subject health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and subjects. Subjects will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

Every effort will be made to recruit all subjects diagnosed and treated on Sponsor clinical trials for Future Biomedical Research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized. No additional risks to the subject have been identified as no additional specimens are being collected for Future Biomedical Research (i.e., only leftover samples are being retained).

The Sponsor has developed strict security, policies and procedures to address subject data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

13. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker
2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html
3. Industry Pharmacogenomics Working Group. Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
4. Industry Pharmacogenomics Working Group. Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

12.3 Approximate Blood Volumes Drawn/Collected by Trial Visit and by Sample Types

Panels A and B	Pre-trial	Treatment Periods	Post-trial	Total Collections	mL Per Collection	Total mL/ Test
Laboratory safety tests	2	2 x 5 Periods	1	13	7.5	97.5
FSH (if applicable)	1	0	0	1	3.5	3.5
HIV/Hepatitis Screen	1	0	0	1	3.5	3.5
Blood for Planned Genetic Analysis OR Blood (DNA) for Future Biomedical Research	1	0	0	1	8.5	8.5
[redacted]						
Blood for MK-7252	0	12 x 5 Periods	0	60	4.0	240.0
Total Maximum Blood Volume Per Female Subject†						453.0
Total Maximum Blood Volume Per Male Subject†						449.5

† If additional pharmacokinetic/pharmacodynamic and/or safety analysis is necessary, additional blood (up to 50 mL) may be obtained. Note: never to exceed 50 mL

Panel C	Pre-trial	Treatment Periods	Post-trial	Total Collections	mL Per Collection	Total mL/ Test
Laboratory safety tests	2	2 x 5 Periods	1	13	7.5	97.5
FSH (if applicable)	1	0	0	1	3.5	3.5
HIV/Hepatitis Screen	1	0	0	1	3.5	3.5
Blood for Planned Genetic Analysis OR Blood (DNA) for Future Biomedical Research	1	0	0	1	8.5	8.5
[redacted]						
Blood for MK-7252	0	14 x 5 Periods	0	70	4.0	280.0
Total Maximum Blood Volume Per Female Subject†						493.0
Total Maximum Blood Volume Per Male Subject†						489.5

† If additional pharmacokinetic/pharmacodynamic and/or safety analysis is necessary, additional blood (up to 50 mL) may be obtained. Note: never to exceed 50 mL

12.4 Algorithm for Assessing Out-of-Range Laboratory Values

For all laboratory values obtained at prestudy (screening) visit and/or predose evaluation:

A. If all protocol-specified laboratory values are normal, the subject may enter the study.

B. If a protocol specified laboratory value is outside of the parameter(s) outlined in the inclusion/exclusion criteria (including a repeat if performed), the subject will be excluded from the study.

C. If ≥1 protocol-specified laboratory value not specified in the inclusion/exclusion criteria is outside the normal range, the following choices are available:

   1. The subject may be excluded from the study;

   2. The subject may be included in the study if the abnormal value(s) is not clinically significant (NCS) (the investigator must annotate the laboratory value "NCS" on the laboratory safety test source document).

   3. The subject may be included in the study if the abnormality is consistent with a pre-existing medical condition which is not excluded per protocol (e.g., elevated eosinophil count in a subject with asthma or seasonal allergies) the medical condition should be annotated on the laboratory report or

   4. The abnormal test may be repeated (refer items a. and b. below for continuation of algorithm for repeated values).

      a. If the repeat test value is within the normal range, the subject may enter the study.

      b. If the repeat test value is still abnormal, the study investigator will evaluate the potential subject with a complete history and physical examination, looking especially for diseases that could result in the abnormal laboratory value in question. If such diseases can be ruled out, and if the abnormal laboratory value is not clinically relevant, then the subject may enter the study.

D. If there is any clinical uncertainty regarding the significance of an abnormal value, the subject will be excluded from the study.

12.5 12-Lead Electrocardiogram Abnormality Criteria

12-Lead Electrocardiogram Abnormality Criteria		
	Screen Failure Criteria	**Potentially Significant Post-Randomization Findings (clarification on action to take)**
RHYTHM		
Sinus Tachycardia	>110 beats per minute (bpm)	HR >110 bpm and HR increase of ≥ 25 bpm from baseline
Sinus Bradycardia	<40 bpm	HR <40 bpm and HR decrease of ≥5 bpm from baseline
Sinus Pause/Arrest	>2.0 seconds	>2.0 seconds
Atrial premature complex	>1 beat	≥3 beats
Ventricular premature complex	All	≥3 beats
Ectopic Atrial Rhythm	None	None
Junctional Rhythm	Junctional Rhythm with HR <40 bpm	Junctional Rhythm with HR <40 bpm
Idioventricular Rhythm	All	All
Atrial Fibrillation	All	All
Atrial Flutter	All	All
Supraventricular Tachycardia	All	All
Ventricular Tachycardia	All	All
AXIS		
Left Axis Deviation	RBBB with Left Anterior Hemiblock (LAHB)	New onset LAHB
Right Axis Deviation	RBBB with Left Posterior Hemiblock (LPHB)	New onset LPHB
CONDUCTION		
1st degree A-V Block	PR ≥230 ms	PR ≥230 ms + increase of >15 ms; or PR increase of >25%
2nd degree A-V Block	Mobitz Type II	Mobitz Type II
3rd degree A-V Block	All	All
LBBB	All	All
RBBB	RBBB with LAHB/LPHB as defined above	New onset RBBB (not including rate-related)

12-Lead Electrocardiogram Abnormality Criteria		
	Screen Failure Criteria	**Potentially Significant Post-Randomization Findings (clarification on action to take)**
Incomplete Right BBB (ICRBBB) (QRS<120 ms)	No exclusion	Nothing
Short PR/ Preexcitation syndrome	Delta wave + PR <120 ms	Delta wave + PR <120 ms
Other Intra-ventricular Conduction Delay	QRS ≥130 ms	QRS ≥ 130 ms + increase of ≥ 10 ms
QTc (B or F)		
Male	QTc ≥470 ms	QTc ≥500 ms or increase of ≥60 ms from baseline
Female	QTc ≥480 ms	QTc ≥500 ms or increase of ≥60 ms from baseline
HYPERTROPHY		
Atrial abnormalities	Definite evidence of P mitrale or P pulmonale	Definite evidence of P mitrale or P pulmonale
Ventricular abnormalities	Voltage criteria for LVH plus Strain Pattern	Voltage criteria for LVH plus Strain Pattern
MYOCARDIAL INFARCTION		
Acute or Recent	All	All
Old	All	All
ST/T MORPHOLOGY		
ST elevation suggestive of Myocardial Injury	In 2 or more contiguous leads	In 2 or more contiguous leads
ST depression suggestive of Myocardial Ischaemia	In 2 or more contiguous leads	In 2 or more contiguous leads
T-wave Inversions suggestive of Myocardial Ischaemia	In 2 or more contiguous leads	In 2 or more contiguous leads
Non-specific ST-T changes (In 2 or more leads)	No exclusion	In 2 or more contiguous leads
PACEMAKER	All	All
Baseline is defined as Predose Day 1 ms=milliseconds, mm=millimeter		

12.6 Sample Taste Questionnaire

Date (DD-MMM-YYYY): _____ **Time (24 hr. clock):** _____

Timepoint (circle one):

0 minutes postdose (immediately after dosing) 10 minutes postdose

Subject Evaluation

(The following questions are to be completed by the subject.)

Please answer each question by placing an X in the box of your choice.

1. Does the medication have any taste?

Yes	
No	

If No, please skip to question 10.

2. How do you like the taste of the medicine?

Like very much	
Like moderately	
Like slightly	
Neither like nor dislike	
Dislike slightly	
Dislike moderately	
Dislike very much	

3. Is the flavor of the medication sweet?

Yes	
No	

4. Is the flavor of the medication sour?

Yes	
No	

5. Is the flavor of the medication bitter?

Yes	
No	

6. Is the flavor of the medication salty?

Yes	
No	

7. Is the flavor of the medication metallic?

Yes	
No	

8. Is the flavor of the medication astringent (burning, irritating)?

Yes	
No	

9. How strong is the taste?

No taste	
Mild	
Moderate	
Strong	
Very strong	

10. If you feel numbness of your tongue/mouth, how severe is it?

No numbness	
Mild	
Moderate	
Severe	
Very severe	

11. If the study drug were to be prescribed by your doctor, how likely would you be to take the medication each day?

Very likely	
Somewhat Likely	
A little bit likely	
Not at all likely	

12.7 Targeted Neurological Examination

The Targeted Neurological Examination is intended to include evaluations which may best demonstrate potential neurological effects of MK-7252. It includes the following tests:

MODULE 1 – MENTAL STATUS EXAMINATION

A. General Level of Arousal (generally assess general level of alertness, attentiveness, and concentration throughout the interview. Regarding attentiveness, note evidence of impaired attention or concentration. For example difficulty remembering or following instructions or distractibility may be signs of inattention)

MODULE 2 – CRANIAL NERVE ASSESSMENT

B. II, III – Pupil Size and Reactivity

C. III, IV, VI – Extraocular Movements (range of motion, smooth pursuit, saccades, nystagmus

1. Observe for nystagmus during eye movements, increased nystagmus at the end of gaze or other oculomotor changes (mild nystagmus at extremes of gaze is normal). Note direction of nystagmus

MODULE 3 - MOTOR SYSTEM

B. MuscleStrength

1. Ask the subject to stand up from sitting position without using hands

***Grade*: NORMAL, IMPAIRED and describe abnormality**

MODULE 5 - COORDINATION AND GAIT

D. Gait

1. Ask the volunteer to walk heel-to-toe in a straight line (tandem gait).

***Grade*: NORMAL or IMPAIRED and describe abnormality**

MODULE 6 - SENSORY

A. Light touch sense: cotton wisp on skin of forearms and legs, bilaterally.

12.8 Criteria for Limiting Dose Escalation and /or Discontinuation of Dosing

Overall dose escalation will be limited by any of the following: (1) completion of scheduled dose escalation; or (2) agreement between the investigator and Sponsor of unacceptable safety/tolerability of the administered treatment; or (3) concern based on reasonable evidence that dose escalation will result in exposures exceeding those corresponding to the NOAEL of 20 mg/kg established in GLP toxicology study in the dogs.

Individual discontinuation criteria are established for safety purposes. If these are achieved at any point during dosing, no further dose escalation will occur for that individual.

Hemodynamic Stopping Criteria - *Individual Stopping Criteria*

During any of the treatment periods, if a particular subject demonstrates a ***sustained change*** (defined below) in any ***one*** of the following parameters, that subject will not participate in additional dose escalation. For assessing change from baseline, mean of triplicate postdose values at each timepoint will be compared to the Day 1 mean predose baseline established by 3 semi-recumbent measurements of heart rate and blood pressure obtained ~1-2 minutes apart within 3 hours prior to dosing as per protocol.

During any of the treatment periods if a particular subject demonstrates change in any *one* of the following parameters lasting ≥ 120 minutes, dose escalation in that subject will be halted and the subject may be withdrawn from the study or re-challenged at the same dose or at a lower dose or divided dose. Subjects that meet criteria listed below will be followed up until parameters no longer meet stopping rule criteria. Each subject will individually define his limit for continuation.

Heart Rate:

- Resting, semi-recumbent HR increase of >30 bpm above the mean predose baseline HR.
- Resting, semi-recumbent HR >120 bpm
- Orthostatic, HR >120 bpm, if associated with symptoms
- If an individual exceeds the HR limits as defined above, a 12-lead ECG will be performed to confirm sinus rhythm. If the subject is not in sinus rhythm or expert input is otherwise indicated, consultation with a cardiologist should occur.

Blood pressure:

- Resting, semi-recumbent SBP increase >30 mmHg relative to the mean predose baseline
- Resting, semi-recumbent SBP ≥160 mmHg
- Resting, semi-recumbent DBP ≥110 mmHg
- In the case of hemodynamic instability, activation of emergency medical services for cardiac monitoring and definitive care will be implemented.

Definitions for HR and BP

Subjects must be resting and semi-recumbent for *at least* 10 minutes prior to obtaining *any* measurements used to limit dose escalation (except for changes noted while obtaining orthostatic signs).

- ***Baseline HR and BP****:* These will be the mean of triplicate values, prior to dosing.

- ***Sustained changes*** are defined as semi-recumbent changes lasting greater than or equal to 120 minutes and orthostatic changes occurring at all measurements over a 12 hour period.

Guidance for Additional Hemodynamic Monitoring

If any of the resting, semi-recumbent parameters defined above are exceeded, that subject must remain resting and semi-recumbent for at least the next 120 minutes. During that time, semi-recumbent BP (systolic and diastolic) will be obtained every 60 minutes (i.e., at 60 and 120 minutes following). HR and BP will be measured with the BP device.

Following 120 minutes, if, in the opinion of the investigator, the subject requires further observation, the subject will remain resting and semi-recumbent until HR and/or BP return to baseline.

If any of the orthostatic parameters defined above are exceeded, that subject will continue to have orthostatic assessments according to the schedule of events. Orthostatic re-checks and additional semi-recumbent assessments can be done at the discretion of the investigator.

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in Section 7.0 – TRIAL PROCEDURES (Assessing and Recording Adverse Events). I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	