



NCT03712280

## **CLINICAL STUDY PROTOCOL**

**A Randomized, Open-Label, Phase 2a Comparator Study to Assess the Pharmacodynamics, Safety and Pharmacokinetics of Oral Administration of MNK6106 (L-Ornithine Phenylacetate) Versus Rifaximin in Subjects With Hepatic Cirrhosis and a History of Prior Episodes of Hepatic Encephalopathy**

**Regulatory Agency Identification Number: IND #115524**

**Protocol Number: MNK61062107**

**Date of Original Protocol: 15 October 2018**

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**Date of Protocol Amendment 2: 04 April 2019**

**Date of Protocol Amendment 3: 08 October 2019**

**Date of Protocol Amendment 4 Version 5.0: 21 April 2020**

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**SPONSOR SIGNATURE**

My signature, in conjunction with the signature of the investigator, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and applicable laws and other regulations including, but not limited to, the International Council for Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the US Code of Federal Regulations (CFR) (where applicable), all applicable national and local regulations, protections for privacy, and generally accepted ethical principles for human research such as the Declaration of Helsinki.

Nothing in this document is intended to limit the authority of a physician to provide emergency medical care.

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Sponsor Signature

*Refer to e-signature page*

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Date of Signature  
(DD Month YYYY)

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Sponsor Name (print)

**INVESTIGATOR SIGNATURE**

My signature confirms that the clinical study will be conducted in accordance with the protocol and applicable laws and other regulations including, but not limited to, the International Council for Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the US Code of Federal Regulations (CFR) (where appropriate), all applicable national and local regulations, protections for privacy, and generally accepted ethical principles such as the Declaration of Helsinki.

Nothing in this document is intended to limit the authority of a physician to provide emergency medical care.

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Investigator's Signature

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Date of Signature  
(DD Month YYYY)

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Investigator's Name and Title (print)

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## CHANGES TO THE PROTOCOL

### Protocol Amendment 4 – Summary of Changes:

The primary purpose of Amendment 4 is to add 14 days to the screening period to give subjects more time to complete screening assessments due to extenuating circumstances of the COVID-19 pandemic. The changes to the protocol are listed below.

1. Section 1.2 Study Schematic: the following changes have been made:
    - a. Change: The Screening Visit from “Day -14 to Day -1” to read: “Day -28 to Day -1.”
    - b. Add footnote “a” to the table heading for Final Visit (7 days post-dosing) (+ 3 day<sup>a</sup> window) that reads: “If circumstances occur such that this visit cannot occur within the specified window, the visit window may be extended to 14 days, after discussion with the Sponsor.”
  2. Section 1.3 Schedule of Study Events: Change: Screening from “Day -14 to Day -1” to read: “Day -28 to Day -1.”
  3. Section 4.1 Overall Design:
    - 2<sup>nd</sup> paragraph, 2<sup>nd</sup> sentence: Change: “Subjects may participate in the study for a total of up to approximately 3 to 4 weeks, including a screening period of up to 14 days” to read: “Subjects may participate in the study for a total of up to approximately 6 weeks, including a screening period of up to 28 days.”
    - Add 3<sup>rd</sup> paragraph: “The final visit window may be extended, due to extenuating circumstances, to 14 days after discussion with the Sponsor.”
  4. Section 5.2: Add exclusion criterion #19: “Has hyponatremia, defined as blood sodium level  $\leq 125$  mmol/L.” Subsequent exclusion criterion renumbered accordingly.
  5. Section 5.4 Screen Failures:
    - 2<sup>nd</sup> paragraph: Change: “The period from the start of screening related procedures at the Screening Visit to randomization must not exceed 14 days, inclusive of any repeat screening procedures.” to read: “The period from the start of screening related procedures at the Screening Visit to randomization must not exceed 28 days, inclusive of any repeat screening procedures.”
    - 4<sup>th</sup> paragraph: Change: “Subjects may be rescreened for a subsequent episode of acute HE, provided that the subject was not randomized.” to read: Subjects may be rescreened provided that the subject was not randomized.
  6. Section 8.1 Screening:
    - Heading: Change: “Screening (Day -14 to Day -1)” to read: Screening (Day -28 to Day -1)”
    - Third bullet: Change: “Record medical/surgical history” to read: Record medical/surgical history (including history of exposure to COVID-19).
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- Last paragraph: Change: "...screening (up to 14 days before Day 1)." to read: "...screening (up to 28 days before Day 1)."
7. Section **8.4 Final Visit (Week 2)**:
- 2<sup>nd</sup> paragraph: Add: "The final visit window may be extended, due to extenuating circumstances, to 14 days after discussion with the Sponsor."
  - Add: Section **8.9 Provisions for Remote Assessment Methods**  
"For emergency situations where there are extenuating circumstances that prohibit physically coming to the clinical site or when the safety of subjects may be compromised by physical visits to the site, remote assessments may be considered after discussion with the Sponsor."

Other minor edits to text (including updating page headers/footers with current protocol template) were made to the document that did not affect study conduct.

### **Protocol Amendment 3 – Summary of Changes:**

The 3<sup>rd</sup> amendment was implemented to make minor changes to the inclusion/exclusion criteria and prohibited medications to clarify criteria for and required documentation defining HE to facilitate enrollment in the study based on investigator observations/input during the trial.

1. **Table 1** (Schedule of Study Events):
    - Clarification that C-P and MELD scores do not need to be repeated at the time of confinement (Day -1) as they will be performed at screening (Days -14 to Day -1).
    - Clarification that urinalysis will be performed on Days 1 to 5 (not Days 1 to 6 as for chemistry and hematology laboratories). This change was also made to text in Section **8.3** (Treatment Period [Week 1; Day 1 to Day 5/ET] and Day 6 [Discharge]).
    - Urine pregnancy test added to Day -1 (first day of confinement) for women of child-bearing potential. Text has also been added to Section **8.1** (Screening [Day -14 to Day -1]), Section **8.6.6**, and Section **10.2** (Clinical Laboratory Tests).
  2. Section **3.3** added: Outcome measures are identified to facilitate clinical trial registration and patient access to basic results disclosed on public clinical trial registries.
    - Primary: Number of participants with a change in ammonia at Day 5.
    - Secondary: Number of participants with adverse events or deaths during the study.
  3. Section **5.1** Inclusion Criteria:
    - Inclusion criterion **#4** was changed from "A history of at least 2 or more documented episodes of HE within the last 12 months, with 1 episode within the last 6 months." To read: "A history of at least 1 or more documented episodes of HE within the last 12 months."
    - Inclusion criterion **#5** was changed from "Hyperammonemia at screening." To read: "Hyperammonemia (defined as an ammonia level  $\geq 37$   $\mu\text{mol/L}$ ) at screening."
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4. Section 5.2 Exclusion Criteria: Exclusion criterion #16 (second bullet) was changed from “Platelet count no more than 50,000 cells/ $\mu$ L” to read “Platelet count no more than 25,000 cells/ $\mu$ L.”
  5. Section 6.5.1 Prohibited Concomitant Therapies (Second bullet) was changed from “Current use of drugs whose plasma concentration may be affected by MNK6106, such as alfentanil, cyclosporine, midazolam, quinidine, metformin, or cimetidine.” To Read: “Current use of drugs whose plasma concentration may be affected by MNK6106, such as alfentanil, cyclosporine, midazolam, quinidine, or cimetidine. Metformin use is permitted at low doses. Doses of metformin > 1,000 mg should be discussed with the medical monitor prior to enrollment.”
  6. Section 10.8 (Stages of Hepatic Encephalopathy According to HESA):
    - Replaced HESA sheet with HESA sheet approved for use in the study and added reference (Hassanein et al, 2008).
    - Added a sentence to describe the new HESA scale with respect to the severity as follows: “It consists of a 5-point scale (Grade 0 to 4), with 4 indicating most severe.”

Other minor issues (document conversion to Accenture StartingPoint Authoring Template, adding references, removing a web address, etc) were addressed; none affected study conduct.

### Protocol Amendment 2 – Summary of Changes

The second amendment to the protocol was implemented to clarify and ensure consistency of text throughout the protocol. Changes to the protocol are summarized below.

1. Section 1, Table 1 (Schedule of Study Events): added MELD score and HESA score limited physical examination to Day 6 (end of confinement); added complete physical examination on Day -1; included collection of concomitant medications/therapies at screening (Day -14 to -1) and on Day -1; removed hepatitis and HIV serology from Day -1 and added to screening; added weight to be assessed on Day 1; and, added footnote f next to “Laboratories: Urinary drug screen” defined below the table as “Methadone will be tested at screening only.” All subsequent footnote letters reordered accordingly.
2. Section 1, Table 1, footnote h, Section 8.1 (Screening Day -14 to Day-1), and Section 10.2 (Clinical Laboratory Tests): revised the statement regarding FSH testing as follows: removed “performed only at screening,” and added “required for postmenopausal women.”
3. Section 3.2 (Secondary Objectives/Endpoints: Removed secondary endpoint “Absolute change and percent change in C-P, MELD, Conn, and HESA scores.
4. Section 8.1 (Screening Day -14 to Day-1), added the following text to Urinary Drug Screen: “including a screen for methadone at screening only.”

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5. Section 4.2 (Study Design Rationale), changed text in the study design rationale from “...to correlate the plasma AMM reduction with dosing regimen administered...” to ‘...to characterize the PK/PD of MNK6106 in subjects.’”
  6. Section 5.2 (Exclusion Criteria), exclusion criterion #7 replaced “gastrointestinal hemorrhage” with “gastrointestinal bleeding.”
  7. Section 5.2 (Exclusion Criteria), exclusion criterion #8: replaced “estimated glomerular filtration rate” with “creatinine clearance calculated using the Cockcroft-Gault formula.”
  8. Section 5.2 (Exclusion Criteria), exclusion criterion #13, changed ‘psychiatric disorders’ to psychotic disorders “
  9. Section 10.2 (Clinical Laboratory Tests), added “FSH test (required for postmenopausal women).”
  10. Table 6 (C-P Classification for Severity of Liver Disease), removed incorrect table (former Table 10-4) and replaced with the correct table in former Section 10.8 (C-P Score).

Additional changes were made for formatting, spelling, punctuation, and clarification throughout protocol.

### **Protocol Amendment 1 – Summary of Changes**

The first amendment to the protocol was implemented to incorporate FDA requested changes and to correct oversight. Additional changes were made for clarification, to correct typos and certain hyperlinks, and for format errors. Detailed protocol changes are summarized below.

1. Included CTCAE (Common Terminology Criteria for AEs). Section 7.1, pg 36, Section 10.3.3, pg 58 and Section 10.7, pg 63 were revised.
2. Included INR as part of the laboratory assessments. Section 10.5, pg 61, Section 10.6.3, pg 62, Table 10.4, pg 63 and Section 10.8, pg 64 were revised.
3. Included the MELD score as part of the daily assessments. Section 8.1, pg 39, Section 8.3, pg 40 and Section 8.4, pg 41 were revised.
4. Included the MELD score as part of the exclusion criteria. Section 5.2, pg 28 was revised.
5. Included waist circumference at screening, Day 1 and last assessment in the clinic on Day 6. Table 1-1, pg 16 and Section 8.3, pg 39 were revised.
6. Added FSH testing for postmenopausal women. Table 1-1, pg 16 and Section 8.1, pg 39 were revised.
7. HESA score assessment was added at screening and every day during confinement. Table 1-1, pg 16, and Section 8.3, pg 40 were revised.
8. Child-Pugh and Conn score assessments were added at screening and every day. Table 1-1, pg 16, Section 8.1, pg 39, Section 8.3, pg 40 and Section 8.4, pg 41 were revised.

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9. Harmonized all liver and neurological assessments throughout the protocol. Former sections 8.5 and 9.4.1 were moved to Section 10.6.
  10. Eliminated the upper limit of ammonia levels in inclusion criterion #5. Section 5.1, pg 27, inclusion criterion #5 was revised.
  11. Removed remission of hepatic encephalopathy at enrollment (Conn score 0/1). Section 5.1, pg 27, former inclusion criterion #8 was deleted.
  12. Added an exclusion criterion for HESA Grade 4. Section 5.2, pg 28, was revised to add exclusion criterion #6.
  13. Clarify language of exclusion criterion words "therapy or". Section 5.2, pg 28, exclusion criterion #11 was revised.
  14. Added an exclusion criterion of "Has a history of prior cognitive impairment". Section 5.2, pg 28, exclusion criterion #12 was added.
  15. Added an exclusion criterion of: History of psychiatric disorders including but not limited to schizophrenia, dementia or other severe psychiatric disorders that would interfere with evaluation of HE. Section 5.2, pg 28, exclusion criterion #13 was added.
  16. Added an exclusion criterion of "Positive screening results for drugs and alcohol. (except for subjects positive to cannabinoids)". Section 5.2, pg 28, exclusion criterion #14 was added.
  17. Added text under Sedatives, "Any psychoactive agents including strong analgesics, antidepressants, and/or anxiolytics should be avoided such as but not limited to methadone." Section 6.5.1.1, pg 34, second paragraph, was revised
  18. Removed text in Meals and Fluids, "Water will be provided ad libitum except for 1 hour before and 2 hours after dosing". Section 6.5.3, pg 35 was revised to delete the sentence.
  19. Changed text in Meals and Fluids to remove "but." Section 6.5.3, pg 35, third paragraph was revised.
  20. Text for HESA Score was revised to add further explanation. Section 9.5, pg 49 was revised.
  21. Added prothrombin time/INR to clinical laboratories section. Section 10.2, pg 55 was revised.
  22. Added text to clarify CTCAE v5.0. Section 10.7, pg 63 was revised to add a link to current CTCAE information.
  23. Added a link under liver function clarification for the previous language for MELD and C-P scores. Links to Section 10.6 were added to Section 9.3.4 and Section 9.4, pg 49.
  24. Changed the methadone collection to screening only. Section 8.1, pg 38 was revised regarding urinary drug screen for methadone; Section 10.2, Urine Drug of Abuse and Alcohol Screen, pg 55 was revised to add methadone at screening.
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25. Added a new section for AEs of special interest. Section 10.3.5, pg 60 was added as a new section.
26. A new secondary endpoint was added: Absolute change and percent change in C-P, MELD, Conn and HESA scores. Section 1.1, Secondary Endpoints, pg 13 and Section 3.2, Secondary Objectives/Endpoints, pg 24 were revised.
27. Added “active control” to study design description. Section 1.1, Overall Design, pg 14 and Section 4.1, Overall Design, pg 24 were revised.
28. Changed Day 5 to Day 5/ET globally.
29. Clarified the rescreening text to read “Subjects may be rescreened for a subsequent episode of acute HE, provided that the subject was not randomized. All Screening Visit procedures must be repeated”. Section 5.4, Screen Failures, pg 30 was revised.
30. Deleted the PD population since it is included in the mITT population. Section 9.2, Populations for Analysis, pg 48 was revised.
31. Both pretreatment and treatment-emergent periods were added to safety summaries. Section 9.3.3, Safety Analyses, pg 49 was revised.
32. Analysis methods were added for C-P, MELD, Conn and HESA scores. A new section 9.3.4, pg 49 was created.
33. Analysis of treatment compliance was added. Section 9.5.1, pg 50 was revised.
34. Added amendment date to title page and revised the page headers to indicate incorporation of amendment #1.

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**LIST OF ABBREVIATIONS**

<b>Abbreviation</b>	<b>Term</b>
AE	Adverse event
AESI	Adverse event of special interest
AMM	Ammonia
CFR	Code of Federal Regulations
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
C-P	Child-Pugh
CTCAE	Common Terminology Criteria for AEs
ECG	Electrocardiogram
eCRF	Electronic case report form
ET	end of treatment
FDA	Food and Drug Administration (US)
FSH	follicle stimulating hormone
GCP	Good Clinical Practices
HCV	Hepatitis C virus
HE	Hepatic encephalopathy
HESA	Hepatic Encephalopathy Scaling Algorithm
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HRT	hormonal replacement therapy
ICF	Informed consent form
ICH	International Council for Harmonisation
ID	Identification
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IR	Immediate release
IRB	Institutional Review Board

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<b>Abbreviation</b>	<b>Term</b>
IV	Intravenous
mITT	Modified intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End Stage Liver Disease
MM	Medical monitor
MNK6105	L-Ornithine phenylacetate intravenous solution
MNK6106	L-Ornithine phenylacetate tablets
ORN	L-Ornithine
PAA	Phenylacetate
PAGN	Phenylacetylglutamine
PD	Pharmacodynamic
PK	Pharmacokinetic
PT	Prothrombin time
QTcF	QT interval corrected using Fridericia's formula
SAE	Serious adverse event
ULN	Upper limit of normal
US	United States

## 1. PROTOCOL SUMMARY

### 1.1. Synopsis

<b>Study Title:</b> A Randomized, Open-Label, Phase 2a Comparator Study to Assess the Pharmacodynamics, Safety and Pharmacokinetics of Oral Administration of MNK6106 (L-Ornithine Phenylacetate) Versus Rifaximin in Subjects With Hepatic Cirrhosis and a History of Prior Episodes of Hepatic Encephalopathy	
<b>Protocol Number:</b> MNK61062107	<b>Type:</b> Interventional/Phase 2a
<b>Condition/Disease:</b> Hepatic Cirrhosis and a History of Prior Episodes of Hepatic Encephalopathy	
<b>Approximate Number of Subjects:</b> 48	<b>Approximate Duration of Subject Participation:</b> 6 weeks
<p><b>Rationale:</b></p> <p>Current treatment strategies for the prevention of overt hepatic encephalopathy (HE) are limited to the correction or removal of precipitating factors, as well as the imperfect reduction of circulating ammonia (AMM) levels by dietary changes and/or pharmacological approaches. Pharmacological approaches include non-absorbed disaccharides (eg, lactulose) and antibiotics (eg, neomycin and rifaximin), which target AMM absorption and change the gut microbiome to non-urease-producing bacteria reducing intestinal AMM production, respectively. Lactulose is orally/rectally administered, does not directly target AMM metabolism, has limited efficacy in subjects with acute episodes of overt HE, is difficult to administer, and requires doses taken frequently throughout the day.</p> <p>Rifaximin is indicated for reduction in risk of overt HE recurrence in patients at least 18 years of age. In the trials of rifaximin for HE, 91% of the subjects were using lactulose concomitantly. Differences in the treatment effect of those subjects not using lactulose concomitantly could not be assessed.</p> <p>In the Phase 1/2a study OCR002-SP103, which was conducted with the oral formulation of MNK6106 (L-Ornithine phenylacetate tablets) although the percentage change in blood AMM concentrations was highly variable, MNK6106 dosing of 4 g and 7 g 3 times daily was seen to lower AMM concentrations or at least prevent increases in AMM concentrations following the discontinuation of lactulose.</p> <p>MNK6105 (Intravenous formulation of L-Ornithine phenylacetate) has been evaluated in 2 Phase 1 studies OCR002-HV201 (healthy subjects) and OCR002-HE201 (subjects with Child-Pugh Class A or B cirrhosis and in 2 investigator initiated Phase 2 studies OP-GIB (subjects with cirrhosis and active gastrointestinal bleeding) and OCR002-HE209 (subjects with cirrhosis and HE). In the recently completed OCR002-HE209 study with MNK6105 (10 g/day, 15 g/day, and 20 g/day IV for 5 days), data suggested better clinical improvement, plasma AMM-lowering/normalizing pharmacodynamics (PD) effects ratio and decrease in AMM concentrations in subjects receiving MNK6105 compared to placebo.</p>	
<b>Objectives and Endpoints:</b>	
<b>Primary Objective</b>	<b>Endpoint</b>
To evaluate the pharmacological activities through plasma AMM concentration as a PD marker following oral administration of MNK6106 with rifaximin as a comparator in subjects with hepatic cirrhosis and a history of prior episodes of HE.	Absolute and percentage change of plasma AMM from baseline.

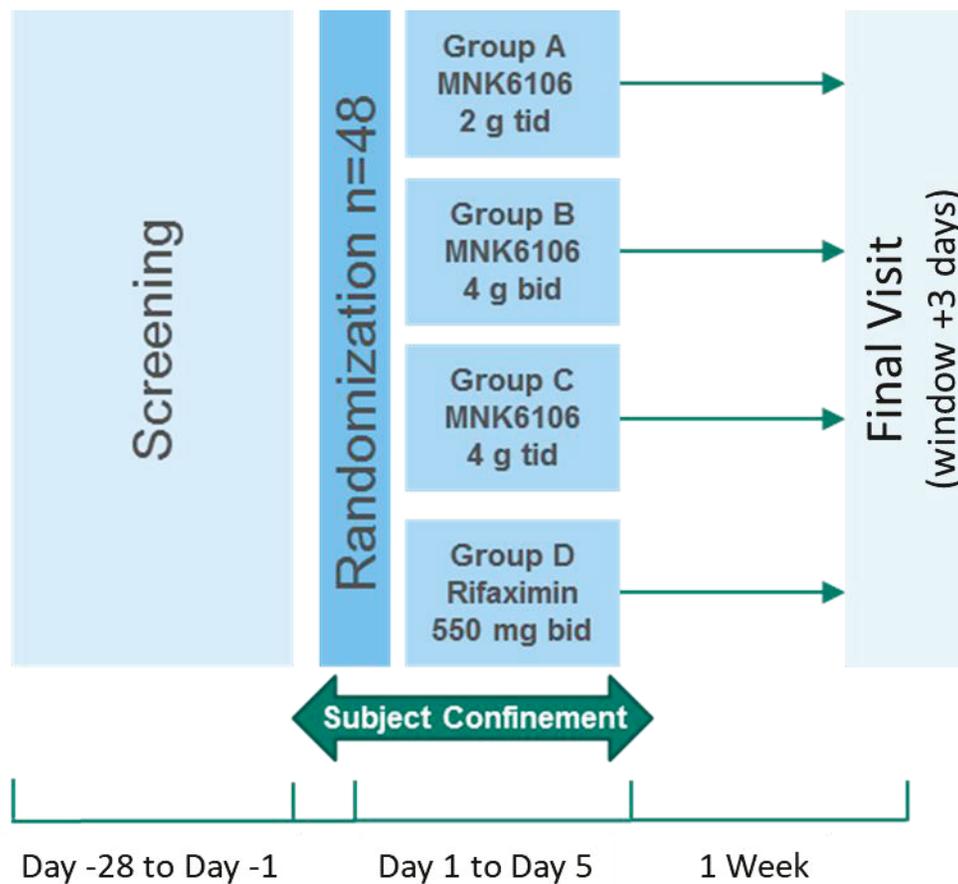
<b>Study Title:</b> A Randomized, Open-Label, Phase 2a Comparator Study to Assess the Pharmacodynamics, Safety and Pharmacokinetics of Oral Administration of MNK6106 (L-Ornithine Phenylacetate) Versus Rifaximin in Subjects With Hepatic Cirrhosis and a History of Prior Episodes of Hepatic Encephalopathy	
<b>Protocol Number:</b> MNK61062107	<b>Type:</b> Interventional/Phase 2a
<b>Secondary Objectives</b>	<b>Secondary Endpoints</b>
To determine the safety and tolerability of MNK6106 following oral administration of MNK6106 in subjects with hepatic cirrhosis and a history of prior episodes of HE.	Adverse event (AEs) and serious adverse event (SAEs).
To evaluate the exposure response (PD and safety) relationships following the oral administrations of MNK6106 in subjects with hepatic cirrhosis and a history of prior episodes of HE.	Plasma exposure of phenylacetate (PAA), L-ornithine (ORN) and phenylacetylglutamine (PAGN) with AMM reduction, and total renal elimination of PAGN.  PAA exposure and neurotoxicity.
<b>Outcome Measures</b>	
Outcome measures are identified to facilitate trial registration and patient access to basic results disclosed on public registries.	
<ul style="list-style-type: none"> <li>The primary outcome measure in the study is the number of participants with a change in ammonia at Day 5.</li> <li>The secondary outcome measure in the study is the number of participants with adverse events or deaths during the study.</li> </ul>	
<b>Overall Design:</b>	
<p>This is a randomized, open-label, parallel group, multiple-dose, dose-ranging, active control, Phase 2a study. The objective of the study is to assess the PD, safety and pharmacokinetics (PK) of different doses of MNK6106 (oral administration) vs rifaximin in subjects 18 to 80 years of age (inclusive) with hepatic cirrhosis and a history of prior episodes of HE.</p> <p>Approximately 48 subjects will be randomized to meet the primary objective. Subjects may participate in the study for a total of up to approximately 6 weeks, including a screening period of up to 28 days, a treatment period of 1 week (5 days), and a final visit 7 days (+ 3 day window) after ending study treatment.</p> <p>The final visit window may be extended, due to extenuating circumstances, to 14 days after discussion with the Sponsor.</p> <p>Subjects will be confined to the study center overnight during the 5-day treatment period and randomly assigned to receive 1 of 3 dosing regimens of MNK6106 or the comparator rifaximin for 5 days.</p> <p>Approximately 48 subjects will be 1:1:1:1 randomized to 1 of the 4 groups. Subjects will receive either 1 of 3 MNK6106 dosing regimens (2 g three times daily, 4 g twice daily, or 4 g three times daily) or rifaximin (550 mg twice daily) taken orally for 5 days. Samples for plasma AMM levels will be drawn at screening and on Days 1, 3 and 5/ET, predose in the morning immediately before breakfast and 4 hours (<math>\pm 15</math> minutes) after the morning dose, as well as at the final visit 1 week (7 days [+ 3 day window] after the last dose). Samples for plasma PAA, ORN and PAGN will be drawn prior to the first dose on Day 1 (within 15 minutes prior to the morning dose) and then prior to (within 10 minutes) and 1 hour (<math>\pm 15</math> minutes) after the last dose on Days 1, 3, and 5/ET. Subjects will remain in the clinic overnight during Day 5/ET and be discharged on Day 6 after the last 24 hour urine collection is completed.</p> <p>Approximately 1 week after the end of the treatment period, subjects will complete a final visit.</p>	

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<b>Study Title:</b> A Randomized, Open-Label, Phase 2a Comparator Study to Assess the Pharmacodynamics, Safety and Pharmacokinetics of Oral Administration of MNK6106 (L-Ornithine Phenylacetate) Versus Rifaximin in Subjects With Hepatic Cirrhosis and a History of Prior Episodes of Hepatic Encephalopathy	
<b>Protocol Number:</b> MNK61062107	<b>Type:</b> Interventional/Phase 2a
<b>Number of Subjects:</b> Approximately 48 subjects will be randomized to meet the primary objective. Subjects may participate in the study for a total of up to approximately 6 weeks, including a screening period of up to 28 days, an treatment period of 1 week (5 days), and a final visit to occur 1 week (7 days [+ 3 day window]) after ending study treatment.	
<b>Treatment Groups and Duration:</b> All treatment groups will be dosed orally as follows: Group A: MNK6106 2 g (2 tablets), three times daily for 5 days (6 g daily dose and 30 g total dose). Group B: MNK6106 4 g (4 tablets), twice daily for 5 days (8 g daily dose and 40 g total dose). Group C: MNK6106 4 g (4 tablets), three times daily for 5 days (12 g daily dose and 60 g total dose). Group D: Rifaximin 550 mg tablet (1 tablet), twice daily for 5 days (1.1 g daily dose and 5.5 g total dose).	

### 1.2. Study Schematic

Figure 1: Study Schematic



### 1.3. Schedule of Study Events

**Table 1: Schedule of Study Events**

Assessment/Procedure	Screening	Begin Confinement (Day -1)	Treatment Period (Days)					End Confinement (Day 6)	Final Visit (7 days post-dosing) (+ 3 day <sup>a</sup> window)
			1	2	3	4	5/ET		
<b>Week</b>			<b>1</b>						<b>2</b>
<b>Day</b>	<b>-28 to -1</b>	<b>-1</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5/ET</b>	<b>6<sup>b</sup></b>	<b>12</b>
<b>Study Visit Number</b>	<b>1</b>		<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>		<b>7</b>
Informed consent	X								
Inclusion/exclusion criteria review	X								
Child-Pugh (C-P) score	X		X	X	X	X	X	X	X
Model for End Stage Liver Disease (MELD) score	X		X	X	X	X	X	X	X
Conn score	X	X	X	X	X	X	X	X	X
Hepatic Encephalopathy Scaling Algorithm (HESA) score	X	X	X	X	X	X	X	X	X
Demographics	X								
Medical/surgical history (including history of exposure to COVID-19)	X								
Prior medication/therapies	X	X							
Complete physical examination	X	X							X

**Table 1: Schedule of Study Events (Continued)**

Assessment/Procedure	Screening	Begin Confinement (Day -1)	Treatment Period (Days)					End Confinement (Day 6)	Final Visit (7 days post-dosing) (+ 3 day <sup>a</sup> window)
			1	2	3	4	5/ET		
Week			1						2
Day	-28 to -1	-1	1	2	3	4	5/ET	6 <sup>b</sup>	12
Study Visit Number	1		2	3	4	5	6		7
Limited physical examination			X					X	
Height and weight <sup>c</sup>	X		X					X	X
Waist circumference	X		X					X	
Vital signs <sup>d</sup>	X		X	X	X	X	X	X	X
Electrocardiogram (ECG)	X		X <sup>e</sup>		X		X		
Laboratories: PD plasma AMM <sup>f</sup>	X		X		X		X		X
Laboratories: PK plasma PAA, ORN, PAGN <sup>g</sup>			X		X		X		
Laboratories: PK urine PAGN <sup>h</sup>			X	X	X	X	X	X	
Laboratories: safety (chemistry and hematology)	X		X	X	X	X	X	X	X
Laboratories: safety (urinalysis)			X	X	X	X	X		
Laboratories: Urinary drug screen <sup>i</sup>	X	X							

**Table 1: Schedule of Study Events (Continued)**

Assessment/Procedure	Screening	Begin Confinement (Day -1)	Treatment Period (Days)					End Confinement (Day 6)	Final Visit (7 days post-dosing) (+ 3 day <sup>a</sup> window)
			1	2	3	4	5/ET		
<b>Week</b>			<b>1</b>						<b>2</b>
<b>Day</b>	<b>-28 to -1</b>	<b>-1</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5/ET</b>	<b>6<sup>b</sup></b>	<b>12</b>
<b>Study Visit Number</b>	<b>1</b>		<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>		<b>7</b>
Laboratories: hepatitis and human immunodeficiency virus (HIV) serology <sup>j</sup>	X								
Serum pregnancy test/FSH <sup>k</sup>	X								X
Urine pregnancy test <sup>l</sup>		X							
Concomitant medications/therapies	X	X	X	X	X	X	X	X	X
Adverse events <sup>m</sup>	X	X	X	X	X	X	X	X	X
Study drug dosing <sup>n</sup>			X	X	X	X	X		
Subject confinement		X	X	X	X	X	X		

ET = end of treatment; FSH = follicle stimulating hormone; ORN = Ornithine; PAA = Phenylacetate; PAGN = Phenylacetylglutamine; PD = pharmacodynamics; PK = pharmacokinetics.

<sup>a</sup> If circumstances occur such that this visit cannot occur within the specified window, the visit window may be extended to 14 days, after discussion with the sponsor.

<sup>b</sup> Subjects may be discharged from the clinic after the final PK samples are obtained. Subjects will be instructed to return for the final visit (7 days [+ 3 day window] after the last dose is administered).

<sup>c</sup> Height at screening only.

<sup>d</sup> Blood pressure, respiratory rate, pulse rate, and body temperature.

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- <sup>e</sup> ECGs on Days 1, 3, and 5/ET should be recorded one hour after last dose ( $\pm$  15 minutes). Complete ECG prior to PK sample collection if the timing is the same. Subject needs to be supine for greater than 10 min prior to ECG.
- <sup>f</sup> Samples for plasma AMM levels will be drawn at screening and on Days 1, 3 and 5/ET, predose in the morning immediately before breakfast and 4 hours ( $\pm$  15 minutes) after the morning dose, as well as at the final visit.
- <sup>g</sup> Samples for plasma PAA, ORN and PAGN will be drawn prior to the first dose on Day 1 (within 15 minutes prior to morning dose) and then prior to (within 10 min) and 1 hour ( $\pm$  15 minutes) after the last dose on Days 1, 3, and 5/ET.
- <sup>h</sup> Urine collection with start/end time and volume recorded for measurement of PAGN concentration will be collected daily. The 24 hour interval will start following the first dose of the day, eg, if the first dose of the day is given at 8 AM, urine will be collected starting at 8 AM and continue until 8 AM of the next day. A predose urine sample will be collected on Day 1.
- <sup>i</sup> Methadone will be tested at screening only.
- <sup>j</sup> Hepatitis B surface antigen, Hepatitis B core antibody, HCV antibody and HIV. HCV polymerase chain reaction testing will be performed only for subjects positive for HCV.
- <sup>k</sup> FSH test is required for postmenopausal women.
- <sup>l</sup> A urine pregnancy test will be performed on women of child-bearing potential on Day -1 to ensure that pregnancy did not occur since the time of screening.
- <sup>m</sup> AEs will be assessed on an ongoing basis; all AEs (serious and non-serious) occurring from the time of signing informed consent until completion of the Final Visit will be recorded in the electronic case report form (eCRF) (refer to Section 8.7; full details provided in Section 10.3 and its subsections).
- <sup>n</sup> Study drug/formulation will be administered under fed (30 minutes after start of meal) conditions. Lunch and dinner will be served at approximately 30 minutes prior to dosing.

## 2. INTRODUCTION

MNK6106 is a novel ammonia (AMM)-lowering agent that uses pathways of AMM removal to reduce plasma AMM concentration in subjects with varying degrees of hepatic encephalopathy (HE).

MNK6106 (ornithine phenylacetate), in the form of the L-ornithine (ORN) salt of phenylacetate (PAA), is a single new chemical entity that allows for alternative pathways for the excretion of AMM in the setting of cirrhosis through the enhanced elimination of AMM ([Jalan et al, 2007](#)). L-ornithine stimulates the activity of glutamine synthetase, inducing body muscle to trap circulating AMM in the form of glutamine, which is a nontoxic carrier of AMM. Glutamine is then conjugated with PAA to form PAGN, which is excreted in urine. This strategy prevents the eventual recirculation and degradation of glutamine by glutaminase and avoids re-formation of AMM.

L-Ornithine phenylacetate was granted orphan drug status in 2010 by the US Food and Drug Administration (FDA); for the treatment of hyperammonemia and associated hepatic encephalopathy in patients with acute liver failure or acute or chronic liver disease.

A detailed description of the chemistry, pharmacology, efficacy, and safety of products containing L-Ornithine phenylacetate is provided in the Investigator's Brochure ([Mallinckrodt, 2019](#)).

### 2.1. Background

Although the onset of HE can rarely be pinpointed clinically, it is a landmark in patients with advanced liver disease ([Wijdicks, 2016](#)). An estimated 60% to 70% of cirrhotic patients have at least subtle signs of neurocognitive impairment. Overt HE has a prevalence of approximately 30% in patients with end-stage liver disease, and accounts for about 150,000 hospitalizations annually in the United States ([Al Sibae et al, 2009](#)). Severe HE in patients with cirrhosis is associated with a mortality of more than 50% in the first year alone ([Wijdicks, 2016](#)).

HE is a neuropsychiatric disorder that occurs when gut derived toxins, primarily AMM, bypass a failing liver, which would normally detoxify such agents. These toxins enter the circulation and cross the blood brain barrier, resulting in impairment of neurotransmission and central nervous system (CNS) function. HE can arise in the setting of acute liver failure, chronic progressive liver disease in the context of advanced liver cirrhosis (overt HE), and/or as a result of portocaval shunting with or without liver disease. The pathogenesis of HE has been incompletely understood but the increase in plasma AMM levels remains central to the understanding of HE ([Wijdicks, 2016](#)), supporting the need for novel, safe, and effective AMM lowering therapies to treat as well as to prevent episodes of HE.

Dietary protein restriction had long been advocated as a strategy to reduce circulating AMM in patients with cirrhosis. However, recent data have shown that this strategy is not effective in preventing HE and may harm these patients by making them more prone to muscle wasting ([Cordoba et al, 2004](#)).

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Current treatment guidelines for episodic overt HE recommend lactulose, a non-absorbed disaccharide, at a dose of 25 mL twice daily as first line agent, adjusted for the production of 3 bowel movements daily ([American Association for the Study of Liver Diseases, 2014](#)). Rifaximin, which alters gut microbiota, is recommended as an add-on therapy to lactulose for prevention of HE recurrence ([American Association for the Study of Liver Diseases, 2014](#)); ([Wijdsicks, 2016](#)). However, recent data suggest that a significant number of patients receiving lactulose and rifaximin are hospitalized with a recurrence of HE ([Kulkarni et al, 2018](#)).

MNK6106 (L-Ornithine phenylacetate), in the form of an orally administered ORN salt of PAA, is a single new chemical entity that allows for alternative pathways for the excretion of AMM in the setting of cirrhosis through the enhanced elimination of AMM.

### **2.1.1. Nonclinical Safety Data**

The nonclinical safety of L-Ornithine phenylacetate was evaluated in a series of in vitro and in vivo studies which included evaluation of the potential undesirable pharmacodynamic (PD) effects of L-Ornithine phenylacetate on physiological functions in relation to exposure in the therapeutic range and above (safety pharmacology core battery), evaluation of the mutagenic and clastogenic potentials of L-Ornithine phenylacetate (in vitro and in vivo test battery for genotoxicity), evaluation of the short- and longer-term functional and morphologic effects associated with L-Ornithine phenylacetate exposure in whole animal models (mammalian toxicology program), evaluation of the effects of L-Ornithine phenylacetate on fertility and embryo-fetal development, and evaluation of local intravenous (IV) and gastrointestinal tract effects of L-Ornithine phenylacetate administration. The results of the toxicology program indicate that L-Ornithine phenylacetate does not present a genotoxic hazard and is associated with a low potential for local (oral/IV) and systemic toxicity in humans. Potential adverse effects of L-Ornithine phenylacetate on sperm parameters (count and morphology) and embryo-fetal development were noted at high doses/systemic exposures.

### **2.1.2. Clinical Safety Data**

Safety data from completed sponsor and investigator-initiated clinical studies demonstrated that a single IV dose of 20 g L-Ornithine phenylacetate IV solution (MNK6105) infused over 4 hours or daily 20 g IV doses infused over 24 hours for up to 5 days, were generally well tolerated.

Regarding oral administration with MNK6106 (L-Ornithine phenylacetate tablets), Study OCR002-SP103 was an open-label Phase 1/2a, 2-part crossover study in 30 adult subjects with varying degrees of cirrhosis, who received oral administration of MNK6106. The safety conclusions were that MNK6106 was safe and well-tolerated when administered at doses up to 21 g/day for 5 days. There were no deaths, 1 serious adverse event (SAE) was reported during Part 2 of the study (SAE of urinary tract infection in a subject while receiving 21 g/day; the event was considered not related to study drug treatment). In addition, safety data from completed Phase 1/2a clinical studies with a single IV dose of 5 g given as an oral solution, as well as oral administration of MNK6106 tablets (6 g, 12 g, and 21 g per day for 3 periods, 5 days per period with a minimum 4-day washout in between) indicate that both IV and oral administration of L-

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Ornithine phenylacetate were generally well tolerated. No Phase 2/3 studies of MNK6106 have been initiated.

A detailed description of the chemistry, pharmacology, efficacy, and safety of L-Ornithine phenylacetate is provided in the Investigator's Brochure ([Mallinckrodt, 2019](#)).

## 2.2. Study Rationale

Current treatment strategies for the prevention of overt HE are limited to the correction or removal of precipitating factors, as well as the imperfect reduction of circulating AMM levels by dietary changes and/or pharmacological approaches. Pharmacological approaches include non-absorbed disaccharides (eg, lactulose) and antibiotics (eg, neomycin and rifaximin), which target AMM absorption and change the gut microbiome to non-urease-producing bacteria reducing intestinal AMM production, respectively.

Lactulose is orally/rectally administered, does not directly target AMM metabolism, has limited efficacy in subjects with acute episodes of overt HE, is difficult to administer, and requires doses taken frequently throughout the day.

Rifaximin is indicated for reduction in risk of overt HE recurrence in patients at least 18 years of age.

In the trials of rifaximin for HE, 91% of the patients were using lactulose concomitantly. Differences in the treatment effect of those patients not using lactulose concomitantly could not be assessed ([American Association for the Study of Liver Diseases, 2014](#)); ([Wijdicks, 2016](#)); ([Horizon Therapeutics, 2017](#)).

In a Phase 1/2a Study OCR002-SP103, dosing of 4 g or 7 g 3 times daily lowered AMM concentrations or prevented increases in AMM concentrations following the discontinuation of lactulose, although the percentage change in blood AMM concentrations was highly variable. MNK6106 dosing of 4 g and 7 g 3 times daily was seen to lower AMM concentrations or at least prevent increases in AMM concentrations following the discontinuation of lactulose.

MNK6105 has been evaluated in two Phase 1 studies: OCR002-HV201 (healthy subjects) and OCR002-HE201 (subjects with Child-Pugh [C-P] Class A or B cirrhosis) and in two investigator initiated Phase 2 studies:

- OP-GIB study (in subjects with cirrhosis and active gastrointestinal bleeding) and
- OCR002-HE209 (in subjects with cirrhosis and HE).

The OCR002-HE209 study with MNK6105 (10 g/day, 15 g/day, and 20 g/day IV for 5 days) data suggested better clinical improvement, plasma AMM-lowering/normalizing PD effects ratio and decrease in AMM concentrations in subjects receiving MNK6105 compared to placebo.

## 2.3. Assessment of Potential Benefits and Risks

The results of nonclinical pharmacological studies support the clinical use of L-Ornithine phenylacetate in the treatment of hyperammonemia and acute HE. The studies demonstrated

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AMM reduction in pig (Ytrebo et al, 2009) and rat models (Davies et al, 2009) - effects not seen with anti-inflammatory therapy (with a tumor necrosis factor alpha antagonist) if hyperammonemia remained untreated (Wright et al, 2011). Significant reduction in AMM levels was replicated in 2 other studies using L-Ornithine phenylacetate in a bile duct ligated cirrhotic rat model (Mookerjee et al, 2009);(Vairappan et al, 2009).

L-Ornithine phenylacetate increases AMM elimination by upregulating ORN aminotransferase and glutamine synthetase (action of ornithine) and its excretion as PAGN (action of PAA). L-Ornithine phenylacetate also reduces AMM production by normalizing gut glutaminase activity (action of ORN), demonstrating the synergistic effect of the 2 pharmacophores (Jover-Cobos et al, 2014).

L-Ornithine phenylacetate prevented neurophysiological abnormalities in a portacaval shunted rat model following a simulated gastrointestinal bleed. L-Ornithine phenylacetate treatment significantly blunted the rise in AMM generated by a simulated gastrointestinal bleed. The reduction in plasma AMM was associated with normalization of neurophysiologic function as assessed by motor evoked potential. These studies provide the pharmacological rationale for using L-Ornithine phenylacetate in cirrhotic patients to prevent hepatic encephalopathy precipitated by gastrointestinal bleeding (Oria et al, 2012).

The conclusion, based on the adverse event (AE) data from the nonclinical pharmacological studies supporting the clinical use of L-Ornithine phenylacetate in the treatment of hyperammonemia and acute HE, is that a 20 g dose infused over 24 hours, appears to be well tolerated.

In aggregate, the clinical data presented provide assurance of appropriate benefit/risk for the administration of MNK6105 in patients hospitalized with HE in acute need of intervention. The safety and PK data collected to date from completed studies OCR002-HV201, OCR002-HE201, OCR002-HE209 along with the information supplied in the product label for RAVICTI<sup>®</sup> (glycerol phenylbutyrate) and similar other products, support the selection of MNK6105 infused up to 20 g/24 hours for 5 days in subjects with acute overt HE.

The individual components of L-Ornithine phenylacetate, namely ORN and PAA, have been used in the treatment of hyperammonemia for over 20 years; ORN as an over the counter nutritional supplement and PAA to treat hyperammonemia in patients with urea cycle disorders. Substantial data therefore exists on the safety of both L-ornithine, sodium PAA and phenylbutyrate; albeit PAA data supports the use of the compound in the treatment of urea cycle disorders.

Toxicity with sodium PAA has been observed in PK studies in both healthy volunteers and patients with cancer. In these studies, the drug was administered rapidly over 90 minutes with resultant high peak plasma concentrations of PAA.

Side effects have been reported to generally correlate with PAA maximum plasma concentration. Dose-related adverse effects in these studies were gastrointestinal (eg, nausea and vomiting) and CNS (eg, somnolence, fatigue, and headache) in nature.

Concentrations over 400 µg/mL of PAA have been associated with nausea and vomiting [Summary Basis of Approval for AMMONUL®] and concentrations over 490 µg/mL have been associated with CNS-related AEs when administered in bolus doses in prior PK studies in healthy adult volunteers and in patients with cancer.

Some cancer patients treated with sodium phenylacetate had signs and symptoms of PAA neurotoxicity including somnolence, fatigue, lightheadedness, headache, dysgeusia, hypoacusis, disorientation, impaired memory, and exacerbation of preexisting peripheral neuropathy. In this study, these adverse effects were reported to be generally transient and reversible (Thibault et al, 1994); (Thibault et al, 1995).

Some patients with urea cycle disorders treated in clinical trials with RAVICTI have experienced headache, fatigue, symptoms of peripheral neuropathy, seizures, tremor and/or dizziness. No correlation between PAA levels and neurotoxicity symptoms was identified but PAA levels were generally not measured at the time of neurotoxicity symptoms (Horizon Therapeutics, 2017).

Appropriate dosing for MNK6106 has not yet been determined.

More detailed information about the known and expected benefit, risks, and reasonably expected AEs associated with L-Ornithine phenylacetate can be found in the Investigator's Brochure (Mallinckrodt, 2019).

### 3. OBJECTIVES AND ENDPOINTS

#### 3.1. Primary Objective/Endpoint

Primary Objective	Endpoint
To evaluate the pharmacological activities through plasma AMM concentration as a PD marker following oral administration of MNK6106 with rifaximin as a comparator in subjects with hepatic cirrhosis and a history of prior episodes of HE.	Absolute and percentage change of plasma AMM from baseline.

#### 3.2. Secondary Objectives/Endpoints

Secondary Objectives	Secondary Endpoints
To determine the safety and tolerability of MNK6106 following oral administration of MNK6106 in subjects with hepatic cirrhosis and a history of prior episodes of HE.	AEs, SAEs.
To evaluate the exposure response (PD and safety) relationships following oral administration of MNK6106 in subjects with	Plasma exposure of PAA, ORN and PAGN with AMM reduction, and total renal elimination of PAGN. PAA exposure and neurotoxicity.

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Secondary Objectives	Secondary Endpoints
hepatic cirrhosis and a history of prior episodes of HE.	

### 3.3. Outcome Measures

Outcome measures are identified to facilitate clinical trial registration and patient access to basic results disclosed on public clinical trial registries.

The primary outcome measure in the study is the number of participants with a change in ammonia at Day 5.

The secondary outcome measure in the study is the number of participants with adverse events or deaths during the study.

## 4. STUDY DESIGN

### 4.1. Overall Design

This is a randomized, open-label, parallel group, multiple-dose, dose-ranging, active control, Phase 2a study. The objective of the study is to assess the PD, safety and PK of different doses of MNK6106 (oral administration) vs rifaximin in subjects 18 to 80 years of age (inclusive) with hepatic cirrhosis and a history of prior episodes of HE.

Approximately 48 subjects will be randomized to meet the primary objective. Subjects may participate in the study for a total of up to approximately 6 weeks, including a screening period of up to 28 days, a treatment period of 1 week (5 days), and a final visit 1 week (7 days [+ 3 day window]) after ending study treatment.

The final visit window may be extended, due to extenuating circumstances, to 14 days after discussion with the Sponsor.

Subjects will be confined to the study center overnight during the 5-day treatment period and randomly assigned to receive 1 of 3 dose regimens of MNK6106 or the comparator rifaximin for 5 days.

Approximately 48 subjects will be 1:1:1:1 randomized to 1 of the 4 groups. Subjects will receive either 1 of the 3 MNK6106 dosing regimens (2 g three times daily, 4 g twice daily, or 4 g three times daily) or rifaximin (550 mg twice daily) taken orally for 5 days. Samples for plasma AMM levels will be drawn at screening and on Days 1, 3 and 5/ET, predose in the morning immediately before breakfast and 4 hours ( $\pm$  15 minutes) after the morning dose as well as at the final visit. Samples for plasma PAA, ORN and PAGN will be drawn prior to the first dose on Day 1 (within 15 minutes prior to the morning dose) and then prior to (within 10 minutes) and 1 hour ( $\pm$  15 minutes) after the last dose on Days 1, 3, and 5/ET. Subjects will remain in the clinic overnight during Day 5/ET and be discharged on Day 6 after the last 24 hour urine collection is completed.

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All treatment groups will be dosed orally as follows:

- Group A: MNK6106 2 g (2 tablets), three times daily for 5 days (6 g daily dose and 30 g total dose).
- Group B: MNK6106 4 g (4 tablets), twice daily for 5 days (8 g daily dose and 40 g total dose).
- Group C: MNK6106 4 g (4 tablets), three times daily for 5 days (12 g daily dose and 60 g total dose).
- Group D: Rifaximin 550 mg tablet (1 tablet), twice daily for 5 days (1.1 g daily dose and 5.5 g total dose).

Approximately 1 week after the end of the treatment period, subjects will complete a final visit.

## **4.2. Study Design Rationale**

This Phase 2a dose-ranging safety study will be the first to evaluate the oral administration of MNK6106 tablets vs rifaximin 550 mg tablets twice daily as well as to characterize the PK/PD of MNK6106 in subjects.

### **4.2.1. Dose Rationale**

In Study OCR002-SP103 with, oral administration of MNK6106 at dose levels of 2 g, 4 g and 7 g three times daily (total 6 g, 12 g, and 21 g daily), the reduction in AMM concentrations appeared to be similar at the doses of 12 g and 21 g daily, with 6 g being able to prevent increases in AMM concentrations. This observation was consistent with MNK6105 (L-Ornithine phenylacetate IV formulation), where the effect of L-Ornithine phenylacetate was maximized at a dose of 15 g/day. Given the fact that MNK6106 (L-Ornithine phenylacetate oral formulation) has demonstrated excellent absolute bioavailability (greater than 95%), the 12 g oral formulation is expected to achieve comparable exposure as MNK6105 15 g. Therefore, the high dose in this study was selected as 12 g/day (4 g three times daily). The low dose of 6 g/day was chosen because it was able to prevent an increase in AMM concentrations.

Since a twice daily dose is favorable for compliance, a 4 g twice a day (8 g daily) regimen was selected, to maximize the reduction in AMM following each administration.

## **4.3. End of Study Definition**

A subject will have completed the study if the final visit at Week 2/Visit 7 is completed or if the subject dies or is otherwise lost to follow-up.

The end of the study is defined as the completion of the final assessment for the last subject enrolled in the study.

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## 5. STUDY POPULATION

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

### 5.1. Inclusion Criteria

To be eligible to participate in the study, at the Screening Visit each subject must:

1. Be adequately informed and understand the nature and risks of the study and must be able to provide a signature and date on the informed consent form (ICF).
2. Be at least 18 and no more than 80 years of age at the Screening Visit. Subjects may be male or female.
3. Have known or evident liver cirrhosis. Diagnosis of liver cirrhosis may be based on clinical, radiological, and or histological criteria, including 1 or more of the following:
  - a. Liver biopsy (documented by histology);
  - b. Clinical evidence of cirrhosis, defined as aspartate aminotransferase greater than alanine aminotransferase, platelet count less than 150,000  $\mu\text{L}$ , and nodular liver surface on computed tomography scan or magnetic resonance imaging;
  - c. Clinical evidence of significant portal hypertension, based on current or history of gastroesophageal varices on endoscopy, evidence of portosystemic collaterals (on contrast computed tomography or magnetic resonance imaging with contrast), and/or presence of ascites;
  - d. Transient elastography consistent with cirrhosis, ie, a result of greater than 13.0 kPa.
4. A history of at least 1 or more documented episodes of HE within the last 12 months.
5. Hyperammonemia (defined as an ammonia level  $\geq 37 \mu\text{mol/L}$ ) at screening.
6. Currently using lactulose (minimum of 5 days prior to Day -1).
7. If using rifaximin at the Screening Visit, it must be discontinued at least 5 days before the first dose of study drug.
8. If female, be of non-childbearing potential (history of hysterectomy, bilateral oophorectomy, bilateral tubal ligation; or postmenopausal with no history of menstrual flow in the 12 months prior to the Screening Visit); or, if of childbearing potential, be non-pregnant, non-lactating and agree to use 2 forms of effective contraception when with a male partner for the duration of the study and for 28 days after any active treatment period. Acceptable forms of contraception include hormonal measures (oral contraceptive pills, contraceptive patch, contraceptive ring, injections), intrauterine devices, double barrier method (condom plus diaphragm, condom or diaphragm plus spermicidal gel or foam, surgical sterilization of the male partner), and abstinence.
9. If male with reproductive potential, agree to use 2 forms of effective contraception (abstinence, surgical sterilization [vasectomy], or condom with spermicide) with a female partner for the duration of the study and for 28 days after any active treatment period.

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10. Be able to communicate effectively with study personnel.
  11. Be able and willing to follow all protocol requirements and study restrictions.
  12. Be able and willing to return for all study visits.

## 5.2. Exclusion Criteria

A subject is ineligible for study participation if, at the Screening Visit, the subject:

1. Is from a vulnerable population, as defined by the US Code of Federal Regulations (CFR) Title 45, Part 46, Section 46.111(b) and other local and national regulations, including but not limited to, employees (temporary, part-time, full time, etc.) or a family member of the research staff conducting the study, or of the sponsor, or of the contract research organization, or of the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).
  2. Has a history of sensitivity or allergy to MNK6106, ORN, PAA, L-ornithine L-aspartate, phenylbutyrate or rifaximin.
  3. Has expectation of liver transplantation within 1 month after the Screening Visit.
  4. Had placement of a portosystemic shunt or transjugular intrahepatic portosystemic shunt within 3 months before the Screening Visit.
  5. Has a Model for End Stage Liver Disease (MELD) score greater than 25.
  6. Has HESA score Grade 4.
  7. Had gastrointestinal bleeding within 3 months of the Screening Visit.
  8. Has severe renal impairment (Creatinine Clearance rate no more than 30 mL/min) calculated using the Cockcroft-Gault formula.
  9. Has intercurrent infection or active spontaneous bacterial peritonitis.
  10. Has known immune compromised status (not related to disease/condition under study), including but not limited to individuals who have undergone organ transplantation or who are known to be positive for the human immunodeficiency virus (HIV).
  11. Has any solid tumor malignancy currently diagnosed or undergoing therapy or has received therapy for any solid tumor malignancy in the 5 years prior to the Screening Visit; with the exception of treated and cured basal cell carcinoma, treated and cured squamous cell carcinoma of the skin, and treated and cured carcinoma in situ of the cervix.
  12. Has a history of prior cognitive impairment.
  13. Has a history of psychotic disorders including but not limited to schizophrenia, dementia, or other severe psychotic disorders that would interfere with evaluation of HE.
  14. Has a positive screening result for drugs and alcohol (except for subjects positive to cannabinoids).
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15. Has a QT interval corrected using Fridericia's Formula (QTcF) of at least 500 msec at screening.
  16. Has any of the following laboratory abnormalities at the Screening Visit:
    - Hemoglobin < 8.0 g/dL.
    - Platelet count < 25,000 cells/ $\mu$ L.
    - Absolute neutrophil count < 1000 cells/ $\mu$ L.
  17. Has any other clinically significant disease, disorder or laboratory abnormality, which, in the opinion of the investigator, might put the subject at risk due to participation in the study, or may influence the results of the study or the subject's ability to complete the study.
  18. Inability to swallow the study drug whole.
  19. Has hyponatremia, defined as blood sodium level  $\leq$  125 mmol/L.
  20. Is participating in or plans to participate in any other interventional research study from the time of screening and throughout this study.

### **5.3. Lifestyle Considerations**

Subjects should not donate blood or plasma for the duration of this study and for 28 days after study exit.

Subjects will be instructed to refrain from strenuous exercise from 48 hours prior to randomization through to 24 hours after the final PK sample is taken.

### **5.4. Screen Failures**

Screen failures are defined as subjects who consent to participate in the study but are not subsequently randomized.

The period from the start of screening related procedures at the Screening Visit to randomization must not exceed 28 days, inclusive of any repeat screening procedures.

Subjects who do not meet all of the eligibility criteria at the end of the screening period will be deemed a screen failure, and the following information must be recorded for all subjects who are screen failures:

- Demography (age, gender, race/ethnicity).
- Reason for screen failure.
- Eligibility criteria.
- Any AE/SAE experienced by the subject.

Subjects may be rescreened provided that the subject was not randomized. All Screening Visit procedures must be repeated.

Subjects may be rescreened only once. Subjects who are re-screened should not be assigned a new subject number. The original subject number should be retained.

## 6. STUDY TREATMENT

Study treatment is defined as any investigational treatment, marketed products, placebo, or device intended to be administered to a study subject according to the study protocol. Subjects enrolled in this study will receive study treatment under open-label conditions.

The study treatments will be dispensed by the investigator or investigator's designee. The treatment groups, frequency and dose are summarized in [Table 2](#).

### 6.1. Treatment Administration

The following treatments will be administered:

Product	Supplied as:
MNK6106	1 g immediate release (IR) MNK6106 tablet
Rifaximin	550 mg tablet

MNK6106 tablets, 1 g, are supplied as white, film coated immediate release tablets for oral administration. Each tablet contains 1 g of L-Ornithine phenylacetate. The inactive ingredients include [REDACTED]

Rifaximin tablets, 550 mg, are supplied as a pink-colored, oval, biconvex tablet with "rfx" debossed on 1 side and plain on the other.

**Table 2: Summary of Treatment Groups, Frequency and Dose**

Treatment	Frequency	Dose	Total Daily Dose	Total Dose (5 days)
MNK6106	tid	2 g	6 g	30 g
MNK6106	bid	4 g	8 g	40 g
MNK6106	tid	4 g	12 g	60 g
Rifaximin	bid	550 mg	1.1 g	5.5 g

Note: bid = twice daily; tid = 3 times daily.

For the 3 times daily dosing regimen, the doses will be given at 8 AM, 1 PM, and 6 PM ( $\pm 60$  minutes); for twice daily dosing, the doses will be given at 8 AM and 6 PM ( $\pm 60$  minutes). Each dose will be administered with an 8 oz glass of room temperature water, and the subject will be required to swallow the tablet whole without chewing or crushing it, and to drink all the water. The date and actual (clock) time that the subject receives the MNK6106 study drug and the dose amount administered will be recorded on the electronic case report form (eCRF). Any

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deviations from the dosing schedule and instructions described in this protocol will also be recorded. Each subject will be closely supervised for ingesting each of the doses and the required amount of water. The entire dose must be administered within 15 minutes.

Any loss of the study drugs will be documented and reported to Mallinckrodt Clinical Supply Management, with the approximate amount lost estimated and recorded. Replacements will be made accordingly.

The study drugs will be administered under fed (30 minutes after start of meal) conditions. Lunch and dinner will be served at approximately 30 minutes prior to dosing.

After each dose, the subjects will be required to remain in an upright position for at least 2 hours after dosing. In addition, subjects will also be required to refrain from anything more than light exercise while confined at the study site.

## **6.2. Study Treatment Preparation/Handling/Storage/Accountability**

MNK6106 tablets are packed into high-density polyethylene bottles with child-resistant caps, 60 tablets per bottle.

The bottles of MNK6106 and rifaximin should be stored at room temperature 20°C to 25°C (68°F to 77°F); excursions are permitted between 15°C to 30°C (59°F to 86°F).

The sponsor will supply MNK6106 and rifaximin. The investigator or investigator's designee will maintain the following records: receipt of shipments, dispensation to subjects, and return of empty, partially used, and unopened bottles. Reasons for departure from the expected dispensing regimen must also be recorded.

Study drug should not be returned before the designated study monitor has checked the drug accountability records with the study site personnel after database lock.

Upon receipt of the study drug supplies, the investigator or investigator's designee will conduct an inventory, follow the process for acknowledging receipt of the study drug, and complete appropriate form(s). One copy of the receipt and the packing slip must be retained.

At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all study treatments will be reconciled and retained or destroyed according to applicable regulations.

The investigator or designee will confirm that appropriate temperature control conditions have been maintained during transit for all study treatments received and confirm that any discrepancies are reported and resolved prior to study treatment administration.

The study treatment will be maintained in a monitored, environmentally controlled (in accordance with treatment labeling), secure, locked area with restricted access at the study site.

Only subjects enrolled in the study will receive study treatment and only authorized study staff will dispense study treatment.

In accordance with the International Council for Harmonisation (ICH) requirements, at all times the investigator will be able to account for all study treatment furnished to the study site. An accountability record will be maintained for this purpose. The investigator must maintain accurate records indicating dates and quantity of study treatment received, to whom it was administered (subject-by-subject accounting) and accounts of any study treatment accidentally or deliberately destroyed. All unused study treatment not involved in immediate subject treatment will be maintained under locked, temperature-controlled storage at the study site.

### **6.3. Measures to Minimize Bias**

This is an open-label study. Subjects will be randomized according to a pre-specified, validated computer-generated allocation scheme to receive the 4 treatments described above based on a 1:1:1:1 ratio.

Each subject will be assigned a unique identification (ID) number. The subject ID number will be assigned electronically by the INFORM database system when the study site staff enters the required information into the INFORM system. The subject ID number will be used to identify the subjects for the duration of the study within all systems and documentation. A subject with a signed ICF in place will be assigned a 4-digit sequential subject number preceded by the 4-digit study site number with a “dash” in between (ie, XXXX-XXXX). Each part must start with a non-zero number.

If the subject is not eligible to receive study treatment, or should discontinue from the study, the subject ID number will not be reassigned to another subject.

In the event that a subject repeats any evaluation during the screening window, they will not receive a new ID number. In addition, subjects who fail screening and are rescreened will not receive a new subject ID number. Qualified subjects who meet all of the eligibility criteria will be randomized into the study.

The investigator must maintain a subject master log linking the subject ID to the subject’s name. The investigator must follow all applicable privacy laws in order to protect a subject’s privacy and confidentiality. Information that could identify a subject will be masked on material received by the sponsor.

Subjects will be randomized according to a treatment allocation scheme that will be sent to each site. The treatment assigned will be recorded in the source documentation.

Based on the randomized treatment assignment, the investigator or investigator’s designee will dispense the study treatment tablets (MNK6106 or rifaximin) for each subject.

### **6.4. Study Treatment Compliance**

Treatment compliance will be determined by drug accountability and dosing information recorded in the eCRF.

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## 6.5. Prior and Concomitant Therapy

Use of all relevant concomitant medications/therapies will be recorded in the subject's eCRF.

The start and stop date, dose, unit, frequency, route of administration, and indication for all prior (taken within the 30 days prior to the Screening Visit) and concomitant (taken from the Screening Visit through to the Final Visit) medications and nondrug therapies (eg, blood transfusions, oxygen supplementation, physical therapy, etc.) received will be recorded.

### 6.5.1. Prohibited Concomitant Therapies

The following treatments will not be permitted during the study (from Randomization through to the Final Visit):

- Current use of drugs that could potentially interfere with renal excretion of PAGN, such as corticosteroids, haloperidol, valproic acid probenecid, estrone sulfate, ibuprofen, cimetidine, or diclofenac. Use of L-ornithine L-aspartate is prohibited.
- Current use of drugs whose plasma concentration may be affected by MNK6106, such as alfentanil, cyclosporine, midazolam, quinidine, or cimetidine. Metformin use is permitted at low doses. Doses of metformin > 1,000 mg should be discussed with the medical monitor prior to enrollment.
- Current use of AMMONUL<sup>®</sup> (sodium benzoate with sodium PAA), BUPHENYL<sup>®</sup> (sodium phenylbutyrate), RAVICTI, or other medications containing sodium benzoate or sodium phenylbutyrate.
- Current use of rifaximin (except for subjects randomized to rifaximin), oral neomycin, oral vancomycin or any other oral or parenteral antibiotic that could potentially alter gut flora. There should be a 5-day washout period for rifaximin use prior to the first dose of study drug.
- Current use of repaglinide.
- Receipt of an investigational product or device, or participation in a drug research study within a period of 30 days (or 5 half-lives of the drug, whichever is longer) before the first dose of study treatment.
- Any investigational drug, device, or procedure administered as part of a research study.

Exceptions to these restrictions during the subject selection process must be approved by the investigator and sponsor and will be discussed on a case-by-case basis. Once the study has started, if a subject is unable to comply with the restrictions described above, their participation in the study will be re-evaluated by the investigator, again in consultation with the sponsor. The decision to continue a subject who has received a concomitant medication as directed by the investigator for the treatment of an AE will also be made mutually between the investigator and sponsor.

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If any prohibited medication is taken during the study, all pertinent information will be recorded in source documents and the eCRF. The designated study medical monitor (MM) must be informed immediately so the sponsor may determine whether to continue the subject in the study.

#### **6.5.1.1. Sedatives**

Due to the importance of accurately measuring mental status during the treatment period of this study, sedation is an important potential confounder, and thus, sedatives should not be used during the study period. Sedatives such as benzodiazepines (eg, alprazolam, alcyon, midazolam, oxazepam, triazolam, lorazepam, estazolam, temazepam, diazepam, chlordiazepoxide, clonazepam, flurazepam, clorazepate) and sleep aids (eg, haloperidol, zolpidem, Midol PM<sup>®</sup>, Sominex<sup>®</sup>, trazodone [Desyre1<sup>®</sup>], Sleep-eze<sup>®</sup>), are not allowed during the treatment period through completion of the final visit and, if applicable, + 24 hours after final visit assessments.

Any psychoactive agents including strong analgesics, antidepressants, and/or anxiolytics should be avoided. Narcotic use should be avoided due to subject sensitivity to these agents. Any use of sedation must be consistent with standard medical therapy. If sedation is unavoidable, use drugs with a short half-life (eg, diprivan) as well as drugs that do not have synergistic effects with endogenous promoters of HE (eg, avoid benzodiazepines).

Mind-altering agents (such as barbiturates, opioids, or benzodiazepines) should be avoided during the treatment period through completion of the final visit and, if applicable, + 24 hours after final visit assessments.

#### **6.5.1.2. Neuroactive Agents**

Avoid agents that can precipitate confusion or neurological changes or cause central nervous system disturbances, such as prochlorperazine (Compazine<sup>®</sup>), promethazine (Phenergan<sup>®</sup>), trimethobenzamide (Tigan<sup>®</sup>), dronabinol (Marinol<sup>®</sup>), metoclopramide (Reglan<sup>®</sup>), or any of the benzodiazepines. These drugs are not allowed during the treatment period until after completion of all assessments at the final visit and, if applicable, + 24 hours after final visit assessments.

#### **6.5.2. Other Restricted Substances**

Subjects should refrain from consumption of food and beverages containing alcohol from 72 hours prior to dosing until completion of the last PK sample collection. The use of drugs of abuse and legal narcotic agents is not permitted while subjects are enrolled in this study. If a subject is unable to comply with the restrictions described above, their continued participation in the study will be re-evaluated by the investigator, in consultation with the sponsor. Subjects must abstain from tobacco products, including vaping, during confinement at the study center.

#### **6.5.3. Meals and Fluids**

The study drugs will be administered under fed conditions (30 minutes after the start of a standardized meal). Lunch and dinner will be served at approximately 30 minutes prior to dosing.

For all subjects, standardized, balanced meals will be provided while subjects are confined at the research unit. The meals will be nutritionally balanced and will contain sufficient fiber/roughage to maintain normal bowel activity.

Snacks are permitted throughout the day, except on Day 1, Day 3, and Day 5/ET beginning 8 hours before the breakfast dose until 2 hours after the lunch dose. Snacks must be captured in the eCRF.

The total amount of protein per subject per day (including all meals and snacks) should not exceed 1.5 g/kg body weight per day.

In order to facilitate urine production, subjects will be encouraged to drink fluids frequently throughout the confinement period.

## **7. DISCONTINUATION OF STUDY TREATMENT AND SUBJECT DISCONTINUATION/WITHDRAWAL**

The duration of the study is defined for each subject as the date that signed written informed consent is provided until completion of the final visit or until premature withdrawal from the study for any other reason (eg, death, physician decision, subject/caregiver withdraws consent, lost to follow-up).

Subjects (or their caregivers) may withdraw consent from the study at any time and for any reason, without prejudice to their future medical care by the investigator or others at the study site. Every effort should be made to keep subjects in the study. The reason for study treatment discontinuation or subject withdrawal from the study will be recorded in the subject's eCRF.

### **7.1. Discontinuation of Study Treatment**

Subjects who discontinue, or are withdrawn from study treatment for any reason, will be encouraged to complete the final visit and provide any additional follow-up information as required by the study, unless the subject specifically indicates that they will not participate in any further evaluations.

Permanent study treatment discontinuation is required for any of the following:

- A 'serious' adverse reaction (ie, an SAE considered at least possibly related to the study treatment administration) in 1 subject.
  - Grade 4 AEs as per Common Terminology Criteria for AEs (CTCAE) v5.0 that are not expected in the context of underlying medical conditions.
  - The investigator considers study treatment discontinuation to be in the subject's best interest for any other reason.
  - Major protocol violation.
  - Symptoms of an intercurrent illness not consistent with the protocol requirements or that justify withdrawal.
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- The subject becomes pregnant.

Discontinuation of study treatment for abnormal liver function should be considered by the investigator when a subject meets one of the conditions outlined in Section 10.5.

Additional reasons for permanent study treatment discontinuation include, but are not limited to, the following:

- Subject/caregiver withdraws consent to receive study treatment.
- Death.

If a clinically significant cardiac finding is identified (including but not limited to changes from baseline in QTcF) after the start of study treatment, the investigator or a qualified designee will determine if the subject can continue in the study and if any change in management is needed.

The reason for study treatment discontinuation will be recorded.

No dose modifications or temporary treatment discontinuations are permitted in this study.

## **7.2. Subject Discontinuation/Withdrawal From the Study**

Subjects may withdraw from the study at any time at their own (or per caregiver's) request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

If the subject/caregiver withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such withdrawal of consent. If a subject/caregiver withdraws from the study, the subject/caregiver may request destruction of any samples taken and not tested, and the investigator must document this in the study site study records.

The reason for study discontinuation/withdrawal will be recorded. A subject may be discontinued from the study for the following medical or administrative reasons including, (but not limited to) the following:

### ***Noncompliance***

The subject is noncompliant with the protocol.

### ***Intercurrent Illness***

The subject has symptoms or an intercurrent illness that is not consistent with the protocol requirements or that justify withdrawal.

### ***Withdrawal by Subject***

Subjects will be free to discontinue from the study at any time.

***Adverse Event***

If a dosed subject suffers an AE that, in the judgment of the investigator, sponsor, or MM; presents an unacceptable consequence or risk to the subject, the subject will be discontinued from study treatment.

***Death***

In the event that a subject dies during the study, death will be the reason for discontinuation.

***Lost to Follow-up***

Every effort should be used to maintain contact with subjects during their participation in the study. A subject may be considered lost to follow-up if there is no response to at least 3 attempts to reach the subject by telephone and no response to a certified letter (or equivalent) sent to the last known address of the subject, if possible. Efforts to contact the subject should be noted in the source documentation.

***Met Withdrawal Criteria***

Discontinuation for safety and/or tolerability issues as outlined in Section 7.1.

***Other***

If the above reasons are not applicable, please use the “Other” option in the eCRF and provide the appropriate reason for subject withdrawal.

**8. STUDY ASSESSMENTS AND PROCEDURES****8.1. Screening (Day -28 to Day -1)**

Subjects should be screened within 28 days prior to administration of the first dose of study treatment on Day 1. Written consent must be obtained from each subject before the initiation of any screening procedure. A sufficient number of subjects will be screened to identify 48 subjects fulfilling all entry criteria.

Once written consent has been obtained, the following procedures will be performed at the Screening evaluation:

- Review inclusion/exclusion criteria.
  - Record demographics.
  - Record medical/surgical history (including history of exposure to COVID-19).
  - Record all prior medication/therapies.
  - Record concomitant medications/therapies
  - Perform a complete physical examination.
  - Measure the subject’s height, weight and waist circumference.
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- Measure the subject's vital signs.
  - Record an electrocardiogram (ECG).
  - Collect a blood sample for plasma AMM. Results will be used to determine eligibility for Inclusion Criterion #5.
  - Collect samples for chemistry, hematology, and urinalysis.
  - Perform a urinary drug screen including a screen for methadone at screening only.
  - Collect blood samples for hepatitis and HIV serology.
  - Record the Conn, MELD, HESA and C-P scores.
  - Record/collect AEs/SAEs (including AEs of special interest [AESI]) after the consent process is completed.
  - Perform a serum pregnancy test/follicle stimulating hormone (FSH) test (FSH is required for postmenopausal women).

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range (greater than 40 mIU/mL) may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Eligible subjects will be instructed about the restrictions on concomitant medication usage and other substances (see Section 6.5) and will be asked to return to the clinic for dosing. If deemed necessary, additional subjects may be requested to report to the clinic to serve as possible replacements for any subject(s) who become unavailable or who are later deemed ineligible to participate.

Subjects will be confined to the study site from Day -1. On Day -1, a urine pregnancy test will be performed on women of child-bearing potential to confirm that the subject did not become pregnant since the time of screening (up to 28 days before Day 1).

## 8.2. Randomization

After confirming that the inclusion and exclusion criteria are satisfied and after the screening visit procedures are completed, subjects will begin the study.

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### 8.3. Treatment Period (Week 1; Day 1 to Day 5/ET) and Day 6 (Discharge)

After randomization, subjects will enter the study, and receive active treatment (1 of 3 MNK6106 dose regimens or rifaximin) for 5 days. Subjects will be confined to the study center overnight during the treatment period and discharged on Day 6. The following procedures will be carried out on Days 1, 2, 3, 4 and 5 unless otherwise stated:

- Perform a limited physical examination (Day 1 only).
- Record the subject's weight and waist circumference (Day 1 and Day 6 only).
- Record the subject's vital signs (Day 1 through Day 6).
- Record ECG (Days 1, 3 and 5/ET only) at 1 hour after the last dose ( $\pm$  15 minutes). Complete the ECG prior to the PK sample collection if the timing is the same.
- Collect blood samples for plasma AMM (to be drawn on Days 1, 3 and 5/ET only, predose in the morning immediately before breakfast and 4 hours ( $\pm$  15 minutes) after the morning dose), as well as on the day of the final visit.
- Collect a blood sample for plasma PAA, ORN and PAGN (to be drawn on Days 1, 3 and 5/ET only). A baseline sample will be drawn prior to the first dose on Day 1 (within 15 minutes prior to the morning dose) and then prior to (with 10 minutes) and 1 hour ( $\pm$  15 minutes) after the last dose on Days 1, 3, and 5/ET.
- Collect a urine sample for PAGN. For each 24-hour collection following the first dose of the day, all urine will be collected during the specified intervals, with the last collection for Day 5/ET being collected on Day 6. A baseline urine sample will also be collected predose on Day 1.
- Collect samples for chemistry, hematology, (Days 1 through 6) and urinalysis (Days 1 through 5 only).
- Record the Conn, MELD, HESA and C-P scores (Days 1 through 6).
- Perform study drug dosing.
- Record all concomitant medications/therapies (Days 1 through 6).
- Record and assess AEs/SAEs, including AESI (Days 1 through 6).

On the Day 6 visit (discharge):

If no clinical or laboratory abnormalities are observed, subjects will be discharged from the study on the morning of Day 6. The 24-hour urine collection for PAGN will be completed on Day 6 at the end of confinement.

Additional follow-up visits will be scheduled if a subject shows any clinical or laboratory abnormalities at this visit, as deemed appropriate by the investigator/designee (classified as unscheduled visits).

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Generally, clinically significant abnormal laboratory values will be monitored periodically until resolution or until they are considered irreversible. If a subject discontinues from the study prematurely, then every attempt will be made to conduct all the above evaluations at the time of discontinuation and at the final visit (approximately 7 days after the last dose of study drug).

#### **8.4. Final Visit (Week 2)**

Subjects will return to the clinic site for the final visit. The final visit will be conducted approximately 7 days (+ 3 day window) after the end of the active treatment period.

The final visit window may be extended, due to extenuating circumstances, to 14 days after discussion with the sponsor.

The following procedures will be carried out at the final visit:

- Perform a complete physical examination.
- Record the subject's weight.
- Record the subject's vital signs.
- Collect a blood sample for plasma AMM.
- Collect samples for chemistry, hematology, and urinalysis.
- Perform a serum pregnancy test.
- Record the Conn, MELD, HESA and C-P scores.
- Record all concomitant medications/therapies.
- Record and assess AEs (including AESI)

#### **8.5. Pharmacodynamic and Pharmacokinetic Assessments**

##### **8.5.1. Pharmacodynamic Sampling**

Plasma AMM data are extremely important, but these samples are exquisitely sensitive. For this reason, great care must be taken with the collection, handling, processing, and storage of plasma AMM samples.

Samples for plasma AMM levels will be drawn at screening, on Days 1, 3 and 5/ET predose in the morning immediately before breakfast and 4 hours ( $\pm$  15 minutes) after the morning dose, and at the final visit.

Before the blood draw to collect a sample for venous AMM, place the collection tube on ice for at least 10 minutes. Immediately after drawing blood, *gently* invert the specimen approximately 8 to 10 times, place the specimen on wet ice, separate the plasma by refrigerated centrifugation as soon as possible, and freeze the plasma specimen for analysis at  $-70^{\circ}\text{C}$  or colder immediately after centrifugation. This specimen will be processed by the laboratory or by trained personnel

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per facility standard operating procedures. All plasma for AMM testing must be prepared and stored in a -70°C or colder freezer with the greatest speed feasible. All frozen samples will be transported to a laboratory testing site. Review the Laboratory Manual/sample handling guide for complete information.

Venous AMM draws are predicated on timing, which is of paramount importance; however, for subjects able to eat, it is preferable to obtain the blood sample prior to food intake (if feasible). *Because of the exquisite delicacy of this analyte stringent before drawing, blood draw and specimen processing parameters must be adhered to; documentation of each step of preanalytic specimen preparation and processing is required for each time point inclusive of date and time for each step recorded on the laboratory requisition and source documentation.* It is essential that venous AMM plasma samples be correctly prepared to avoid spurious results; if the specimen integrity is compromised by inappropriate handling, it would be preferable not to send that sample to the laboratory for analysis.

## **8.5.2. Pharmacokinetic Sampling (Plasma PAA, ORN and PAGN)**

### **8.5.2.1. Blood Sampling for Plasma PAA, ORN and PAGN Measurement**

Blood samples for analysis of PAA, ORN, and PAGN will be collected on the days and within the time windows specified below and in the Schedule of Study Events ([Table 1](#)) and shipped to the designated bioanalytical laboratory for analysis.

Blood samples for plasma concentration of PAA, ORN, and PAGN will be drawn prior to the first dose on Day 1 (within 15 minutes prior to morning dose) and then prior to (within 10 minutes) and 1 hour ( $\pm$  15 minutes) after the last dose on Days 1, 3, and 5/ET. The date and time of each sample collection will be recorded.

Peripheral venous blood samples (3 mL each) for analysis of plasma PAA concentrations will be drawn into pre-labeled VACUTAINER<sup>®</sup> tubes containing spray-dried potassium ethylene diaminetetraacetic acid by individual venipuncture (if possible) or a peripheral venous catheter. If a peripheral catheter is used, the catheter should be kept patent using a diluted heparin or saline drip; and prior to drawing each blood sample, a small volume of blood (~1 mL) should be withdrawn from the catheter using a syringe and then discarded so that an undiluted blood sample will be collected into the VACUTAINER<sup>®</sup> tube. The date and exact (clock) time that each blood sample is drawn will be recorded on the eCRF.

Immediately after collection, the blood collection tubes will be gently inverted 8 to 10 times to allow mixing with the anticoagulant and then kept on wet ice or refrigerated until centrifugation. Each blood sample will be centrifuged within 1 hour after blood collection in a refrigerated centrifuge at the following approximate parameters to separate the plasma: 4°C, 1000  $\times$  times gravity, and 15 minutes to separate the plasma. All the plasma for each sample will be equally divided and transferred to 2 storage tubes of adequate capacity and appropriately pre-labeled. Note that 4 mL NUNC CRYOVIAL<sup>®</sup> polypropylene biofreeze tubes (3.6 mL fill) with screw cap (Order # 366524) are preferred. The storage tubes will be labeled, at a minimum, with the sponsor company, protocol number, subject number, sample matrix, study day, scheduled sample

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time and tube number (eg, #1 or #2). The tubes will be stored in an upright position in a non-self-defrosting freezer with the temperature maintained at approximately  $-80^{\circ}\text{C}$  until shipment to the designated bioanalytical laboratory where samples will be stored at approximately  $-80^{\circ}\text{C}$ . Samples should be placed into the freezer within 2 hours of blood collection.

Every attempt will be made to collect samples at the protocol-specified times. The time of each sample will be recorded to the nearest minute.

### 8.5.3. Urine Sampling for PAGN Measurement

Urine collection (with start/end time and volume recorded) for measurement of PAGN, the study drug metabolite excreted in urine, will be collected for 24 hour intervals following the first dose of the day. Collect a baseline sample prior to initial dosing on Day 1.

- Urine collection will start at the initiation of study drug (predose urine sample).
- The next collection interval time starts immediately following the first dose administration of the day. For example, if the first dose of the day is administered at 8 AM, all urine volume will be collected through the following morning at approximately 8 AM.
- Measure total volume during each time interval, document collection start/stop times, obtain 2 aliquots and freeze immediately as per Laboratory Manual instructions.
- The final urine collection time interval on Day 5/ET is from the first dose on Day 5/ET until the following day, Day 6 (24 hour interval).

Urine samples for analysis of PAGN elimination will be collected into pre-labeled polyethylene containers for each collection interval. For each 24-hour collection, all urine will be collected during the specified intervals in the Schedule of Study Events (Table 1). Subjects will be asked to void at the end of each collection interval, but if a subject voids more than once in a single collection interval, each void will be added to the collection container for that interval and thoroughly mixed. The start and stop time of each collection will be recorded on the eCRF. Care should be taken to avoid spillage of urine outside of the collection vessel.

Once the collection for a time interval is complete, the container (with cumulative urine) will be gently shaken (for at least 30 seconds) to mix the urine thoroughly. The total urine volume in each collection interval will be measured and recorded. Two 5 mL aliquots of well-mixed urine from each collection (including the predose void) will then be transferred to 2 pre-labeled storage tubes of adequate capacity with screw caps. The storage tubes will be stored in an upright position in a freezer set at approximately  $-80^{\circ}\text{C}$  until shipment to the designated bioanalytical facility, where samples will be stored at approximately  $-80^{\circ}\text{C}$ . All storage tubes should be labeled with a preprinted label displaying, at a minimum, the sponsor company, protocol number, subject number, sample matrix, study day, scheduled collection interval and aliquot number (eg, #1 or #2). Samples should be placed into the freezer within 2 hours from the end of each collection interval.

#### **8.5.4. Bioanalytical Methodology**

Plasma samples will be analyzed for concentrations of ORN, PAA, and PAGN using a validated liquid chromatography–tandem mass spectrometry method. Urine samples will be analyzed for concentrations of PAGN using a validated liquid chromatography-tandem mass spectrometry method. In addition, plasma samples will be also analyzed for AMM concentrations. Please refer to the Bioanalytical Report for more direction.

#### **8.5.5. Sample Shipment**

Contact and shipping information for PK samples will be provided by the sponsor.

Following completion of the treatment period, the plasma and urine samples collected for PK assessments will be shipped to laboratories designated by Mallinckrodt for analysis. The first aliquot of each plasma and/or urine sample will be shipped together to the sponsor's designated bioanalytical or central laboratory, while the second aliquot of each sample will be retained at the investigator site until further instruction for shipment. The samples to be shipped will be clearly labeled for sample identification, inventoried and organized in sample boxes. A copy of the inventory documentation must accompany each shipment. The original inventory documentation will be kept at the study site. The sample boxes should be placed in a Styrofoam (1.5 inch-thick) shipping box with sufficient dry ice to maintain the samples in a frozen state for at least 2 days. Shipment will be made on Monday, Tuesday, or Wednesday to ensure weekday receipt by the sponsor's designated bioanalytical laboratory. Contact information will be provided to address any questions concerning the collection, handling or packaging of the samples. It is the responsibility of the investigator to ensure that all samples for interstate transport are appropriately handled (packaged and shipped). Failure to comply with these regulations can result in imprisonment and/or fines.

### **8.6. Safety Assessments**

All safety assessments will be performed at times outlined in the Schedule of Study Events (Table 1). Additional (unscheduled) safety assessments may be performed as needed.

#### **8.6.1. Medical and Surgical History**

Medical and surgical history will be obtained at screening. Medical history will include a review of the following systems: general, dermatological, respiratory, cardiovascular, gastrointestinal/hepatobiliary (including history of ascites and episodes of hepatic encephalopathy), genitourinary, gynecological, endocrine, musculoskeletal, hematological, neuropsychological, immune (allergies), and head, eyes, ears, nose, and throat. Historical and current medical conditions including date of last menstrual period for female subjects will be recorded.

#### **8.6.2. Electrocardiogram**

A 12-lead ECG will be obtained at screening and on Days 1, 3 and 5/ET at 1 hour after the last dose ( $\pm$  15 minutes). Complete the ECG prior to PK sample collection if the timing is the same.

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Subject needs to be supine for greater than 10 minutes prior to ECG. The investigator (or investigator's designee who is a physician) will interpret the ECG and will record a global interpretation of the ECG (ie, "Normal" or "Abnormal") on the tracing.

Each ECG tracing must also include the signature of the investigator and the date that the ECG was interpreted. If the global interpretation is abnormal, the investigator will indicate on the tracing whether the abnormality is clinically significant or not clinically significant. A copy of each ECG and the physician's assessment will be filed with the source documents.

### **8.6.3. Physical Examination**

The complete physical examination will be performed at screening and the final visit and will include evaluation of the head, eyes, ears, nose, throat, neck (including thyroid), cardiovascular system (including assessment of heart, peripheral pulses, presence or absence of edema), lungs, abdomen (including liver and spleen, bowel sounds), lymph nodes, musculoskeletal system (including spine, joints, muscles) neurological system (including cranial nerves, reflexes, sensation, strength), skin, extremities, and other conditions of note.

A limited physical examination will be performed during the treatment period (Day 1 and Day 6) and will include evaluation of lungs, cardiovascular system, abdomen, and extremities.

The findings of the physical examinations will be recorded. Any change from the screening physical examination that is considered clinically significant by the investigator will be recorded as an AE.

### **8.6.4. Height, Weight and Waist Measurements**

The subjects' height, body weight and waist measurement will be collected as outlined in the Schedule of Study Events ([Table 1](#)). Height may be measured with or without shoes. Any change from screening in a subject's body weight or waist measurement that is considered by the investigator to be clinically significant will be recorded as an AE.

### **8.6.5. Vital Signs**

Vital signs will be obtained after the subject has been seated for 5 minutes (minimum) and will include systolic and diastolic blood pressures, pulse rate, respiratory rate, and body temperature. The results, date, and time for all vital sign assessments will be recorded. Any change from the screening vital signs measurements considered clinically significant by the investigator will be recorded as an AE.

### **8.6.6. Clinical Laboratory Tests**

Required clinical laboratory tests are listed in [Section 10.2](#). Specific instructions for collection, processing, storage, and shipment of clinical laboratory samples will be provided in a separate laboratory manual.

Samples for laboratory testing at all visits may be collected under fasted or nonfasted conditions. Fasting early morning samples are preferred, but a random daytime sample is acceptable. The

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date and time of the sample collection must be documented on the laboratory report. Investigators must review and sign laboratory reports and document the clinical significance of each laboratory abnormality. New clinically significant laboratory abnormalities or clinically significant changes in laboratory values will be reported as AEs.

Hematology, serum chemistry, and urinalysis samples will be collected at the specific times starting at screening and throughout the study.

Samples will be taken for hepatitis and HIV serology at the time point outlined in the Schedule of Study Events ([Table 1](#)).

Subjects will also be screened for alcohol and a urinary drug screen will be performed at the time points outlined in the Schedule of Study Events ([Table 1](#)).

In addition, all female subjects of childbearing potential will have serum and urine pregnancy tests at the time points outlined in the Schedule of Study Events ([Table 1](#)). Results must be available prior to protocol mandated study treatment. Subjects with positive results at screening will be ineligible for study entry. Any female subject that becomes pregnant during the study will be immediately withdrawn and will have the pregnancy reported as per Section 10.4.

## **8.7. Adverse Events**

AEs will be recorded from signing of the ICF through the final visit and will be followed by the investigator until the AE is resolved or stabilized. All safety measures (which includes standard of care activities) should be provided by the study site to the subject. Any study site follow-up should be documented.

Refer to Section [10.3](#) for additional details on the handling of AEs and SAEs.

## **8.8. Treatment Overdose**

For this study, any dose of greater than 40 g within a 24-hour ( $\pm$  1 hour) time period will be considered an overdose.

MNK6106 should only be administered in accordance with the individual study protocol being conducted. There is the possibility that overdosage of MNK6106 can result in obtundation, hyperventilation, metabolic acidosis, large anion gap, progressive encephalopathy, cardiovascular collapse, and death. In the event of a suspected overdose, discontinue study treatment immediately and institute appropriate emergency medical monitoring and procedures. Consider hemodialysis in severe cases.

In the event of an overdose, the investigator or designee should perform the following:

- Contact the MM immediately.
- Closely monitor the subject for any AEs/SAEs and laboratory abnormalities until the treatment can no longer be detected (at least 3 days).
- Obtain a blood sample for PK analysis, if requested.

- Document the quantity of the excess dose, as well as the duration of the overdose.

## **8.9. Provisions for Remote Assessment Methods**

For emergency situations where there are extenuating circumstances that prohibit physically coming to the clinical site or when the safety of subjects may be compromised by physical visits to the site, remote assessments may be considered after discussion with the Sponsor.

## **9. STATISTICAL CONSIDERATIONS**

### **9.1. Sample Size Determination**

A total of 48 subjects will be randomized 1:1:1:1 to receive 1 of the 3 dosing regimens of MNK6106 or the comparator rifaximin for 5 days. This study is exploratory in nature. Prematurely discontinued subjects will not be replaced.

### **9.2. Populations for Analysis**

For the purposes of analysis, the following populations are defined

- The Modified Intent-to-Treat (mITT) Population will include all randomized subjects who receive at least 1 study treatment and who contribute any postbaseline PD data to the study.
- The Safety Population will include all subjects who receive 1 or more study treatments.
- The PK population will consist of all subjects in the Safety Population with at least 1 evaluable plasma concentration following treatment with MNK6106.

### **9.3. Statistical Hypothesis and Analyses**

This is an exploratory study and so there is no statistical hypothesis to test.

#### **9.3.1. Pharmacodynamic Analyses**

The descriptive statistics for PD variables, which are the plasma AMM level and the change of the plasma AMM level from baseline, will be used by treatment and by visit. The Mallinckrodt treatments will also be combined for display. The summaries will be based on the mITT population.

For continuous variables, descriptive statistics will include the following: the number of subjects reflected in the calculation (n), mean, median, standard deviation, minimum, and maximum. The 95% confidence intervals will be presented.

The graphic for PD variables by treatment and by visit will also be provided.

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### 9.3.2. Pharmacokinetic and Pharmacodynamic Analyses

The descriptive statistics for concentrations of PAA, ORN and PAGN will be used by treatment and by PK sampling time. Urinary recovery of PAGN will be summarized by treatment and study day. Descriptive statistics will include the following: the number of subjects reflected in the calculation (n), mean, median, standard deviation, minimum, and maximum. The 95% confidence interval will be presented.

Population PK modeling will be developed with the PK data obtained from the study such as concentration of PAA, ORN and PAGN. Sources of variability contributing to the PK will be identified. Exposure response relationships describing the safety and AMM levels following treatment with MNK6106 will be explored.

### 9.3.3. Analysis Methods for C-P, MELD, Conn and HESA Scores

Details of C-P, MELD, Conn and HESA scores are provided in Section 9.5.

## 9.4. Liver Function Classification

Liver function classification details are provided in Section 10.6.

## 9.5. Other Analyses

Summary statistical analyses will be provided for demographics, medical history, physical examination, social history, and risk factor variables at baseline.

For C-P, MELD, Conn, and HESA scores:

- The change and percent change of C-P, MELD, Conn, and HESA scores by visit will be summarized and analyzed using multiple imputation with an analysis of covariance model, respectively.
- The percent of subjects with C-P (A, B, C), MELD (40+, 30-39, 20-29, 10-19, <9), Conn (0,1,2,3,4) and HESA (0,1,2,3,4) will be provided by treatment group and by visit, respectively.
- The percent of subjects with improvement vs no change from baseline in the C-P category, MELD category based on category of 40+, 30 to 39, 20 to 29, 10 to 19, < 9, Conn and HESA will be analyzed by the Cochran–Mantel–Haenszel test stratified by baseline category, respectively.

The graphics for the 4 scores by treatment and by visit will be presented.

### 9.5.1. Safety Analyses

For safety variables, 2 observation periods are defined:

- The pretreatment period is defined as the time from signing the ICF until administration of the first dose of study drug.

- The treatment-emergent period is defined as the time from administration of the first dose of study drug to the end of the study.

Treatment-emergent AEs are defined as those that are not present at start of study drug dosing or that represent the exacerbation of a pre-existing condition during the treatment-emergent period.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) by preferred term within system organ class. The number of AEs and the number of subjects reporting AEs will be listed and summarized descriptively by body system, preferred term, severity, and causality for each treatment group. Both pretreatment and treatment-emergent AEs (events that are new in onset or aggravated in severity following treatment) will be included in all summaries. SAEs (including death) will be summarized. Treatment-emergent AEs leading to permanent treatment discontinuation will be listed and summarized by treatment group.

### **9.5.2. Treatment Exposure**

The duration of drug exposure during the study will be summarized by treatment and calculated as: (Date of last dose – date of first dose).

The number (%) of subjects randomized and exposed to drug will be presented by specific time periods for each treatment group. The time periods of interest will be specified in the statistical analysis plan.

Treatment compliance = (the number of doses of study drug taken during the exposure period)/(the number of planned study drug doses during the exposure period) × 100%.

A summary of the treatment compliance by treatment group will be provided.

### **9.5.3. Interim Analyses**

No interim analyses are planned for this study.

### **9.5.4. Handling Missing Data**

There is no imputation for missing PD data.

## **10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS**

### **10.1. Regulatory, Ethical, and Study Oversight Considerations**

#### **10.1.1. Regulatory and Ethical Considerations**

The study will be conducted in full compliance with applicable international, national and local regulatory requirements; FDA regulations including 21 CFR 314.106 and 312.120, (where applicable), ICH guidelines for Good Clinical Practice (GCP), in accordance with the ethical principles that have their origins in the Declaration of Helsinki, and European regulation 536/2014/EU (where applicable).

It is the responsibility of the investigator to obtain the approval of the IRB/IEC before the start of the study. A copy of the approval letter along with a roster of IRB/IEC members and compliance letter and/or the US Department of Health and Human Services general assurance number (if applicable) will be provided to the sponsor and retained as part of the study records. During the course of the study, the investigator will provide timely and accurate reports to the IRB/IEC on the progress of the study at appropriate intervals (not to exceed 1 year) and at the completion of the study. The investigator will notify the IRB/IEC of SAEs or other significant safety findings per IRB/IEC guidelines. The study protocol, ICF, advertisements (if any), and amendments (if any) will be approved by the IRB/IEC in conformance with international, national and local regulatory requirements.

Any change in the study plan requires a protocol amendment. An investigator must not make any changes to the study without IRB/IEC and sponsor approval except when necessary to eliminate apparent immediate hazards to the subjects. A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, but the change must then be documented in an amendment, reported to the IRB/IEC within 5 working days, and submitted to the appropriate regulatory agency in the required time frame, if appropriate.

#### **10.1.2. Financial Disclosure**

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after the end of the study.

#### **10.1.3. Subject Information and Consent**

The ICF must be approved by the sponsor and the IRB/IEC before any subject provides consent. The investigator will provide Mallinckrodt with a copy of the IRB/IEC-approved ICF and a copy of the IRB/IEC's written approval before the start of the study.

At screening (and at other times as may be required by the study or when changes are made to the consent form), subjects will read the consent form(s) and any privacy authorization as required by local and national regulations (such as the Health Insurance Portability and Accountability Act [HIPAA] authorization form), if applicable after being given an explanation of the study. Before signing the consent form(s) and the privacy authorization form (if applicable), subjects will have an opportunity to discuss the contents of these forms with study site personnel.

Subjects must assent understanding of and voluntarily sign these forms in compliance with ICH GCP and all applicable national and international regulations, before participating in any study-related procedures. Subjects will be made aware that they may withdraw from the study at any time. Subjects unable to give written informed consent must orally assent to the procedures and written informed consent must be obtained from a legally authorized representative in accordance with national and local laws, as applicable.

The ICF must contain all applicable elements of informed consent and the mandatory statements as defined by national and local regulations including confidentiality. All versions of each subject's signed ICF must be kept on file by the study site for possible inspection by regulatory authorities and/or authorized Mallinckrodt personnel. Signed copies of the consent form(s) and the HIPAA authorization form, if applicable, will be given to the subject.

The subjects will be made aware of their right to see and copy their records related to the study for as long as the investigator has possession of this information. If the subject withdraws consent and/or HIPAA authorization, the investigator can no longer disclose health information, unless it is needed to preserve the scientific integrity of the study.

#### **10.1.4. Data Protection**

Study subjects will be assigned a unique identifier by the sponsor or designee. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

The subjects must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure (in accordance with local and/or national law) must also be explained to the subject.

The subjects must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

#### **10.1.5. Dissemination of Clinical Study Data**

Aggregate results data will be provided to the study sites that actively enrolled subjects into this study after the clinical study report is finalized.

Study results and de-identified individual subject data will be released as required by local and/or national regulation.

#### **10.1.6. Data Quality Assurance**

The sponsor performs quality control and assurance checks on all clinical studies that it sponsors. Before enrolling any subjects in this study, sponsor personnel and the investigator review the protocol, the Investigator's Brochure, the eCRF and instructions for their completion, the procedure for obtaining informed consent, and the procedure for reporting AEs and SAEs. A qualified representative of the sponsor will monitor the conduct of the study.

The investigator will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to original source data and documents.

Each subject's eCRF should be fully completed and submitted to the sponsor in a timely fashion.

If an investigator retires, relocates, or otherwise withdraws from conducting the study, the investigator must notify the sponsor to agree upon an acceptable storage solution. Regulatory agencies will be notified with the appropriate documentation.

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Any significant changes in study personnel will require an updated statement of investigator (ie, FDA Form 1572) to be filed with the sponsor.

The investigator must notify their IRB/IEC of protocol deviations in accordance with local regulatory and IRB/IEC requirements.

The eCRF data are stored in a database and processed electronically. The sponsor's MM reviews the data for safety information. The data are reviewed for completeness, and logical consistency. Automated validation programs will identify missing data, out-of-range data, and other data inconsistencies. In addition, clinical laboratory data will be processed electronically. Requests for data clarification are forwarded to the study site for resolution.

#### **10.1.7. Source Documents**

All subject information recorded in the eCRF will be attributable to source data from the study site.

The investigator shall retain and preserve one copy of all data collected or databases generated in the course of the study, specifically including but not limited to those defined by GCP as essential. Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational medicinal product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained. Prior to destruction of any study essential documents, the investigator must first obtain written approval from the sponsor.

#### **10.1.8. Study and Site Closure**

The sponsor may suspend or terminate the study or part of the study at any time for any reason. If the investigator suspends or terminates the study, the investigator will promptly inform the sponsor and the IRB/IEC and provide them with a detailed written explanation. Upon study completion, the investigator will provide the sponsor, IRB/IEC, and regulatory agency with final reports and summaries as required by regulations. Study termination and follow-up will be performed in compliance with the sponsor or designee standard operating procedures.

The sponsor, investigator, or local and national regulatory authorities may discover conditions during the study that indicate that the study or study site should be terminated. This action may be taken after appropriate consultation between the sponsor and investigator.

Conditions that may warrant termination of the study/study site include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study.

- The decision on the part of the sponsor to suspend or discontinue testing or evaluation of the study treatment.
- Failure of the investigator to enroll subjects into the study at an acceptable rate.
- Failure of the investigator to comply with pertinent regulations.
- Submission of knowingly false information from the study site to the sponsor, study monitor, or local and national regulatory authorities.
- Insufficient adherence to protocol requirements.

**10.1.9. Publication Policy**

The sponsor's decision to publish or otherwise publicly communicate the results of this study will be made in accordance with all applicable laws, regulations, and sponsor policies regarding publication and communication of clinical study results.

Terms and provisions of the investigator's publication rights are governed by the Publication Section in the Clinical Trial Agreement.

## 10.2. Clinical Laboratory Tests

<b>Serum Biochemistry</b>	
Alanine aminotransferase	Creatinine
Albumin (total)	Gammaglutamyltransferase
Alkaline phosphatase	Phosphorus
Aspartate aminotransferase	Lactate dehydrogenase
Bicarbonate (or CO <sup>2</sup> )	Potassium
Bilirubin (total, conjugated [direct], and unconjugated [indirect])	Protein (total)
Blood urea nitrogen	Serum glucose
Calcium	Sodium
Chloride	Uric acid
<b>Hematology</b>	
Absolute differential count (neutrophils, lymphocytes, monocytes, eosinophils, basophils)	
Hematocrit	Platelet count
Hemoglobin	Red blood cell count
Mean corpuscular hemoglobin	Reticulocyte count
Mean corpuscular hemoglobin concentration	White blood cell count
Prothrombin time/INR	Mean corpuscular volume
<b>Urinalysis</b>	
Blood	pH
Glucose	Protein
Ketones	Specific gravity
Leukocyte esterase	Nitrites
<b>Other Analyses</b>	
Serum pregnancy tests (females)	FSH test (required for postmenopausal women)
Urine pregnancy test (females of childbearing potential)	
<b>Serology</b>	
Hepatitis B surface antigen	Hepatitis B core antibody
HIV	Hepatitis C virus (HCV) antibody
HCV polymerase chain reaction testing will be performed only for subjects positive for HCV.	
<b>Urine Drugs of Abuse and Alcohol Screen (local laboratory only)</b>	
Amphetamines	Alcohol
Barbiturates	Methadone (at screening only)
Benzodiazepines	Opiates
Cannabinoids	Cocaine

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### **10.3. Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up and Reporting**

#### **10.3.1. Safety**

For safety information about MNK6106, refer to the most recent version of the Investigator's Brochure.

#### **10.3.2. Definitions**

##### ***Adverse Event***

An AE is any untoward or undesirable medical occurrence in a subject who is administered a study treatment, which does not necessarily have to have a causal relationship with this treatment. Examples of AEs include but are not limited to:

- Clinically significant laboratory findings.
- Clinically significant changes in physical examination findings.
- An AE occurring due to study treatment overdose whether accidental or intentional.
- An AE occurring from study treatment abuse.
- An AE associated with study treatment withdrawal.
- Unexpected AE.

An unexpected AE is defined as an AE, the nature and severity of which is not consistent with the applicable product information in the most recent version of the Investigator's Brochure.

##### **Serious Adverse Event**

An SAE is defined as any untoward medical occurrence that at any dose results in any of the following outcomes:

- Death.
- Life-threatening AE.
- Inpatient hospitalization or prolongation of existing hospitalization.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Results in a congenital anomaly/birth defect.
- Other serious (important medical events).

##### ***Death***

Death is an outcome of an event. The cause of death should be recorded and reported on the SAE form. All causes of death must be reported as SAEs. The investigator should make every effort to

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obtain and send death certificates and autopsy reports to the sponsor or designee, or state not available.

### ***Life-Threatening Event***

An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. For example, hepatitis that resolved without evidence of hepatic failure would not be considered life threatening, even though hepatitis of a more severe nature can be fatal. Similarly, an allergic reaction resulting in angioedema of the face would not be life threatening, even though angioedema of the larynx, allergic bronchospasm, or anaphylaxis can be fatal.

### ***Hospitalization***

Hospitalization is defined as an official admission to a hospital. Hospitalization or prolongation of a hospitalization constitutes a criterion for an AE to be serious. The following situations should not be reported as SAEs:

- A hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol.
- A hospitalization or prolongation of hospitalization is part of a routine procedure followed by the center (eg, stent removal after surgery). This should be recorded in the study file.
- A hospitalization for a pre-existing condition that has not worsened.

### ***Important Medical Events***

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

AEs (serious or non-serious) that commonly occur in the study population or background regimen will be considered anticipated events. Such events include known consequences of the condition under investigation (eg, symptoms, disease progression) and other events that may be common in this study population. Anticipated events are to be recorded on the eCRF and reported as SAEs when serious. These SAEs will not be expedited to health authorities, but rather, included in aggregate safety reports.

### 10.3.3. Adverse Event and Serious Adverse Event Classifications

The descriptions and grading scales found in CTCAE v5.0 ([U.S. HHS CTCAE Version 5.0, 2017](#)) will be utilized for AE reporting.

#### *Study Drug Relatedness*

The following classifications should be used when evaluating the relationship of AEs or SAEs to study treatment ([Table 3](#)).

**Table 3: Adverse Event Relationships**

<b>Relationship</b>	<b>Definition</b>
Not Related	No relationship between the AE and the administration of study treatment; the AE cannot be explained by other etiologies such as concomitant medications or subject's clinical state.
Unlikely Related	The current state of knowledge indicates that a relationship to study treatment is unlikely.
Possibly Related	An AE that follows a plausible temporal sequence from administration of the study treatment to the start of the AE and follows a known response pattern to the suspected study treatment. The reaction might have been caused by the subject's clinical state or concomitant medications.
Related	The AE that follows a plausible temporal sequence from administration of the study treatment to the start of the AE and follows a known response pattern to the study treatment. The suspected causality can be confirmed with a positive re-challenge test or supporting laboratory data.

#### *Severity Assessment*

For purposes of consistency, if required, the investigator may use the severity grades presented in [Table 4](#).

**Table 4: Adverse Event Severity Grades**

<b>Grade</b>	<b>Definition</b>
Grade 1	Mild AE
Grade 2	Moderate AE
Grade 3	Severe AE
Grade 4	Life-threatening AE
Grade 5	Death

Not all grades are appropriate for all AEs. In particular, Grade 5 (Death) is not appropriate for all AEs and therefore will not be considered an option for grading severity of AEs; instead, death, if it occurs, should be recorded as the outcome of a serious AE.

To ensure there is no confusion or misunderstanding of the difference between the terms “serious” and “severe,” which are not synonymous, the following note of clarification is provided:

The term “severe” is used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical importance (such as a severe headache). This is not the same as “serious,” which is based on the subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

If an AE increases in severity (eg, from moderate to severe); decreases in severity (eg, changes from moderate to mild); or if there is a change in seriousness, a new AE will be opened, and the original AE will be closed. If an AE is still ongoing at the time of a subject’s completion of the Final Visit, the resolution/stop date and time is left blank.

#### 10.3.4. Adverse Event and Serious Adverse Event Recording and Reporting

AEs and SAEs will be recorded from signing of the ICF through completion of the final visit. The investigator is required to record the AE or SAE regardless of the severity of the event or its relationship to study treatment. The investigator must follow up on all AEs and SAEs reported to have occurred through the final visit until the event has resolved or stabilized or at such time the investigator refers the subject to a nonstudy physician. The investigator will document the further follow-up information in the subject’s source document.

During the period specified above, the investigator will:

- Record all AEs and SAEs from the signing of the ICF through the completion of the final visit.
- Report all SAEs on an SAE Report Form to Mallinckrodt Global Pharmacovigilance or designee.
- Report all pregnancies to Mallinckrodt Global Pharmacovigilance or designee on the appropriate form.
- Submit any Expedited Safety Report or Suspected Unexpected Serious Adverse Reaction from Mallinckrodt Global Pharmacovigilance or designee to the IRB/IEC.

The reporting requirements for AEs are summarized in [Table 5](#).

**Table 5: Reporting Requirements for Adverse Events**

Seriousness	Reporting Time	Type of Report
All Serious	Within 24 hours of first knowledge of event	Initial report on the SAE Form, appropriate eCRF, and source document
	Within 24 hours of receipt of follow-up information	Follow up report on the SAE Form, appropriate eCRF, and source document

**Table 5: Reporting Requirements for Adverse Events (Continued)**

<b>Seriousness</b>	<b>Reporting Time</b>	<b>Type of Report</b>
Nonserious	Per case report form submission procedure	Appropriate eCRF and source document

### 10.3.5. Adverse Events of Special Interest

An AESI is an event of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. These will be reported on the AE form including start date and time, stop date and time, severity, relation to study drug, any action taken with the study drug, and outcome of the event.

CNS or abuse-related AEs will also be considered as AESIs for this study, based on the recommendation of the FDA to closely monitor these events and report time of onset, duration of the event, dose of drug taken, severity, and outcome. The eCRF page for these AESIs will be designed to capture the above data points. Narratives for all AESIs will be prepared from the data reported on the eCRFs. PK values for each individual subject who experienced these AEs will be provided to understand if there is a temporal correlation between drug plasma levels and AEs.

CNS AESIs include somnolence, fatigue, lightheadedness, headache, dysgeusia, hypoacusis, disorientation, impaired memory, peripheral neuropathy, euphoria, impaired cognition, attention, mood, psychomotor effects, inappropriate affect, and aberrant behavior.

The following are the abuse-related AESIs: abuse, overuse, lost/stolen/missing or unaccounted product, any aberrant behavior in subjects who drop out of the study supposedly due to lack of efficacy, lost to follow-up, noncompliance or overcompliance. Also, any use of a study treatment by individuals other than enrolled subjects need to be reported, if any.

### 10.4. Pregnancy Reporting

Certain information regarding pregnancy, although not considered an SAE, must be recorded, reported, and followed up as indicated. This includes the following:

Subjects should not become pregnant during the study. If a female subject, or the female partner of a male subject, becomes pregnant during any active treatment period, study treatment must be discontinued immediately and the investigator must report the pregnancy by submitting the appropriate form to Mallinckrodt Global Pharmacovigilance, or designee, within 24 hours of confirmation of a pregnancy (ie, positive serum pregnancy test result). The outcome of pregnancy (eg, spontaneous abortion, live birth, still birth, congenital anomalies, birth defects) must be reported by submitting the appropriate form to Mallinckrodt Global Pharmacovigilance, or designee, within 24 hours of the pregnancy outcome being submitted to the study site. If the pregnancy results in a live birth, a post-delivery follow-up will be performed at least 28 days

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after the baby is born and must be reported to Mallinckrodt Global Pharmacovigilance, or designee, within 24 hours of the study site becoming aware of the follow-up information.

### **10.5. Liver Safety: Suggested Actions and Follow-up Assessments**

All events of alanine aminotransferase at least  $3 \times$  the upper limit of normal (ULN) and with total bilirubin at least  $2 \times$  ULN (greater than 35% direct bilirubin) or alanine aminotransferase at least  $3 \times$  ULN and INR greater than 1.5 (if INR is measured) which may indicate severe liver injury must be reported as an SAE as outlined in Section 10.3.4 (excluding studies of hepatic impairment or cirrhosis).

In subjects with cirrhosis and elevated transaminases and bilirubin at baseline, subjects should be discontinued if their alanine aminotransferase or total bilirubin level doubles, or if they develop new symptoms suggestive of drug induced liver injury (jaundice, malaise, abdominal pain, unexplained nausea and anorexia) or decompensation events during the study.

### **10.6. Clinical Function Scoring**

#### **10.6.1. Conn Score**

Subjects will be assessed at screening and every day using the Conn score, to determine if they have a worsening in HE, indicated as an increase in their score by 1 or more grades. The Conn score (also known as the West Haven Criteria) is an extensively used grading scale for assessment of HE severity. It consists of a 5-point scale (Grade 0 to 4) as follows:

- Grade 0: no apparent personality or behavioral abnormality;
- Grade 1: trivial lack of awareness, euphoria or anxiety; shortened attention span; impairment of addition or subtraction;
- Grade 2: lethargy; disorientation for time; obvious personality change; inappropriate behavior;
- Grade 3: somnolence to semi-stupor, responsive to stimuli; confused; gross disorientation; bizarre behavior;
- Grade 4: coma; unable to test mental state.

#### **10.6.2. HESA Score**

The HESA score will be assessed at the screening visit to assess study eligibility, and will also be assessed on Days 1 through 5/ET, to determine if subjects have a worsening in their condition. The HESA implements objective ways of measuring the parameters of the West Haven scale. The HESA utilizes clinical indicators combined with validated neuropsychological tools and well-defined criteria for each stage (see HESA algorithm in Section 10.8). The use of the HESA is still limited and its metric characteristics have not been fully analyzed. One favorable characteristic of the HESA is that it identifies low grades of HE precisely. It consists of a 5-point scale (Grade 0 to 4), with 4 indicating most severe ([Hassanein et al, 2008](#)).

### 10.6.3. MELD Score

Subjects will be assessed at the screening visit to assess eligibility into the trial. Additionally, subjects will be assessed at each visit using the MELD score, to determine if they have a worsening in their condition. MELD is a scoring system for assessing the severity of chronic liver disease. It was initially developed to predict mortality within 3 months of surgery in patients who had undergone a transjugular intrahepatic portosystemic shunt procedure and was subsequently found to be useful in determining prognosis and prioritizing for receipt of a liver transplant. MELD uses the patient's values for serum bilirubin, serum creatinine, and the INR for prothrombin time to predict survival. It is calculated using the following formula:

$$\text{MELD} = 3.78 \times \ln[\text{serum bilirubin (mg/dL)}] + 11.2 \times \ln[\text{INR}] + 9.57 \times \ln[\text{serum creatinine (mg/dL)}] + 6.43$$

### 10.6.4. Child-Pugh Score

Subjects will be assessed at screening and every day using the C-P score, in order to assess the prognosis and liver safety evaluations. The C-P score (or the Child–Turcotte–Pugh score or Child Criteria) is used to assess the prognosis of chronic liver disease, mainly cirrhosis. Although it was originally used to predict mortality during surgery, it is now used to determine the prognosis, as well as the required strength of treatment and the necessity of liver transplantation. The score employs 5 clinical measures of liver disease. Each measure is scored 1 to 3, with 3 indicating the most severe damage.

The C-P classification scheme shown in [Table 6](#) will be used to define 3 subgroups of subjects based on their liver function. Each subject will be included in one of the following liver function subgroups based on observations and laboratory values at the baseline evaluation:

- C-P Class A (5-6 points): mild liver disease.
- C-P Class B (7-9 points): moderate liver disease.
- C-P Class C (10-15 points): severe liver disease.

**Table 6: C-P Classification for Severity of Liver Disease**

Measure	1 point	2 points	3 points
Encephalopathy	None	Minimal	Advanced (coma)
Ascites	Absent	Controlled	Refractory
Total bilirubin (μmol/L)	< 34	34 to 50	> 50
Total bilirubin (mg/dL)	< 2	2 to 3	> 3
Albumin (g/dL)	> 3.5	2.8 to 3.5	< 2.8
Prothrombin time (sec)	< 4	4 to 6	> 6
INR equivalent (approximate)	< 1.7	1.7 to 2	> 2

**Table 6: C-P Classification for Severity of Liver Disease (Continued)**

Measure	1 point	2 points	3 points
References:			
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**10.7. Common Terminology Criteria for AEs**

CTCAE v5.0 will be used to report adverse events in this study ([U.S. HHS CTCAE Version 5.0, 2017](#)).

**10.8. Stages of Hepatic Encephalopathy According to Hepatic Encephalopathy Scoring Algorithm (HESA)**

**HESA Grading Sheet**

Time  __  :  __    24 Hour Clock	
4	<input type="radio"/> No eyes opening <input type="radio"/> No verbal/voice response <input type="radio"/> No reaction to simple commands
	All applicable ⇒ Grade 4      otherwise continue
3	<input type="radio"/> Somnolence <input type="radio"/> Confusion <input type="radio"/> Disoriented to place <input type="radio"/> Bizarre Behavior / Anger/Rage <input type="radio"/> Clonus/Rigidity / Nystagmus / Babinsky <input type="checkbox"/> Mental Control = 0
	3 or more applicable ⇒ Grade 3      otherwise continue
2	<input type="radio"/> Lethargy <input type="radio"/> Loss of time <input type="radio"/> Slurred Speech <input type="radio"/> Hyperactive Reflexes <input type="radio"/> Inappropriate Behavior <input type="checkbox"/> Slow responses <input type="checkbox"/> Amnesia of recent events <input type="checkbox"/> Anxiety <input type="checkbox"/> Impaired simple computations
	2 or more <input type="radio"/> and 3 or more <input type="checkbox"/> applicable ⇒ Grade 2      otherwise continue
1	<input type="radio"/> Sleep disorder / Impaired Sleep Pattern <input type="radio"/> Tremor <input type="checkbox"/> Impaired complex computations <input type="checkbox"/> Shortened attention span <input type="checkbox"/> Impaired construction ability <input type="checkbox"/> Depression
	4 or more applicable ⇒ Grade 1      otherwise Grade 0
Hepatic Encephalopathy Grade  __	



Reference: [Hassanein et al, 2008](#).

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