| | |
|---|---|
| **Official Protocol Title:** | A Phase 2a Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of MK-4482 in Healthy Participants Inoculated with Experimental Influenza Virus |
| **NCT number:** | NCT05818124 |
| **Document Date:** | 14-Aug-2023 |

# TITLE PAGE

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**Protocol Title:** A Phase 2a Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of MK-4482 in Healthy Participants Inoculated with Experimental Influenza Virus

**Protocol Number:** 019-01

**Compound Number:** MK-4482

**Sponsor Name:** Merck Sharp & Dohme LLC (hereafter called the Sponsor or MSD)

**Legal Registered Address:**

126 East Lincoln Avenue
P.O. Box 2000
Rahway, NJ 07065 USA

**Regulatory Agency Identifying Number(s):**

| | |
|---|---|
| NCT | Not Applicable |
| EU CT | Not Applicable |
| EudraCT | Not Applicable |
| JRCT | Not Applicable |
| WHO | Not Applicable |
| UTN | Not Applicable |
| IND | Not Applicable |

**Approval Date:** 14 August 2023

## Sponsor Signatory

| | |
|---|---|
| Typed Name:<br>Title: | Date |

**Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).**

## Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

| | |
|---|---|
| Typed Name:<br>Title: | Date |

## DOCUMENT HISTORY

| Document | Date of Issue | Overall Rationale |
|---|---|---|
| Amendment 01 | 14-AUG-2023 | The key reason for this amendment is to revise inclusion criterion #6 to align with contraception requirements for the overall MK-4482 program. Clarifications the PCL were also incorporated into the amendment. |
| Original Protocol | 10-FEB-2023 | Not applicable |

## PROTOCOL AMENDMENT SUMMARY OF CHANGES

**Amendment:** 01

### Overall Rationale for the Amendment:

The key reason for this amendment is to revise inclusion criterion #6 to align with contraception requirements for the overall MK-4482 program. Clarifications from a PCL were also incorporated into the amendment.

### Summary of Changes Table

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| **Primary Reason for Amendment** | | |
| Section 5.1: Inclusion Criteria | Added acceptable user dependent contraception methods for WOCBP to inclusion criterion #6. | Text was revised to align with contraception requirements for the overall MK-4482 program. |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| **Additional Changes** | | |
| Throughout | Formatting and other editorial changes | Editorial modifications were incorporated to address minor errors including corrections in formatting. |
| Section 1.3 Schedule of Activities Parts 1 and 2 | Moved the 'X' for Calculation of eGFR to Day -2/-1 rather than Day -90 | Calculation of eGFR will occur upon admission for study specific eligibility. |
| Section 1.3 Schedule of Activities Parts 1 and 2 | Moved the 'X' for Assignment of Study-Specific Screening Number to Day -2/-1 rather than Day -90 | The study specific screening number is assigned after study specific consent on Day -2/-1. |
| Section 1.3 Schedule of Activities Part 2 only | Replaced 'Assignment of Allocation Number' with 'Assignment of Randomization Number' | Participants in Part 2 will receive a randomization number prior to dosing rather than an allocation number (as in Part 1). |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 1.3 Schedule of Activities Parts 1 and 2 | Removed the 'X' under 'Serum for Exploratory Immunological Biomarkers' for Study Days 7, 8, and 28 | Based on newly available information, collections for PD assessment at these time points are no longer needed to support the study objectives. |
| Section 1.3 Schedule of Activities Parts 1 and 2 | Added note that Serum for Exploratory Immunological Biomarker samples for Study Days 1-6 are collected in the PM | Clarification for when the sample is collected was provided. |
| Section 1.3 Schedule of Activities Parts 1 and 2 | Removed 'X' for Days 1-8 Nasal Sample for Mucosal Antibodies and Inflammatory Markers' | Based on newly available information, collections for respiratory samples at these time points are no longer needed to support the study objectives. |
| Section 1.3 Schedule of Activities Parts 1 and 2 | Removed the 'X' for AE review at the timepoint for Day 0, challenge virus | AE review will not occur on Day 0, challenge virus. |
| Section 1.3 Schedule of Activities Parts 1 and 2 | Added 'and global impression questions' to row for FLU-PRO Plus© Questionnaire | Text was added to clarify that data from the FLU-PRO Plus© will be analyzed based on multiple time points, in addition to 1- item patient global impression questions, as described in Section 8.4.2 of the study protocol |
| Synopsis 1.1 Intervention Groups and Duration<br>Section 6.1 Study Intervention Administered | Replaced unit dose strength from 800 mg to 200 mg for MK-4482 | A typographical error in the unit dose column was corrected. The dosage level is 800 mg (4 x 200-mg capsules). |
| Section 6.1 Study Intervention Administered | Replaced cross references for Table 2 and Table 3 with Table 3 and Table 4 | A typographical error in the cross-referencing was corrected. |
| Section 10.5.2 Contraception Requirements | Revised table to include highly effective contraceptive methods that are user dependent. | The table was revised to align with contraception requirements for the overall MK-4482 program. |

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## LIST OF TABLES

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# 1 PROTOCOL SUMMARY

## 1.1 Synopsis

**Protocol Title:** A Phase 2a Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of MK-4482 in Healthy Participants Inoculated with Experimental Influenza Virus

**Short Title:** Phase 2a Influenza Human Challenge Study of MK-4482 in Healthy Participants

**Acronym:** Not applicable.

**Hypotheses, Objectives, and Endpoints:**

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

This study will be conducted in healthy participants.

| **Primary Objective** | **Primary Endpoint** |
|---|---|
| Part 1 | |
| Objective 1: To evaluate the infectivity rate of the influenza challenge virus in healthy adult participants. | Day 1 PM to planned discharge, Day 2 PM to planned discharge:<br>• Quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR)-confirmed influenza infection |
| Objective 2: To assess the safety of the influenza challenge virus in healthy adult participants | Viral challenge to Follow-up Visit:<br>• Adverse events (AEs) related to viral challenge |

| | |
|---|---|
| Part 2 | |
| Objective 3: To evaluate the effectiveness of MK-4482 (800 mg Q12H for 5 days) as a post-exposure intervention in reducing influenza viral load, as compared to placebo.<br><br>Hypothesis (Post-exposure prophylaxis [PEP]): MK-4482 (800 mg Q12H for 5 days), initiated 12 h following intranasal inoculation of the influenza challenge virus reduces the peak viral load (as determined by quantitative viral culture) compared to placebo.<br><br>Hypothesis (Treatment): MK-4482 (800 mg Q12H for 5 days), initiated 2 days following intranasal inoculation of the influenza challenge virus reduces the viral load AUC (as determined by quantitative viral culture) compared to placebo. | PEP (MK-4482) Day 1 PM to planned discharge:<br><br>• Peak viral load (PVL) (by quantitative viral culture)<br><br>Treatment (MK-4482) First dose of study drug to planned discharge:<br><br>• Area under the viral load-time curve (VL-AUC) (by quantitative viral culture) |
| **Secondary Objectives** | **Secondary Endpoints** |
| Part 1 | |
| Objective 4: To characterize the virological profile of the influenza challenge virus in healthy adult participants | Day 1 PM to planned discharge, Day 2 PM to planned discharge:<br>• Quantitative viral culture-confirmed influenza infection<br>• VL-AUC (qRT-PCR and quantitative viral culture)<br>• PVL (qRT-PCR and quantitative viral culture)<br>• Duration of quantifiable influenza (qRT-PCR and quantitative viral culture) |

| | |
|---|---|
| Objective 5: To characterize the clinical symptom profile of the influenza challenge virus in healthy adult participants. | Day 1 AM to planned discharge, Day 2 middle of day to planned discharge:<br>• Area under the total symptom score-time curve (TSS-AUC)<br>• Peak total symptom score (TSS)<br>• Daily maximum TSS<br>• Duration (days) of Grade ≥2 symptoms<br>• Time (days) to symptom resolution<br>• Time (days) to peak daily maximum TSS |
| <u>Part 2</u> | |
| Objective 6: To estimate the effect of MK-4482 (800 mg Q12H for 5 days) as post-exposure prophylaxis (initiated 12 h following intranasal inoculation of influenza challenge virus) or as treatment (initiated 2 days following intranasal inoculation of influenza challenge virus) on the reduction of influenza viral load, as compared to placebo.<br><br>Objective 7: To estimate the effect of oseltamivir (75 mg Q12H for 5 days) as treatment (initiated 2 days following intranasal inoculation of influenza challenge virus) on the reduction of influenza viral load, as compared to placebo | PEP (MK-4482) – Virology: Day 1 PM to planned discharge:<br>Symptoms and temperature Day 1 AM to planned discharge:<br>• VL-AUC (qRT-PCR and quantitative viral culture)<br>• PVL (qRT-PCR)<br>• qRT-PCR-confirmed influenza infection<br>• qRT-PCR-confirmed symptomatic influenza infection<br>• qRT-PCR-confirmed moderately severe symptomatic influenza infection<br>• qRT-PCR-confirmed febrile influenza infection<br>• Quantitative viral culture-confirmed influenza infection<br>• Quantitative viral culture-confirmed symptomatic influenza infection<br>• Duration of quantifiable influenza (qRT-PCR and quantitative viral culture)<br>• Time (days) to confirmed negative test (qRT-PCR and quantitative viral culture) |

| | |
|---|---|
| | • Time (days) to peak viral load (qRT-PCR and quantitative viral culture)<br><br>Treatment (MK-4482 and oseltamivir) – first dose study drug to planned discharge:<br><br>• VL-AUC (qRT-PCR and quantitative viral culture)<br>• PVL (quantitative viral culture and qRT-PCR)<br>• Duration of quantifiable influenza (qRT-PCR and quantitative viral culture)<br>• Time (days) to confirmed negative test (qRT-PCR and quantitative viral culture)<br>• Time (days) to peak viral load (qRT-PCR and quantitative viral culture) |
| Objective 8: To evaluate the effect of MK-4482 (800 mg Q12H for 5 days) as PEP (initiated 12 h following intranasal inoculation of influenza challenge virus) or as treatment (initiated 2 days following intranasal inoculation of the influenza challenge virus) on the course of clinical symptoms following intranasal inoculation with the influenza challenge virus, compared to placebo<br><br>Objective 9: To evaluate the effect of oseltamivir (75 mg Q12H for 5 days) as treatment (initiated 2 days following intranasal inoculation of influenza challenge virus) on the course of clinical symptoms following intranasal inoculation with the influenza challenge virus, compared to placebo | PEP (MK-4482) – Day 1 AM to planned discharge;<br>Treatment (MK-4482 and oseltamivir) – first dose study drug to planned discharge:<br>• TSS-AUC<br>• Peak TSS<br>• Daily maximum TSS<br>• Duration (days) of Grade ≥2 symptoms<br>• Time (days) to symptom resolution<br>• Time (days) to peak daily maximum TSS |

| | |
|---|---|
| Objective 10: To assess the safety and tolerability of MK-4482 (800 mg Q12H for 5 days) | PEP (MK-4482) and Treatment (MK-4482) – from first dose of study drug to Follow-up Visit:<br>• All AEs |
| Objective 11: To monitor the safety of the influenza challenge virus in healthy adult participants | Viral challenge to Follow-up Visit:<br>• AEs related to viral challenge<br>• Concomitant medication use |
| Objective 12: To assess the plasma PK of NHC following administration of MK-4482 (800 mg Q12H for 5 days) | PEP (MK-4482) and Treatment (MK-4482):<br>• NHC Cmax, Tmax, t1/2, AUC0-12hr, AUC0-last, Ctrough following multiple dose administration of MK-4482 |

**Overall Design:**

| | |
|---|---|
| Study Phase | Phase 1 |
| Primary Purpose | Treatment |
| Indication | Influenza |
| Population | Serosuitable healthy male and female participants 18 to 55 years (inclusive) of age |
| Study Type | Interventional |
| Intervention Model | This is a single site study. |
| Type of Control | Placebo |
| Study Blinding | Double-blind |
| Blinding Roles | Participants or Subjects<br>Investigator<br>Sponsor |
| Estimated Duration of Study | The Sponsor estimates that the study will require approximately 3 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact. |

## Number of Participants:

Approximately 160 participants will be allocated/randomized.

## Intervention Groups and Duration:

| Arm Name | Intervention Name | Unit Dose Strength(s) | Dosage Level(s) | Route of Administration | Regimen/ Treatment Period/ Vaccination Regimen | Use |
|---|---|---|---|---|---|---|
| Active | MK-4482 | 200 mg | 800 mg | Oral | MK-4482 PEP Q12H x 5 days<br><br>MK-4482 Treatment: Q12H x 5 days | Test Product |
| Placebo | Placebo | N/A | N/A | Oral | Matched Placebo: Q12H x 7 days<br><br>MK-4482 Treatment: Q12H Day 5 PM and Day 6<br><br>MK-4482 Treatment: Q12H Day 0 PM and Day 1 | Placebo |
| Placebo | Placebo | N/A | N/A | Oral | Oseltamivir Treatment: Q12H Day 0 PM and Day 1 | Placebo |
| Comparator | Oseltamivir | 75 mg | 75 mg | Oral | Oseltamivir Treatment: Q12H x 5 days | Comparator |
| Virus Inoculation | Influenza A Virus | Approximately 5 to 7 TCID50* | Approximately 5 to 7 TCID50* | Intranasal | Single Administration | Challenge Agent |

PEP = Post-exposure prophylaxis; Q12H = every 12 hours

*The Influenza A/France/759/21 [H1N1] challenge virus used in Part 1 will be prepared to have an inoculum concentration of between approximately 5 and 7 Log10 tissue culture infective dose 50% (TCID50/mL). The Influenza A challenge virus used in Part 2 will either be Influenza A/France/759/21 [H1N1] (inoculum concentration of between approximately 5 and 7 Log10 TCID50/mL) or an alternative virus eg, A/Perth/16/2009 [H3N2] or A/California 2009-like [H1N1]; the inoculum concentration for an alternative virus is provided in Appendix 11, and final details of the virus will be outlined in the Analytical Plan.

| | |
|---|---|
| Total Number of Intervention Groups/Arms | 4 |
| Duration of Participation | Each participant will participate in the study for up to approximately120 days from the time the participant provides documented informed consent through the final contact. Participants will be screened for suitability for the study under a separate study site generic screening process. After a screening period of 12 weeks, each participant will be in the treatment period for approximately 8 days, including PK sampling and safety assessments. After the end of the treatment period, each participant will be followed for 3 weeks. |

**Study Governance Committees:**

| | |
|---|---|
| Executive Oversight Committee | No |
| Data Monitoring Committee | No |
| Clinical Adjudication Committee | No |

**Study Accepts Healthy Participants:** Yes

A list of abbreviations is in Appendix 12.

## 1.2 Schema

The study design is depicted in Figure 1 and Figure 2. The study interventions for Part 2 are shown in Table 1.

Figure 1 Study Schematic

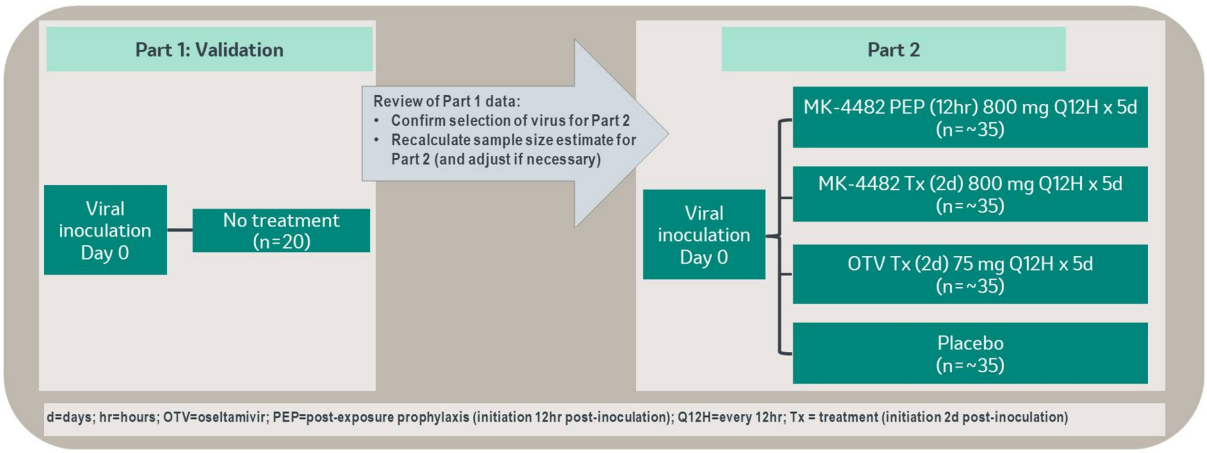


Figure 2 Study Schema

| Day -90 | Day -2 | Day 0 – Day 8 | Day 8 | Day 28 |
|---|---|---|---|---|
| Generic screening | Admission to Quarantine Unit | Quarantine period | Discharge from unit | Follow-up visit |
| • Serology<br>• GP letters<br>• Generic screening consent<br>• Medical history<br>• Assessments (eligibility) | • Check-in<br>• Study-specific consent<br>• Assessments (eligibility, safety) | • Inoculation with challenge virus (Day 0)<br>• IMP administration (Part 2 only, starting Day 0 PM)<br>• Safety assessments<br>• Virology<br>• Symptom reporting<br>• FLU-PRO Plus© questionnaire<br>• Mucus weights<br>• Blood sampling for PK (Part 2 only) | • Safety assessments<br>• Pre-discharge NPS (if needed) | • Safety assessments |

GP=general practitioner; IMP=investigational medicinal product; NPS=nasopharyngeal swab; PK=pharmacokinetics

Table 1 Study Interventions – Part 2

| Intervention[a] | Day 0 PM – Day 1 PM (inclusive) | Day 2 AM-Day 5 AM (inclusive) | Day 5 PM -Day 6 PM (inclusive) |
|---|---|---|---|
| MK-4482 PEP | MK-4482 800 mg[b] Q12H | MK-4482 800 mg[b] Q12H | Placebo (MK-4482)[c] Q12H |
| MK-4482 Tx | Placebo (MK-4482)[c] Q12H | MK-4482 800 mg[b] Q12H | MK-4482 800 mg[b] Q12H |
| OTV Tx | Placebo (OTV)[d] Q12H | OTV 75 mg[e] Q12H | OTV 75 mg[e] Q12H |
| Placebo | Placebo (MK-4482)[c] Q12H | Placebo (MK-4482)[c] Q12H | Placebo (MK-4482)[c] Q12H |

OTV = oseltamivir, PEP = post-exposure prophylaxis, Q12H = every 12 hours, Tx = treatment

a. Participants will be randomly assigned to one of four interventions, which will be dosed in a blinded fashion. In order to maintain the blind, all participants will receive 4 capsules at each dose administration and will be blindfolded during dosing.

b. MK-4482 will be dosed as 4 x 200 mg capsules

c. Placebo (MK-4482) is an identical match to MK-4482, ie, 4 capsules

d. Placebo (OTV) is a similar size and weight to OTV; 4 capsules will be administered

e. 1 capsule of OTV 75 mg plus 3 capsules of placebo (OTV) will be administered

## 1.3 Schedule of Actvities

| Part 1[a] | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Period:** | **Screening[b]** | **Inpatient Quarantine[c]** | | | | | | | | | | | | | | **Follow up** | **Early Withdrawal[d]** | **Notes** |
| **Scheduled Day[c]** | **Day -90 to Day -2/-1** | **D-2[e]** | **D-1[e]** | **D0** | | | **D1** | **D2** | **D3** | **D4** | **D5** | **D6** | **D7** | **D8** | | **D28 (+/- 3 days)** | **Post-Challenge** | |
| | | | | **Pre** | **Challenge** | **Post** | | | | | | | | | | | | |
| **Administrative/Study Procedures** | | | | | | | | | | | | | | | | | | |
| Informed Consent | X | X | | | | | | | | | | | | | | | | Sec. 5.1, 8.1.1 |
| Informed Consent for FBR | | X | | | | | | | | | | | | | | | | Sec. 5.1, 8.1.1.2 |
| Participant ID Card | | | | | | | | | | | | | | X | | | | Sec. 8.1.3 |
| Inclusion/Exclusion Criteria | X | X | X | X | | | | | | | | | | | | | | Sec. 5.1, 5.2, 8.1.2 |
| Medical History | X | X | | | | | | | | | | | | | | | | Sec. 8.1.4 |
| Prior/Concomitant Medication Review | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | (X) | Sec. 5.2, 6.5, 8.1.6 |
| Patient Health Questionnaire (PHQ-9) | (X) | (X) | | | | | | | | | | | | | | | | Sec. 8.1.5 |
| Generalized Anxiety Disorder Questionnaire (GAD-7) | (X) | (X) | | | | | | | | | | | | | | | | Sec. 8.1.5 |
| Participant Visits to Clinical Research Unit | X | X | | | | | | | | | | | | | | X | | Sec. 8.1.12, 8.14 |
| Domiciling | | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | Sec. 8.1.12 |
| Assignment of Study-specific Screening Number | | X | | | | | | | | | | | | | | | | Sec. 8.1.7 |
| Assignment of Allocation Number | | | | X | | | | | | | | | | | | | | Assigned prior to virus inoculation. Sec.8.1.8 |
| Influenza Inoculation | | | | | X | | | | | | | | | | | | | Sec. 8.3 |

| Part 1[a] | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Period:** | **Screening[b]** | **Inpatient Quarantine[c]** | | | | | | | | | | | | | | **Follow up** | **Early Withdrawal[d]** | **Notes** |
| **Scheduled Day[c]** | **Day -90 to Day -2/-1** | **D-2[e]** | **D-1[e]** | **D0** | | | **D1** | **D2** | **D3** | **D4** | **D5** | **D6** | **D7** | **D8** | | **D28 (+/- 3 days)** | **Post-Challenge** | |
| | | | | **Pre** | **Challenge** | **Post** | | | | | | | | | | | | |
| **Safety Procedures** | | | | | | | | | | | | | | | | | | |
| Full Physical Examination | X | X | | | | | | | X | | | | | X | | | (X) | Sec. 8.5.1 |
| Directed Physical Examination (including nasal) | | | | X | | | X | X | | X | X | X | X | | | X | | Sec. 8.5.1 |
| Height, Weight, BMI | X | X | | | | | | | | | | | | X | | X | (X) | Height and BMI at Screening only. Sec. 8.5.1 |
| VS (HR, RR, SBP, DBP, SpO2) | X | X | X | X | | | X | X | X | X | X | X | X | X | | X | (X) | Sec. 8.5.2 |
| Body Temperature | X | X | 3X | 3X | | | 3X | 3X | 3X | 3X | 3X | 3X | 3X | X | | X | (X) | Sec. 8.5.2 |
| 12-lead ECG | X | X | | | | | | | X | | | | | X | | X | (X) | Day -2 ECG will be triplicate. All other ECGs will be single measurements .Sec. 8.5.3. |
| Spirometry | X | | | X | | | | | X | | | | X | | | | | Sec. 8.5.4 |
| Calculation of eGFR | | X | | | | | | | | | | | | | | | | Sec. 5.2 |
| Alcohol Breath Test | X | X | | | | | | | | | | | | | | | | App. 2 |
| Urine Drugs of Abuse and Nicotine Screen | X | X | | | | | | | | | | | | | | | | App. 2 |

| Part 1[a] | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Period:** | **Screening[b]** | **Inpatient Quarantine[c]** | | | | | | | | | | | | | | **Follow up** | **Early Withdrawal[d]** | **Notes** |
| **Scheduled Day[c]** | **Day -90 to Day -2/-1** | **D-2[e]** | **D-1[e]** | **D0** | | | **D1** | **D2** | **D3** | **D4** | **D5** | **D6** | **D7** | **D8** | | **D28 (+/- 3 days)** | **Post-Challenge** | |
| | | | | **Pre** | **Challenge** | **Post** | | | | | | | | | | | | |
| Hematology | X | X | | | | | X | X | X | X | X | X | X | | | X | (X) | Sec. 8.5.5, App. 2 & 8 |
| Urinalysis | X | X | | | | | | | | | | | | | | | (X) | Sec. 8.5.5, App. 2 |
| Chemistry | X | X | | | | | | | X | | | | X | | | X | (X) | Sec. 8.5.5, App. 2 & 8 |
| Coagulation (PT/aPTT) | X | | | | | | | | | | | | | | | | | Sec. 4.2.1.3, App. 2 & 8 |
| Thyroid Function Test | X | | | | | | | | | | | | | | | | | Sec. 4.2.1.3, App. 2 & 8 |
| Creatine Kinase and Troponin | X | | | | | | | | | | | | | | | | | Sec. 4.2.1.3, App. 2 & 8 |
| Urine Pregnancy Test | X | | | | | | | | | | | | | | | X | (X) | POCBP only. Sec. 8.5.6, App. 2 |
| Serum β-HCG pregnancy test | | X | | | | | | | | | | | | | | | | POCBP only. Sec. 8.5.6, App. 2 & 8 |
| Serum FSH | X | | | | | | | | | | | | | | | | | Postmenopausal females only. Sec. 5.1, App. 2 & 5 |
| HIV, hepatitis B and C screen | X | | | | | | | | | | | | | | | | | Sec. 8.5.5, App. 2 & 8 |

| Part 1[a] | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Period:** | **Screening[b]** | **Inpatient Quarantine[c]** | | | | | | | | | | | | | | **Follow up** | **Early Withdrawal[d]** | **Notes** |
| **Scheduled Day[c]** | **Day -90 to Day -2/-1** | **D-2[e]** | **D-1[e]** | **D0** | | | **D1** | **D2** | **D3** | **D4** | **D5** | **D6** | **D7** | **D8** | | **D28 (+/- 3 days)** | **Post-Challenge** | |
| | | | | **Pre** | **Challenge** | **Post** | | | | | | | | | | | | |
| AE review | | X | X | X | | X | X | X | X | X | X | X | X | X | | X | (X) | Sec. 8.6, App. 3 |
| **Efficacy Assessments** | | | | | | | | | | | | | | | | | | |
| Symptom diary card | | X | 3X | 3X | | | 3X | 3X | 3X | 3X | 3X | 3X | 3X | X | | | | Sec. 8.4.1 |
| FLU-PRO Plus© Questionnaire and global impression questions | | | X | X | | | X | X | X | X | X | X | X | | | | | Sec. 8.4.2 |
| 24-hour tissue count & nasal discharge weight | | | X | X | | | X | X | X | X | X | X | X | X | | | (X) | Sec. 8.4.3 |
| **Respiratory Samples** | | | | | | | | | | | | | | | | | | |
| NPS - Respiratory Pathogen Screen Including SARS-CoV-2 (eg, Biofire) | | X | | | | | | | | | | | | | | | | Sec. 8.4.4 |
| NPS – Viral Discharge Test | | | | | | | | | | | | | (X) | (X) | | | | Sec. 8.4.4 |
| NPS – Virology | | X | | | | | 2X | 2X | 2X | 2X | 2X | 2X | 2X | X | | | | Sec 8.4.4 |
| Nasal Sample for Mucosal Antibodies and Inflammatory Markers. | | X | | | | | | | | | | | | | | | | Sec 8.4.5 |
| **Biomarkers** | | | | | | | | | | | | | | | | | | |
| Blood - Serum Markers Humoral immunity | X | X | | | | | | | | | | | | | | X | (X) | Sec. 8.2, 8.10 |
| Blood – Serum Exploratory Immunological Biomarkers | | | | X | | | X | X | X | X | X | X | | | | | | Sec. 8.10, collected in the PM |

| Part 1[a] | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Period:** | **Screening[b]** | **Inpatient Quarantine[c]** | | | | | | | | | | | | | | **Follow up** | **Early Withdrawal[d]** | **Notes** |
| **Scheduled Day[c]** | **Day -90 to Day -2/-1** | **D-2[e]** | **D-1[e]** | **D0** | | | **D1** | **D2** | **D3** | **D4** | **D5** | **D6** | **D7** | **D8** | | **D28 (+/- 3 days)** | **Post-Challenge** | |
| | | | | **Pre** | **Challenge** | **Post** | | | | | | | | | | | | |
| Blood for Genetic Analysis | | | | X | | | | | | | | | | | | | | May be collected within 24 hrs prior to or post allocation/randomization. In allocated/randomized participants only. Sec. 8.11.1 & App. 8 |

| Part 1[a] | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Period:** | **Screening[b]** | **Inpatient Quarantine[c]** | | | | | | | | | | | | | | **Follow up** | **Early Withdrawal[d]** | **Notes** |
| **Scheduled Day[c]** | **Day -90 to Day -2/-1** | **D-2[e]** | **D-1[e]** | **D0** | | | **D1** | **D2** | **D3** | **D4** | **D5** | **D6** | **D7** | **D8** | | **D28 (+/- 3 days)** | **Post-Challenge** | |
| | | | | **Pre** | **Challenge** | **Post** | | | | | | | | | | | | |

AE=adverse event; App=Appendix; aPTT=activated partial thromboplastin time; β-HCG=beta human chorionic gonadotropin; BMI=body mass index; D=day; DBP=diastolic blood pressure; ECG=electrocardiogram; FSH=follicle stimulating hormone; GAD=generalized anxiety disorder; HIV=human immunodeficiency virus; HR=heart rate; hrs=hours; ID=identification; NPS=nasopharyngeal swab; PHQ=patient health questionnaire; PI=principal investigator; PT=prothrombin time; RR=respiratory rate; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SBP=systolic blood pressure; $SpO_2$=oxygen saturation; VS=vital signs; POCBP=participant of childbearing potential.

[a] All procedures to be conducted in accordance with site's SOPs (unless otherwise indicated).

[b.] Screening procedures will be performed under a generic screening process. Historical prescreening data collected through the generic screening process within 90 days (90 days for viral serology and 56 days for other assessments including safety laboratory test) prior to inoculation may be used to determine eligibility without the need to repeat the assessments following study-specific consent. Study-specific consent may occur on day of admission, provided all required eligibility information has been collected through the Health Research Authority approved generic screening process.

[c.] All inpatient procedures should occur in line with inoculation day.

[d] Refer to Section 8.1.10 for details on discontinuation/withdrawal

[e.] Participants will be admitted to quarantine on Day -2 or Day -1. If participants are admitted on Day-1 then all procedures on Day-2 may be performed on Day-1 instead, as applicable.

Notes:

- 3X: assessment conducted three times during the 24-hour period
- 2X: assessment conducted twice during the 24-hour period
- X assessment conducted once during the 24-hour period.
- (): indicate an assessment is optional and may be conducted in accordance with PI discretion

| Part 2[a] | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Period:** | **Screening[b]** | **Inpatient Quarantine[c]** | | | | | | | | | | | | | **Follow up** | **Early Withdrawal[d]** | **Notes** |
| **Scheduled Day** | **Day -90 to Day -2/-1** | **D-2[e]** | **D-1[e]** | **D0** | | | **D1** | **D2** | **D3** | **D4** | **D5** | **D6** | **D7** | **D8** | **D28 (+/- 3 days)** | **Post-Challenge** | |
| | | | | **Pre** | **Challenge** | **Post** | | | | | | | | | | | |
| **Administrative/Study Procedures** | | | | | | | | | | | | | | | | | |
| Informed Consent | X | X | | | | | | | | | | | | | | | Sec. 5.1, 8.1.1 |
| Informed Consent for FBR | | X | | | | | | | | | | | | | | | Sec. 5.1, 8.1.1.2 |
| Participant ID Card | | | | | | | | | | | | | | X | | | Sec. 8.1.3 |
| Inclusion/Exclusion Criteria | X | X | X | X | | | | | | | | | | | | | Sec. 5.1, 5.2, 8.1.2 |
| Medical History | X | X | | | | | | | | | | | | | | | Sec. 8.1.4 |
| Prior/Concomitant Medication Review | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | (X) | Sec. 5.2, 6.5, 8.1.6 |
| Patient Health Questionnaire (PHQ-9) | (X) | (X) | | | | | | | | | | | | | | | Sec. 8.1.5 |
| Generalized Anxiety Disorder Questionnaire (GAD-7) | (X) | (X) | | | | | | | | | | | | | | | Sec. 8.1.5 |
| Participant Visits to Clinical Research Unit | X | X | | | | | | | | | | | | | X | | Sec. 8.1.12, 8.14 |
| Domiciling | | X | X | X | X | X | X | X | X | X | X | X | X | X | | | Sec. 8.1.12 |
| Assignment of Study-specific Screening Number | | X | | | | | | | | | | | | | | | Sec. 8.1.7 |
| Assignment of Randomization Number | | | | X | | | | | | | | | | | | | Assigned prior to virus inoculation. Sec.8.1.8 |
| Influenza Inoculation | | | | | X | | | | | | | | | | | | Sec. 8.3 |
| Study Drug Administration | | | | | | X | 2X | 2X | 2X | 2X | 2X | 2X | | | | | Intervention will be administered Q12H. Sec. 8.1.9 |
| **Safety Procedures** | | | | | | | | | | | | | | | | | |
| Full Physical Examination | X | X | | | | | | | | | | | | X | | (X) | Sec. 8.5.1 |

| Part 2[a] | | | | | | | | | | | | | | | | | |
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| **Study Period:** | **Screening[b]** | **Inpatient Quarantine[c]** | | | | | | | | | | | | **Follow up** | **Early Withdrawal[d]** | **Notes** |
| **Scheduled Day** | **Day -90 to Day -2/-1** | **D-2[e]** | **D-1[e]** | **D0** | | | **D1** | **D2** | **D3** | **D4** | **D5** | **D6** | **D7** | **D8** | **D28 (+/- 3 days)** | **Post-Challenge** | |
| | | | | **Pre** | **Challenge** | **Post** | | | | | | | | | | | |
| Directed Physical Examination (Including Nasal) | | | | X | | | (X) | (X) | (X) | (X) | (X) | (X) | (X) | | (X) | | Sec. 8.5.1 |
| Height, Weight, BMI | X | X | | | | | | | | | | | | X | X | (X) | Height and BMI at Screening only. Sec. 8.5.1 |
| VS (HR, RR, SBP, DBP, SpO2) | X | X | X | X | | | X | X | X | X | X | X | X | X | X | (X) | Sec. 8.5.2<br>AM Predose only |
| Body Temperature | X | X | 3X | 3X | | | 3X | 3X | 3X | 3X | 3X | 3X | 3X | X | X | (X) | Sec. 8.5.2 |
| 12-lead ECG | X | X | | | | | (X) | (X) | (X) | (X) | (X) | (X) | (X) | X | X | (X) | Day-2 ECG will be triplicate.<br>All subsequent ECGs will be single measurements Sec. 8.5.3. |
| Spirometry | X | | | | | | (X) | (X) | (X) | (X) | (X) | (X) | (X) | (X) | | | Sec. 8.5.4 |
| Calculation of eGFR | | X | | | | | | | | | | | | | | | Sec. 5.2 |
| Alcohol Breath Test | X | X | | | | | | | | | | | | | | | App. 2 |
| Urine Drugs of Abuse and Nicotine Screen | X | X | | | | | | | | | | | | | | | App. 2 |
| Hematology | X | X | | | | | (X) | (X) | (X) | (X) | (X) | (X) | X | | X | (X) | Sec. 8.5.5, App. 2 & 8 |
| Urinalysis | X | X | | | | | | | | | | | | | | (X) | Sec. 8.5.5, App. 2 |
| Chemistry | X | X | | | | | (X) | (X) | (X) | (X) | (X) | (X) | X | | X | (X) | Sec. 8.5.5, App. 2 & 8 |
| Coagulation (PT/aPTT) | X | | | | | | | | | | | | | | | | Sec. 4.2.1.3, App. 2 & 8 |

| Part 2[a] | | | | | | | | | | | | | | | | | |
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| **Study Period:** | **Screening[b]** | **Inpatient Quarantine[c]** | | | | | | | | | | | | | **Follow up** | **Early Withdrawal[d]** | **Notes** |
| **Scheduled Day** | **Day -90 to Day -2/-1** | **D-2[e]** | **D-1[e]** | **D0** | | | **D1** | **D2** | **D3** | **D4** | **D5** | **D6** | **D7** | **D8** | **D28 (+/- 3 days)** | **Post-Challenge** | |
| | | | | **Pre** | **Challenge** | **Post** | | | | | | | | | | | |
| Thyroid Function Test | X | | | | | | | | | | | | | | | | Sec. 4.2.1.3, App. 2 & 8 |
| Creatine Kinase and Troponin | X | | | | | | | | | | | | | | | | Sec. 4.2.1.3, App. 2 & 8 |
| Urine Pregnancy Test | X | | | | | | | | | | | | | | X | (X) | POCBP only. Sec. 8.5.6, App. 2 |
| Serum β-HCG Pregnancy Test | | X | | | | | | | | | | | | | | | POCBP only. Sec. 8.5.6, App. 2 & 8 |
| Serum FSH | X | | | | | | | | | | | | | | | | Postmenopausal females only. Sec. 5.1, App. 2 & 5 |
| HIV, Hepatitis B and C Screen | X | | | | | | | | | | | | | | | | Sec. 8.5.5, App. 2 & 8 |
| AE Review | | X | X | X | | X | X | X | X | X | X | X | X | X | X | (X) | Sec. 8.6, App. 3 |
| **Efficacy Assessments** | | | | | | | | | | | | | | | | | |
| Symptom Diary Card | | X | 3X | 3X | | | 3X | 3X | 3X | 3X | 3X | 3X | 3X | X | | | Sec. 8.4.1 |
| FLU-PRO Plus© Questionnaire and global impression questions | | | X | X | | | X | X | X | X | X | X | X | | | | Sec. 8.4.2 |
| 24-hour Tissue Count & Nasal Discharge Weight | | | X | X | | | X | X | X | X | X | X | X | X | | (X) | 8.4.3 |
| **Respiratory Samples** | | | | | | | | | | | | | | | | | |
| NPS - Respiratory Pathogen Screen Including SARS-COV-2 (eg, Biofire) | | X | | | | | | | | | | | | | | | Sec. 8.4.4 |

| Part 2[a] | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Period:** | **Screening[b]** | **Inpatient Quarantine[c]** | | | | | | | | | | | | | **Follow up** | **Early Withdrawal[d]** | **Notes** |
| **Scheduled Day** | **Day -90 to Day -2/-1** | **D-2[e]** | **D-1[e]** | **D0** | | | **D1** | **D2** | **D3** | **D4** | **D5** | **D6** | **D7** | **D8** | **D28 (+/- 3 days)** | **Post-Challenge** | |
| | | | | **Pre** | **Challenge** | **Post** | | | | | | | | | | | |
| NPS – Viral Discharge Test | | | | | | | | | | | | | (X) | (X) | | | Sec. 8.4.4 |
| NPS – Virology | | X | | | | | 2X | 2X | 2X | 2X | 2X | 2X | 2X | X | | | Sec. 8.4.4 |
| Nasal Sample for Mucosal Antibodies and Inflammatory Markers. | | X | | | | | | | | | | | | | | | Sec 8.4.5 |
| **Pharmacokinetics[f]** | | | | | | | | | | | | | | | | | |
| Blood for Plasma MK-4482 and/ or Metabolites Assay | | | | X | | | | X | | X | X | X | X | X | | | Sampling Times<br>D0, D2, D4: predose<br>D5: predose, 0.5, 1.5, 4, 8, 12, 24, 48, 72 hr. Sec. 8.8.1 |
| Blood for Plasma Oseltamivir and/or Metabolites Assay | | | | | | | | X | | | | | | | | | At 4 hr post AM dose<br>Sec. 8.8.2 |
| **Biomarkers** | | | | | | | | | | | | | | | | | |
| Blood - Serum Markers Humoral immunity | X | X | | | | | | | | | | | | | X | (X) | Sec. 8.2, 8.10 |
| Blood – Serum Exploratory Immunological Biomarkers | | | | X | | | X | X | X | X | X | X | | | | | Sec. 8.10, collected in the PM |
| Blood for Genetic Analysis | | | | X | | | | | | | | | | | | | May be collected within 24 hrs prior to or post allocation/randomization. In allocated/randomized participants only.. Sec. 8.11.1 & App. 8 |

| Part 2[a] | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Period:** | **Screening[b]** | **Inpatient Quarantine[c]** | | | | | | | | | | | | **Follow up** | **Early Withdrawal[d]** | **Notes** |
| **Scheduled Day** | **Day -90 to Day -2/-1** | **D-2[e]** | **D-1[e]** | **D0** | | | **D1** | **D2** | **D3** | **D4** | **D5** | **D6** | **D7** | **D8** | **D28 (+/- 3 days)** | **Post-Challenge** | |
| | | | | **Pre** | **Challenge** | **Post** | | | | | | | | | | | |

AE=adverse event; App=Appendix; aPTT=activated partial thromboplastin time; β-HCG=beta human chorionic gonadotropin; BMI=body mass index; D=day; DBP=diastolic blood pressure; ECG=electrocardiogram; FSH=follicle stimulating hormone; HIV=human immunodeficiency virus; HR=heart rate; hrs=hours; ID=identification; NPS=nasopharyngeal swab; PI=principal investigator; PT=prothrombin time; RR=respiratory rate; SARS-COV-2=severe acute respiratory syndrome coronavirus 2; SBP=systolic blood pressure; $SpO_2$=oxygen saturation; VS=vital signs; WOCBP=women of childbearing potential.

[a] All procedures to be conducted in accordance with site's SOPs (unless otherwise indicated).

[b] Screening procedures will be performed under a generic screening process. Historical prescreening data collected through a generic screening process within 90 days (90 days for viral serology and 56 days for other assessments including safety laboratory test) prior to inoculation may be used to determine eligibility without the need to repeat the assessments following study-specific consent. Study-specific consent may occur on day of admission, provided all required eligibility information has been collected through the Health Research Authority approved generic screening process.

[c] All inpatient procedures should occur in line with inoculation day.

[d] Refer to Section 8.1.10 for details on discontinuation/withdrawal

[e] Participants will be admitted to quarantine on Day -2 or Day -1. If participants are admitted on Day-1 then all procedures on Day-2 may be performed on Day-1 instead, as applicable.

[f] All samples should be collected with respect to the AM dose of study drug only. All predose and 12 hr samples should be collected prior to the next scheduled dose. Windows for PK sampling are provided in Section 8.14.6.

Notes:

- 3X: assessment conducted three times during the 24-hour period
- 2X: assessment conducted twice during the 24-hour period
- X assessment conducted once during the 24-hour period.
- (): indicate an assessment is optional and may be conducted in accordance with PI discretion

# 2 INTRODUCTION

IAV and IBV generally circulate annually, with several strains predominating in any given season and are responsible for seasonal epidemics of disease nearly every winter in temperate climates. Despite the availability of annual influenza vaccines and a number of approved antiviral treatments, there is still an unmet medical need for the treatment of influenza. During the 2018 to 2019 influenza season, an estimated 29 million cases occurred in the US, resulting in 13 million medical visits, 380,000 hospitalizations, and 28,000 deaths [Centers for Disease Control and Prevention 2022]. Most deaths occur in patients of advanced age, although young children are also at increased risk of severe disease with complications of hospitalizations and infrequently death. Though patterns of viral respiratory disease were disrupted with the COVID-19 pandemic, non-COVID-19 respiratory viruses will continue to present a significant health care burden.

Influenza virus transmission is primarily through direct person-to-person respiratory spread via large droplets or aerosols. Longer range transmission via the airborne route as well as transmission through contact with fomites are also possible. The average incubation period is two days, with a range one to four days. Viral replication takes place predominantly in the respiratory tract epithelial lining. This, in combination with the host immune response, results in lung inflammation. Symptoms may include fever, cough, muscle pain, malaise, sore throat, nasal congestion, and headache. Additionally, gastrointestinal symptoms such as vomiting, diarrhea, nausea, and abdominal pain may occur, although these tend to be more common in children than in adults.

## 2.1 Study Rationale

MK-4482 (molnupiravir) is an orally administered prodrug of the ribonucleoside analogue NHC that inhibits the replication of a range of RNA viruses by viral mutagenesis. Clinical development is ongoing for the treatment and prevention of COVID-19 and is planned for the treatment and prophylaxis of other viral respiratory infections. The purpose of this study is to assess the antiviral activity of a regimen of MK-4482 800 mg Q12H x 5 days in treatment and PEP of acute IAV infection in a human challenge disease model of IAV experimental intranasal inoculation. Virological and clinical data from this study may be used to inform future clinical development of MK-4482 against influenza.

Extensive nonclinical and clinical safety experience have supported the development of MK-4482 to date; furthermore, the proposed dosing regimen for this study (800 mg Q12H x 5 days) is the same as that currently used for the treatment of mild to moderate COVID-19. The current study will provide further assessments of the safety and tolerability of MK-4482, as well as of the plasma PK of NHC and viral dynamics following inoculation with IAV.

### 2.1.1 Overview of Influenza Human Challenge Model

The human viral challenge model has furthered understanding of respiratory viruses such as influenza, providing insight into disease pathogenesis and supporting the development of novel vaccines and therapeutics [Lambkin-Williams, R., et al 2018].

The intent of this study is to use a human challenge model, in which a fixed inoculum of IAV is administered intranasally to healthy adults (whose eligibility for participation includes serosuitability, ie, a requirement for low pre-existing immunity to the challenge virus) in a controlled setting, allowing for an evaluation of MK-4482 (including assessment of nasal viral shedding and prospective symptom evaluation) when initiated at fixed time points relative to a known time of inoculation [Lambkin-Williams, R., et al 2018].

This study will evaluate the impact of MK-4482 on influenza viral load and on clinical symptoms. Previous influenza human challenge studies (using predominantly wild-type A/H1N1 or A/H3N2 subtypes) have reported an increase in viral shedding on the first day post-inoculation, peaking on day 2/3, with a duration of viral shedding of up to ~5 days, and a positive association between quantity of virus shed and symptom severity. Experimental influenza infection with these wild-type challenge viruses typically causes mild to moderate disease with mostly upper respiratory tract and systemic symptoms. As expected in a healthy younger population, the disease is similar in severity to natural community-acquired infection; in particular, healthy younger people very rarely exhibit more severe lower respiratory tract infection requiring hospitalization. Systemic symptoms (fever, myalgia, fatigue, and headache) tended to peak on day 2, whereas respiratory symptoms (with upper respiratory symptoms predominating over lower respiratory symptoms) peaked on day 3 [Carrat, F., et al 2008]. In previous human challenge studies performed by hVIVO with A/Perth/16/2009 [H3N2], infectivity rates of ~69%, 62%, and 48%, defined by detectable by PCR, quantifiable by PCR, and quantifiable by viral culture, respectively, have been observed in untreated/placebo-treated participants. Similarly, in studies with A/California 2009-like [H1N1] performed by hVIVO, infectivity rates of ~50%, 47%, and 33%, defined by detectable by PCR, quantifiable by PCR, and quantifiable by viral culture, respectively, have been observed in untreated/placebo-treated participants. These are comparable to rates seen by other groups using the same challenge virus [Sloan, S. E., et al 2020] [Watson, J. M., et al 2015].

A fixed viral inoculum will be used, based on experience from previous influenza human challenge studies.

Typically, the majority of influenza challenge studies to date have employed IAV strains, with a particular focus on the H1N1 and H3N2 serotypes, reflecting that these two serotypes have been responsible for the majority of influenza pandemics of the 20$^{th}$ and 21$^{st}$ centuries [Balasingam, S. 2016]. An IAV strain will be the challenge agent used in this study. The preferred agent is an influenza H1N1 virus from the 6B.1A.5a.1 clade (A/France/759/21 [H1N1]), isolated from a patient with a community-acquired infection, and produced in a GMP-qualified Vero cell line. According to surveillance reports, the 6B.1A.5a.1 clade is one of the predominant clades in Europe [European Centre for Disease Prevention and Control 2022]. Furthermore, based on surveillance, there is anticipated to be a lower level of immunity in the population to this more recent strain, as compared to influenza viral strains used in previous influenza challenge studies; therefore, higher rates of serosuitability and infectivity are predicted. However, this more recent strain will require validation in humans prior to its use as a challenge agent for the evaluation of MK-4482; this validation will be conducted during Part 1 of this study.

Part 1 (Validation) will characterize the A/France/759/21 [H1N1] strain in 20 participants in the absence of study drug. Assuming a satisfactory outcome of Part 1 (based on safety, tolerability, rate of infectivity, and viral load and symptom profile), Part 2 will use the same challenge virus to evaluate the performance of MK-4482 in the challenge model; alternatively, a different viral strain that has been well-characterized in previous HCS (eg, A/Perth/16/2009 [H3N2] or A/California 2009-like [H1N1]) will be utilized in Part 2. See Appendix 11 for further information on the alternative viral strains.

## 2.2 Background

Refer to the IB/approved labeling for detailed background information on MK-4482.

### 2.2.1 Pharmaceutical and Therapeutic Background

MK-4482 is the 5′-isobutyrate prodrug of the broadly active, direct-acting antiviral ribonucleoside analog NHC. MK-4482 is hydrolyzed by esterases either during or after absorption to deliver NHC into systemic circulation. NHC inhibits replication of multiple RNA virus families including pathogenic Coronaviruses (eg, MERS, SARS-CoV and SARS-CoV-2), influenza viruses (seasonal, pandemic and avian subtypes), and RSV. Inside cells, the active nucleoside triphosphate anabolite of MK-4482 (NHC-TP) acts as a competitive, alternative substrate for the virally encoded RNA-dependent RNA polymerase. Upon incorporation into nascent chain RNA, NHC-TP induces increased mutational frequency in the viral genome resulting in viral error catastrophe and production of nonviable virus [Flavell, R. A., et al 1974] [Gordon CJ, Tchesnokov EP, Schinazi RF, Götte M. 2021] [Kabinger F, Stiller C, Schmitzová J, Dienemann C, Kokic G, Hillen HS, et al. 2021].

Following administration of MK-4482 in humans, NHC appears rapidly in plasma (median $T_{max}$ ranging from approximately 1.5 to 2 hours). Minimal to no accumulation of NHC exposure, in terms of $AUC_{0-12}$ and $C_{max}$, was observed in healthy participants following multiple-dose administration of MK-4482. No significant differences in NHC PK between healthy participants and participants infected with SARS-CoV-2 have been observed.

Currently, four agents are approved for the treatment/prevention of influenza disease: oral oseltamivir, oral baloxavir, inhaled zanamivir, and IV peramivir. However, due to concerns around emerging resistance, there is a continued need for new therapeutic/prophylactic antiviral agents.

### 2.2.2 Preclinical Studies

MK-4482 and NHC inhibit replication of viral pathogens from multiple RNA virus families, including pathogenic coronaviruses (SARS-CoV-2, MERS-CoV), alphaviruses (Venezuelan Equine Encephalitis virus), orthomyxoviruses (influenza) and paramyxoviruses (RSV).

Primary pharmacology studies demonstrating the antiviral activity of MK-4482 when administered as NHC against SARS-CoV-2 and other RNA viruses were conducted in vitro and in mouse, guinea pig, hamster, and ferret models of coronavirus, RSV, and influenza infection.

Published studies by Yoon et al. have demonstrated the antiviral activity of NHC with in vitro and in vivo preclinical models of influenza infection [Yoon, J. J., et al 2018]. NHC exhibits dose-dependent inhibition of viral replication against a broad panel of IAV and IBV laboratory strains and isolates with EC50 values in the low- to sub-micromolar range.

Studies in a ferret model of influenza virus infection demonstrated that administration of MK-4482 provided therapeutic benefit against IAV (H1N1). MK-4482 in doses of 0.8, 2.3, or 7 mg/kg (3.5 mL) by oral gavage BID was tested in a ferret model of influenza virus infection and disease. Animals were infected intranasally with $1 \times 10^5$ pfu (200 µL) of IAV H1N1 virus and MK-4482 dosing was initiated 12 hours later. Treatment with 7 mg/kg BID led to a reduction in shed virus load by multiple orders of magnitude, and alleviated fever and inflammation while improving airway epithelium histopathology. Treatment with 2.3 mg/kg BID resulted in moderate reduction of virus titer but no significant reduction of fever. The 0.8 mg/kg dose BID had no significant therapeutic effect. By 48 hours post-infection, the disease in ferrets began to self-resolve; therefore, initiating treatment up to 36 hours post-infection allows for detection of antiviral activity before self-resolution of disease. Administered in 12-hour intervals, three 7 mg/kg doses of MK-4482 were sufficient for maximal therapeutic benefit against a pandemic IAV and significantly shortened the time to resolution of clinical signs. Ferrets infected with pandemic IAV (H1N1) and treated with MK-4482 at a dose of 7 mg/kg demonstrated significantly less viral shedding and inflammatory cellular infiltrates in nasal lavages but mounted a normal humoral antiviral response [Toots, M., et al 2020]. A similar study using ferrets infected intranasally with $1 \times 10^6$ pfu (200 µL) of IAV H3N2 virus demonstrated the same results for MK-4482 (0.8, 2.3, or 7 mg/kg by oral gavage BID) in the seasonal IAV model. When examining the effect of delayed dosing in a different study in the same pandemic IAV ferret model (H1N1), the study demonstrated that treatment with 20 mg/kg of MK-4482 initiated 24 hours after challenge with IAV (H1N1) resulted in a rapid decrease in both shed virus and fever relative to control, with fever returning to baseline at 24 hours. When OTV (20 mg/kg, corresponding to 2x the human equivalent dose for treatment) was administered prophylactically as a positive control, a modest suppression of fever was observed; however, there was no reduction in shed virus titer [Toots, M., et al 2019].

MK-4482 was evaluated in nonclinical safety studies, including a standard battery of in vitro and in vivo safety pharmacology studies, genotoxicity assays (including Ames assays, in vitro and in vivo micronucleus assays, an in vivo Pig-a assay in rats, and an in vivo mutation assay in Big Blue® transgenic rats), tolerability/dose-range-finding studies in mice, rats, and dogs, repeat-dose toxicity studies of up to 3 months in rats and 1 month in mice and dogs, a 6-month oral carcinogenicity study in rasH2 transgenic mice, fertility studies in male and female rats, embryo-fetal developmental toxicity studies in rats and rabbits, a pre- and postnatal developmental toxicity study in rats, and toxicity studies in juvenile rats. Additional nonpivotal short-term tolerability and/or TK studies were conducted in mice, rats, rabbits, and monkeys.

MK-4482 was devoid of effects on CNS, respiratory, or cardiovascular functions in well-characterized safety pharmacology models. Based on the totality of genotoxicity data, MK-4482 is not mutagenic or genotoxic in in vivo mammalian systems.

Target organs of toxicity identified in the repeat-dose toxicity studies were limited to bone marrow in dogs only, and growth plate in rats only. Hematologic changes observed after 7 days of dosing in the dog 28-day toxicity study were mild and reversible on discontinuation, and hematopoietic effects have not been in clinical studies to date with a dose of 800 mg Q12H x 5 days. The growth plate findings are not relevant to adult humans, because growth plates are no longer present in the mature skeleton of adult humans. MOV was not carcinogenic in a 6-month oral carcinogenicity study in rasH2 transgenic CByB6F1 Tg(HRAS)2Jic hemizygous mice at any dose tested (0, 30, 100, and 300 mg/kg/day).

In fertility studies in rats there were no MK-4482-related effects on female or male fertility, or on early embryonic development up to the highest dose tested, 500 mg/kg/day, (2.3-/6.8-fold [female/male] the clinical NHC exposure at 800 mg Q12H). In pregnant rats administered MK-4482 during the organogenesis period, developmental toxicity including embryolethality (post-implantation losses) and malformations/teratogenicity was observed at 1000 mg/kg/day (8.4-fold the clinical NHC exposure at 800 mg Q12H), and reduced fetal growth was noted at ≥500 mg/kg/day (≥3.2-fold the clinical NHC exposure at 800 mg Q12H). There was no developmental toxicity at doses up to 250 mg/kg/day (0.9-fold the clinical NHC exposure at 800 mg Q12H). Maternal toxicity included decreased food consumption and body weight losses, resulting in the early sacrifice at 1000 mg/kg/day, and decreased body weight gain at ≥500 mg/kg/day. In pregnant rabbits, developmental toxicity was limited to reduced mean fetal body weights at 750 mg/kg/day (20-fold the clinical NHC exposure at 800 mg Q12H).

There was no developmental toxicity in rabbits up to 400 mg/kg/day (7.2-fold the clinical NHC exposure at 800 mg Q12H). Maternal toxicity included decreased food consumption and body weight gain, and abnormal fecal output at ≥400 mg/kg/day. In the pre- and postnatal developmental study in rats, there was no F0 maternal or F1 generation toxicity up to the highest dose evaluated of 500 mg/kg/day (1.8-fold the clinical NHC exposure at 800 mg Q12H).

Further details of preclinical studies are provided in the IB. Collectively, the safety pharmacology and toxicology results support continued clinical development of MK-4482.

### 2.2.3 Completed and Ongoing Clinical Studies

#### 2.2.3.1 Completed Clinical Studies

MK-4482 has been evaluated in 11 completed or clinically completed (ie, the last participant visit was completed but final data are pending) clinical trials, as summarized below. (Refer to the IB Section 5 for additional details of the study designs on each study).

Phase 1 Studies:

MK-4482-004 was a randomized, double-blind, placebo-controlled, first in human study designed to evaluate the safety, tolerability, and PK of MK-4482 following oral administration to healthy participants. Oral doses (50 to 1600 mg as a single dose, including 200 mg with a high-fat meal, and 50 to 800 mg as multiple doses [Q12H for 5.5 days]) of MK-4482 or placebo administered to 130 healthy participants were generally well tolerated.

Out of these 130 participants, 100 received at least one dose of MK-4482. No deaths or SAEs were reported.

MK-4482-008 was a single and multiple dose, randomized, placebo-controlled, double-blind study of MK-4482 in healthy Japanese adult male participants. Single doses of MK-4482 up to 1600 mg, including 800 mg with a high-fat meal, and multiple doses of MK-4482 400 mg and 800 mg Q12H for 5.5 days were generally well tolerated in healthy Japanese male adult participants. Out of 65 randomized participants, 51 received at least 1 dose of MK-4482. No SAEs, deaths or ECIs were reported.

MK-4482-010 was a randomized, 4-treatment, 4-period crossover, single site, open-label, relative bioavailability study of MK-4482 oral granules and MK-4482 reference capsule formulations in healthy adult participants. A total of 16 participants were randomized into 4 treatment sequences consisting of a single 800-mg dose of MK-4482 administered as oral granules in water, apple sauce or pudding or as the reference capsule formulation with water. Relative bioavailability was assessed through repeat evaluations of plasma NHC PK. No SAEs, deaths or ECIs were reported.

MK-4482-012 was a randomized, double-blind, placebo-controlled, multiple ascending dose study to evaluate the safety, tolerability, and PK of MK-4482. Doses of 400, 600, and 800 mg MK-4482 Q12H for 10.5 days were generally well tolerated in healthy adult study participants. Out of 32 randomized participants, 24 received at least 1 dose of MK-4482. No SAEs, deaths or ECIs were reported and no study intervention-related clinically meaningful changes in vital sign values, ECGs, or safety laboratory values (including hematology) were observed as a function of dose or treatment.

MK-4482-016 is a Phase 1 non-randomized, open-label, single dose, clinical study to evaluate the tolerability and PK of a single 800-mg dose of MK-4482 in participants with moderate hepatic impairment (n=7) compared to participants with normal hepatic function (n=7). This study is clinically completed. No SAEs, discontinuations, or serious drug-related AEs were reported.

Phase 1/2, 2a Studies:

MK-4482-005 is a Phase 1/2 randomized, multicenter, seamless, adaptive study to determine the optimal dose, safety, and efficacy of MK-4482 for the treatment of COVID-19. The primary efficacy objective is to determine the ability of MK-4482 to reduce serious complications of COVID-19 including hospitalization, reduction in SaO2 <92%, or death. As of 14-MAR-2022, 18 participants enrolled in Phase 1 (12 received MK-4482; 300 mg n=4; 600 mg n=4; 800 mg n=4), and 178 participants enrolled in Phase 2. This study is clinically completed and final unblinded results are pending. Based on preliminary review of blinded safety data, 5 SAEs were reported, 1 of which (vomiting) was considered related to study intervention by the investigator. No deaths were reported.

MK-4482-006 was a Phase 2a, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and efficacy of MK-4482 (Q12H for 5 days) in nonhospitalized adults with COVID-19. The time to undetectable SARS-CoV-2 of viral RNA

in nasopharyngeal swabs was shorter in participants receiving 800-mg MK-4482 (median: 14 days) compared with those administered placebo (median: 15 days). MK-4482 200 mg (n=23), 400 mg (n=62) or 800 mg (n=55) or placebo (n=62) was generally well tolerated with a comparable incidence of AEs across the intervention groups. Four SAEs were reported (3 participants in the MK-4482 groups combined, 1 in the placebo group); none were considered related to study intervention by the investigator. No participants died while enrolled in the study.

MK-4482-007 is a Phase 2a randomized, placebo-controlled, double-blind clinical study of MK-4482 in adults who have tested positive for SARS-CoV-2 infection via PCR and are hospitalized with a diagnosis of COVID-19 with symptoms of ≤8 days. The primary efficacy objective is to measure the proportion of nasopharyngeal swabs and saliva from recipients becoming undetectable for SARS-CoV-2 RNA at Day 5 of MK-4482 administration compared with placebo. A total of 71 participants were enrolled in the study and received at least one dose of study drug (placebo or MOV 200 mg, 400 mg, or 800 mg). This study is completed. SAEs were reported for 4 participants, 3 in the placebo group and 1 in the MOV 800-mg group (2 SAEs of acute respiratory failure [fatal] and hypovolemic shock); none were considered related to study intervention by the investigator. The only AE leading to discontinuation of the study drug and withdrawal from the study was reported in the MOV 400-mg group. This was an AE of nausea that was moderate, nonserious, and considered related to study drug. There were no obvious treatment- or dose-related trends in any mean laboratory or vital sign data.

Phase 2/3 or 3 Studies:

MK-4482-001 is a Phase 2/3 randomized, placebo-controlled, double-blind clinical study to evaluate the efficacy, safety, and PK of MK-4482 in hospitalized adults with COVID-19. In the Phase 2 portion of the study (Part 1) a total of 218 hospitalized participants with COVID-19 received at least 1 dose of MK-4482 (72 participants received MK-4482 800 mg) and 75 participants received placebo. MK-4482 was generally well tolerated with a comparable incidence of AEs across the intervention groups. SAEs were reported for 15.4% participants (15.1% MK-4482 groups, 16.0% placebo), with 1 SAE deemed related to study intervention by the investigator (Grade 3 urticaria) for 1 participant in the MK-4482 200-mg treatment group. A total of 16 participants had AEs leading to death (6.4% MK-4482 groups combined, 2.7% placebo), none of which were considered study intervention-related by investigator assessment. The study was stopped due to lack of clinical benefit in this population (participants already hospitalized prior to randomization) and did not proceed to the Phase 3 portion of the study (Part 2).

MK-4482-002 is a Phase 2/3, randomized, placebo-controlled, double-blind, multisite study to evaluate the efficacy, safety, and PK of MK-4482 administered to nonhospitalized adults with laboratory-confirmed COVID-19 and symptom onset within 7 days (Part 1, Phase 2) or within 5 days (Part 2, Phase 3) prior to randomization, and all participants must have at least one risk factor for progressing to severe illness from COVID-19. A final total of 1433 participants were enrolled in the study and the study is completed. Unblinded data are available for Part 1 and Part 2 through Day 29 as well as for the Month 7 visit in both Part 1 and Part 2 which includes collection of survival status, current supplemental oxygen use, and

any hospitalizations that occurred since last contact. MK-4482 200 mg (n=74), 400 mg (n=77), 800 mg (n=74) or placebo (n=74) Q12H for 5 days in Part 1 and MK-4482 800 mg (n=710) or placebo (n=701) Q12H for 5 days in Part 2 were generally well tolerated. In both Parts, the proportion of participants with AEs, drug-related AEs (per investigator assessment), SAEs, AEs leading to study intervention discontinuation and laboratory values that met predefined limits of change (worsening Grade 3 or 4), were comparable for the intervention groups. No clinically meaningful trends in changes in liver enzymes or hematology parameters as a function of either dose or treatment were observed. In Part 1, one participant had an AE leading to death in the placebo group. In Part 2, AEs leading to death occurred in a higher proportion of participants who received placebo compared with MK-4482.

MK-4482-013 is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of MK-4482 for the prevention of COVID-19 (laboratory-confirmed SARS-CoV-2 infection with symptoms) in adults residing with a person with COVID-19. 1539 participants were randomized out of a planned total of approximately 1376 participants. This study is clinically completed and final unblinded results are pending. Based on preliminary review of blinded safety data, SAEs were reported by 5 participants during the treatment or follow-up period (COVID-19 pneumonia [3], acute myocardial infarction [1; fatal], and fractured femur [1]); none were considered related to study intervention by the investigator. 4 participants discontinued study drug because of an AE.

#### 2.2.3.2 Ongoing Clinical Studies

MK-4482 is being evaluated in 2 ongoing Phase 1 studies (P003 and P011) and 1 ongoing Phase 2a study (P017) (Refer to the IB Section 5 for the additional details on study designs on each study).

Phase 1 studies:

MK-4482-003 is a Phase 1 non-randomized, open-label, single dose, clinical study to evaluate the tolerability and PK of a single 800-mg dose of MK-4482 in participants with severe renal impairment compared to participants with normal renal function (target enrollment of approximately N = 16-18). This study is ongoing. No SAEs, discontinuations, or serious drug-related AEs have been reported.

MK-4482-011 is a Phase 1 open-label, cross-over, bioequivalence study, evaluating the PK of a MK-4482 tablet formulation in comparison to the MK-4482 capsule formulation in healthy adult participants. Approximately 64 participants are to be randomized. This study is ongoing.

Phase 2a Studies:

MK-4482-017 is a Phase 2a double blind randomized placebo-controlled study to evaluate the efficacy and safety of MK-4482 in healthy adult participants inoculated with experimental RSV. The study is evaluating MK-4482 as pre-exposure prophylaxis and as a post-exposure treatment. As of 06-FEB-2023, 52 participants have been randomized out of a planned total of 105 participants.

### 2.2.4 Information on Other Study-related Therapy

OTV is a neuraminidase inhibitor that interferes with the release of progeny influenza virus from infected cells, thereby preventing new rounds of infection. It is approved for the treatment and prevention (pre-exposure and post-exposure) of influenza, with an adult recommended dose of 75 mg twice daily; the duration for treatment is 5 days, with a longer duration in the prophylactic setting (10 days for PEP and up to 6 weeks for prevention during a community outbreak). The most commonly-reported AEs in clinical trials with OTV are nausea and vomiting [Dutkowski, R., et al 2003].

Oseltamivir is ingested in the form of prodrug (oseltamivir phosphate) that is rapidly converted into the active metabolite, oseltamivir carboxylate (OC). Plasma OC concentrations are near maximal 3 to 4 hours after drug administration. The PK of OC is dose proportional after repeated doses of up to 500 mg BID. Steady state plasma concentrations are achieved within 3 days of 75 mg BID dosing. There is only modest accumulation (<2-fold) of OC prior to reaching steady state [Davies, B. E. 2010] [He, G., et al 1999].

Refer to the OTV SmPC for additional details.

## 2.3 Benefit/Risk Assessment

Participants in clinical studies will not receive direct benefit from treatment during participation as clinical studies are designed to provide information about the safety and properties of an investigational medicine.

The totality of the safety data from Phase 1 through Phase 3 clinical studies and post-authorization surveillance for the use of MK-4482 in the treatment of COVID-19 demonstrate an acceptable safety and tolerability profile of MK-4482.

There were no effects on cardiovascular, neurological, and respiratory function in several well-characterized safety pharmacology experimental models. The integrated assessment of the mutagenic and genotoxic potential of MK-4482 indicates that MK-4482 is not mutagenic or genotoxic in in vivo mammalian systems.

As described in Section 2.2.2, in a 28-day repeat dose toxicity study with MK-4482 in dogs, reversible hematologic toxicities were noted after Day 7 at exposures 0.4-fold those of the anticipated clinical exposures at the 800-mg Q12H dose. However, to date no clinically meaningful hematological changes have been observed in healthy participants up to 800-mg MK-4482 Q12H for up to 10.5 days or in participants with COVID-19 at multiple doses up to 800-mg Q12H for 5 days.

Histopathology results from the 3-month rat toxicity study demonstrated an increase in the thickness of the growth plate/physis, a finding not observed in 1-month studies in rats, dogs, or mice. These findings are not considered to represent a significant new risk to human adults.

In fertility studies in rats there were no MK-4482-related effects on female or male fertility, or on early embryonic development up to the highest dose tested, 500 mg/kg/day, (2.3-/6.8-fold [female/male] the clinical NHC exposure at 800 mg Q12H). While embryolethality (postimplantation losses) and teratogenicity were limited to rats exposed to 8.4-fold the clinical NHC exposure at 800 mg Q12H during the organogenesis period, and these developmental findings were not observed in rats up to 3.2-fold the clinical NHC exposure at 800 mg Q12H and rabbits up to 20-fold the clinical NHC exposure at 800 mg Q12H, WOCBP will be required to use effective contraception for the duration of treatment and for at least 28 days postdose.

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB (for MK-4482), SmPC (for OTV), and informed consent documents.

# 3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

This study will be conducted in healthy participants.

| **Primary Objective** | **Primary Endpoint** |
|---|---|
| Part 1 | |
| Objective 1: To evaluate the infectivity rate of the influenza challenge virus in healthy adult participants. | Day 1 PM to planned discharge, Day 2 PM to planned discharge:<br>• Quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR)-confirmed influenza infection |
| Objective 2: To assess the safety of the influenza challenge virus in healthy adult participants | Viral challenge to Follow-up Visit:<br>• Adverse events (AEs) related to viral challenge |
| Part 2 | |
| Objective 3: To evaluate the effectiveness of MK-4482 (800 mg Q12H for 5 days) as a post-exposure intervention in reducing influenza viral load, as compared to placebo.<br><br>Hypothesis (Post-exposure prophylaxis [PEP]): MK-4482 (800 mg Q12H for 5 days), initiated 12 h following intranasal inoculation of the influenza challenge virus reduces the peak viral load (as determined by quantitative viral culture) compared to placebo.<br><br>Hypothesis (Treatment): MK-4482 (800 mg Q12H for 5 days), initiated 2 days following intranasal inoculation of the influenza challenge virus reduces the viral load AUC (as determined by quantitative viral culture) compared to placebo. | PEP (MK-4482) Day 1 PM to planned discharge:<br>• Peak viral load (PVL) (by quantitative viral culture)<br><br>Treatment (MK-4482) First dose of study drug to planned discharge:<br>• Area under the viral load-time curve (VL-AUC) (by quantitative viral culture) |

| **Secondary Objectives** | **Secondary Endpoints** |
|---|---|
| <u>Part 1</u> | |
| Objective 4: To characterize the virological profile of the influenza challenge virus in healthy adult participants | Day 1 PM to planned discharge, Day 2 PM to planned discharge:<br>• Quantitative viral culture-confirmed influenza infection<br>• VL-AUC (qRT-PCR and quantitative viral culture)<br>• PVL (qRT-PCR and quantitative viral culture)<br>• Duration of quantifiable influenza (qRT-PCR and quantitative viral culture) |
| Objective 5: To characterize the clinical symptom profile of the influenza challenge virus in healthy adult participants. | Day 1 AM to planned discharge, Day 2 middle of day to planned discharge:<br>• Area under the total symptom score-time curve (TSS-AUC)<br>• Peak total symptom score (TSS)<br>• Daily maximum TSS<br>• Duration (days) of Grade ≥2 symptoms<br>• Time (days) to symptom resolution<br>• Time (days) to peak daily maximum TSS |

| | |
|---|---|
| <u>Part 2</u> | |
| Objective 6: To estimate the effect of MK-4482 (800 mg Q12H for 5 days) as post-exposure prophylaxis (initiated 12 h following intranasal inoculation of influenza challenge virus) or as treatment (initiated 2 days following intranasal inoculation of influenza challenge virus) on the reduction of influenza viral load, as compared to placebo.<br><br>Objective 7: To estimate the effect of oseltamivir (75 mg Q12H for 5 days) as treatment (initiated 2 days following intranasal inoculation of influenza challenge virus) on the reduction of influenza viral load, as compared to placebo | PEP (MK-4482) – Virology: Day 1 PM to planned discharge:<br>Symptoms and temperature Day 1 AM to planned discharge:<br><br>• VL-AUC (qRT-PCR and quantitative viral culture)<br>• PVL (qRT-PCR)<br>• qRT-PCR-confirmed influenza infection<br>• qRT-PCR-confirmed symptomatic influenza infection<br>• qRT-PCR-confirmed moderately severe symptomatic influenza infection<br>• qRT-PCR-confirmed febrile influenza infection<br>• Quantitative viral culture-confirmed influenza infection<br>• Quantitative viral culture-confirmed symptomatic influenza infection<br>• Duration of quantifiable influenza (qRT-PCR and quantitative viral culture)<br>• Time (days) to confirmed negative test (qRT-PCR and quantitative viral culture)<br>• Time (days) to peak viral load (qRT-PCR and quantitative viral culture)<br><br>Treatment (MK-4482 and oseltamivir) – first dose study drug to planned discharge:<br><br>• VL-AUC (qRT-PCR and quantitative viral culture)<br>• PVL (quantitative viral culture and qRT-PCR)<br>• Duration of quantifiable influenza (qRT-PCR and quantitative viral culture)<br>• Time (days) to confirmed negative test (qRT-PCR and quantitative viral culture) |

| | |
|---|---|
| | • Time (days) to peak viral load (qRT-PCR and quantitative viral culture) |
| Objective 8: To evaluate the effect of MK-4482 (800 mg Q12H for 5 days) as PEP (initiated 12 h following intranasal inoculation of influenza challenge virus) or as treatment (initiated 2 days following intranasal inoculation of the influenza challenge virus) on the course of clinical symptoms following intranasal inoculation with the influenza challenge virus, compared to placebo<br><br>Objective 9: To evaluate the effect of oseltamivir (75 mg Q12H for 5 days) as treatment (initiated 2 days following intranasal inoculation of influenza challenge virus) on the course of clinical symptoms following intranasal inoculation with the influenza challenge virus, compared to placebo | PEP (MK-4482) – Day 1 AM to planned discharge;<br>Treatment (MK-4482 and oseltamivir) – first dose study drug to planned discharge:<br>• TSS-AUC<br>• Peak TSS<br>• Daily maximum TSS<br>• Duration (days) of Grade ≥2 symptoms<br>• Time (days) to symptom resolution<br>• Time (days) to peak daily maximum TSS |
| Objective 10: To assess the safety and tolerability of MK-4482 (800 mg Q12H for 5 days) | PEP (MK-4482) and Treatment (MK-4482) – from first dose of study drug to Follow-up Visit:<br>• All AEs |
| Objective 11: To monitor the safety of the influenza challenge virus in healthy adult participants | Viral challenge to Follow-up Visit:<br>• AEs related to viral challenge<br>• Concomitant medication use |
| Objective 12: To assess the plasma PK of NHC following administration of MK-4482 (800 mg Q12H for 5 days) | PEP (MK-4482) and Treatment (MK-4482):<br>• NHC Cmax, Tmax, t1/2, AUC0-12hr, AUC0-last, Ctrough following multiple dose administration of MK-4482 |

| Tertiary/Exploratory Objectives | Tertiary/Exploratory Endpoints |
|---|---|
| Part 2 | |
| Objective 13: To explore the effect of MK-4482 as a post viral exposure intervention (PEP or treatment) on the rate of seroconversion to the challenge virus.<br><br>Objective 14: To explore the effect of oseltamivir as treatment on the rate of seroconversion to the challenge virus. | • Number of seroconversions by Day 28 post inoculation |
| Objective 15: To explore the effect of MK-4482 (800 mg Q12H for 5 days), initiated 2 days (treatment) following intranasal inoculation with influenza challenge virus in reducing incidence of influenza infection, symptomatic influenza infection, moderately severe symptomatic influenza infection, and febrile influenza infection, as compared to placebo<br><br>Objective 16: To explore the effect of oseltamivir (75 mg Q12H for 5 days), initiated 2 days following intranasal inoculation with the influenza challenge virus in reducing incidence of influenza infection, symptomatic influenza infection, moderately severe symptomatic influenza infection, and febrile influenza infection, as compared to placebo | Treatment (MK-4482 and oseltamivir) – first dose of study drug to planned discharge:<br>• qRT-PCR-confirmed influenza infection<br>• qRT-PCR-confirmed symptomatic influenza infection<br>• qRT-PCR-confirmed moderately severe symptomatic influenza infection<br>• qRT-PCR-confirmed febrile influenza infection<br>• Quantitative viral culture-confirmed influenza infection<br>• Quantitative viral culture-confirmed symptomatic influenza infection |
| Objective 17: To estimate the effect of MK-4482 (800 mg Q12H for 5 days) on symptom severity scores (total and domains) assessed using a patient-reported outcome measure (FLU-PRO Plus©) following intranasal inoculation with the influenza challenge virus. | PEP (MK-4482) – Day 1 PM to planned discharge;<br><br>Treatment (MK-4482) – Day 2 PM to planned discharge:<br><br>• Symptom severity score (total and domains) by FLU-PRO Plus© questionnaire |

| | |
|---|---|
| Objective 18: To estimate the effect of administration of MK-4482 (800 mg Q12H x 5 days) on mucus production after intranasal inoculation with influenza challenge virus, as compared to placebo. | PEP (MK-4482) – Day 1 AM to planned discharge;<br>Treatment (MK-4482) - Day 2 AM - Day 8 AM:<br>• Total weight of mucus produced<br>• Total number of tissues used by participants |
| Objective 19: To explore baseline immunology and response to infection with the influenza challenge virus. | • Exploratory assays related to respiratory viral infection and immunology (blood and nasal samples) |
| Objective 20: To explore the effect of MK-4482 (800 mg Q12H x 5 days) on the rate of low frequency nucleotide substitutions (LNS) after intranasal inoculation with the influenza challenge virus, as compared to placebo. | LNS quantitation by viral sequencing of nasal samples. |
| Objective 21: To explore the relationship between genetic variation and response to the treatment(s) administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in the study. | Germline genetic variation and association to clinical data collected in this study. |

# 4 STUDY DESIGN

## 4.1 Overall Design

This is a two-part study in healthy male and female participants aged 18 to 55 years (inclusive), who will be inoculated with either the A/France/759/21 [H1N1] strain (from the 6B.1A.5a.1 clade) or an alternative influenza A viral strain eg, A/Perth/16/2009 [H3N2] or A/California 2009-like [H1N1]. This study will be conducted in conformance with GCP.

Initially participants will be screened according to generic criteria for recruitment into a general population of eligible participants. Participants will have serosuitability confirmed during the generic screening process prior to beginning study-specific screening for the challenge study and within 90 days prior to inoculation. Participants having passed both the generic screening process and meeting the study-specific inclusion/exclusion criteria of the study will be admitted to quarantine on Day -2/-1. Prior to viral inoculation, quarantined participants will undergo additional screening to exclude those with respiratory pathogens, and participants who are excluded at this time will not undergo dosing of study intervention. Historical generic screening data collected through the generic screening process may be transferred to this study after the study-specific ICF has been signed by the participant.

Part 1

Part 1 is an open-label validation study, with a cohort of 20 untreated (ie, not receiving study drug) participants undergoing nasal inoculation with the A/France/759/21 [H1N1] strain on Day 0 to confirm viral infectivity and disease. A single inoculum titer will be used based on prior experience with influenza challenge viruses.

Assessment of viral load (twice-daily nasal sampling), symptoms (using a diary card three times per day, in addition to once-daily administration of the FLU-PRO Plus© tool), immunological markers, and safety will be performed during quarantine until discharge on Day 8. Participants will be discharged from the quarantine unit on Day 8 (or may remain longer at the discretion of the investigator). Suitability for discharge will be based on clinical judgment; nasal swab samples may be tested for the presence of virus if deemed necessary prior to discharge. Participants will have a follow up visit at Day 28, which will be the last visit for the study.

Following the completion of Part 1, a review of safety, tolerability, rate of infectivity by plaque assay and PCR, the viral load profile, and symptoms of infection by the the A/France/759/21 [H1N1] strain will be performed by the Sponsor in collaboration with the study site. At a minimum, the review of safety, tolerability, and rate of infectivity by PCR will be required to confirm that Part 2 may proceed using the same challenge strain. The infectivity rate of the A/France/759/21 [H1N1] strain at this inoculum is expected to be >50%; however, in case the infectivity rate is too low to be viable or there are safety concerns that preclude further use of the A/France/759/21 [H1N1] challenge strain then an alternative plan will be to revert to another virus that has been previously well-characterized eg, A/Perth/16/2009 [H3N2] or A/California 2009-like [H1N1]. Further details of the alternative viral strains are provided in Appendix 11.

Additionally, based on review of Part 1 data, the following modifications may be made to Part 2 (see Section 8.16.7):

Sample size re-estimation (this is currently estimated to be ~140 [~35 participants per intervention group], based on data from prior influenza HCSs using A/Perth/16/2009 [H3N2]). The revised sample size is not anticipated to vary (increase or decrease) outside the range of 25 to 50 per intervention group.

Extension of the quarantine period beyond Day 8; this will be at the discretion of the Investigator based on observed prolonged viral shedding in Part 1 and/or a need for prolonged safety monitoring

Removal of discretionary safety monitoring assessments in Part 2. The intent of Part 1 is to define an appropriate level of safety monitoring in Part 2. As such, safety assessments at certain time points in the SoA for Part 2 have been designated as discretionary; the retention vs removal of such time points in Part 2 will be determined by the observed safety profile in Part 1.

Viral inoculum titer adjustment (increase or decrease)

Following the review of Part 1 data, any decisions regarding the conduct of Part 2, including confirmation of viral strain and any of the above-mentioned potential modifications, will be documented in a PCL.

Part 2

Part 2 will be a randomized, double-blind placebo- and active-comparator-controlled study where participants will be inoculated on Day 0 with either the A/France/759/21 [H1N1] virus used in Part 1 or an alternative influenza virus; the challenge agent will thus be referred to as "IAV", to allow for either option.

Participants will be randomly allocated to one of four interventions; each intervention will be received by approximately 35 participants. Active study drug (MK-4482 or OTV) will be administered Q12H for 5 days in total, with dosing of all 4 groups (with active drug or placebo) commencing on Day 0 PM (approximately 12 hours post-inoculation) and completing at Day 6 PM (see Table 1). All participants will be blindfolded during dosing, and an unblinded dosing team will carry out dosing. At each dose administration, each participant will receive a total of 4 capsules. It is important for each capsule to be administered separately, ie, the participant will administer and swallow the first capsule before being given the second capsule by the unblinded dosing team staff member, and so on.

In the MK-4482 PEP group, dosing with MK-4482 (4 x 200 mg capsules) will begin on Day 0 PM (approximately 12 hours post-inoculation) and finish on Day 5 AM. To maintain blinding, participants in this group will complete the dosing period by receiving placebo (identically matched to MK-4482, ie, 4 capsules) from Day 5 PM to Day 6 PM, inclusive.

In the MK-4482 and OTV Treatment groups, participants will receive placebo from Day 0 PM through Day 1 PM. In the MK-4482 group, this will be a placebo identically-matched to

MK-4482 (ie, 4 capsules), and in the OTV group this will be 4 capsules of placebo of similar size and weight, but not appearance, to the OTV capsules. Dosing with MK-4482 or OTV, respectively, will begin on Day 2 AM (ie, 2 days post-inoculation) and finish on Day 6 PM. Each dose administration of MK-4482 will comprise 4 x 200 mg MK-4482 capsules. To maintain participant blinding, each dose administration of OTV will comprise 1 x 75 mg OTV capsule and 3 x placebo capsules.

Participants in the placebo group will receive 4 capsules of the placebo identically matched to MK-4482 from Day 0 PM through Day 6 PM

Assessment of viral load (twice-daily nasal sampling), symptoms (using a diary card three times per day, in addition to once-daily administration of the FLU-PRO Plus© tool), PK, immunological and other exploratory markers, and safety will be performed during quarantine until discharge on Day 8 (or may remain longer at the discretion of the investigator). Suitability for discharge will be based on clinical judgment; nasal swab samples may be tested for the presence of virus if deemed necessary prior to discharge. Participants will have a follow up visit at Day 28, which will be the last visit for the study.

Specific procedures to be performed during the study, including prescribed times and associated visit windows, are outlined in Section 1.3 of the SoA. Details of each procedure are provided in Section 8.

## 4.2 Scientific Rationale for Study Design

The purpose of this influenza challenge study is to provide an assessment of the antiviral activity of MK-4482 against IAV in humans. An influenza human challenge model was selected based on the demonstration in multiple previous influenza HCSs of the ability of the model to generate safe and reproducible mild to moderate infection from a wild-type virus in healthy human participants. Part 1 (Validation study) will characterize the A/France/759/21 [H1N1] viral strain to support its use as a challenge agent in Part 2 for the MK-4482 evaluation.

By assessing MK-4482 as PEP (initiation 12 hours post-inoculation) and Treatment (initiation 2 days post-inoculation), this study provides an opportunity to gain an understanding of the impact of timing of drug initiation on antiviral activity under controlled conditions where the timing of inoculation is known.

The OTV comparator arm will serve a positive control and includes an approved agent known to be clinically effective against IAV.

### 4.2.1 Rationale for Endpoints

Endpoints for Parts 1 and 2 of this study are described separately in Section 3. The primary endpoints of Part 1 (Validation Study) will be used for decision-making for Part 2 (MK-4482 Challenge Study), and the primary endpoints of Part 2 will be used for the evaluation of MK-4482 as a post-exposure intervention in reducing influenza viral load.

The primary endpoints for Part 2 are virological, and further described in 4.2.1.1. Clinical endpoints (described in 4.2.1.2) are intended to provide support to the primary (virology-based) endpoints.

Definitions of the endpoints listed in Section 3 are provided in Table 2 below.

Table 2 Definitions of Study Endpoints

| **Endpoint Type** | **Endpoint** | **Definition** |
|---|---|---|
| PD (virological) | qRT-PCR-confirmed influenza infection | 2 x quantifiable (≥ LLOQ) influenza challenge virus qRT-PCR measurements (reported on ≥2 independent nasopharyngeal samples over 2 days) |
| | Quantitative viral culture-confirmed influenza infection | 1 x quantifiable (≥ LLOQ) influenza challenge virus measurement from quantitative viral culture from a nasopharyngeal sample |
| | Peak viral load (PVL) | Maximum viral load of influenza challenge virus from nasopharyngeal samples (to be determined by both quantitative viral culture and qRT-PCR) |
| | Area under the viral load-time curve (VL-AUC) | Area under the viral load-time curve of influenza challenge virus nasopharyngeal samples (to be determined by both quantitative viral culture and qRT-PCR) |
| | Duration of quantifiable influenza | Time (in days) from the first quantifiable (≥ LLOQ) influenza challenge virus measurement until the first confirmed unquantifiable (ie, <LLOQ detected or not detected) assessment after the peak measure (after which there are no more confirmed quantifiable samples).<br>(Endpoint to be determined by both quantitative viral culture and qRT-PCR) |
| | Time (days) to confirmed negative test (qRT-PCR and quantitative viral culture) | Time (in days) from the beginning of the specified time frame until the first confirmed unquantifiable (ie, <LLOQ detected or not detected) assessment after the peak measure (after which there are no more confirmed quantifiable samples).<br>(Endpoint to be determined by both quantitative viral culture and qRT-PCR) |

| Endpoint Type | Endpoint | Definition |
|---|---|---|
| | Time (days) to peak viral load | Time (in days) from the beginning of the specified time frame until the peak viral load measurement (to be determined by both quantitative viral culture and qRT-PCR) |
| PD (serological) | Number of seroconversions by Day 28 post inoculation | To be determined using HAI and/or neutralization assays.<br>• In HAI assays, seroconversion is defined as one of the following:<br>  ○ an increase from a negative pre-inoculation titer (<10) to a Day 28 titer of ≥40<br>  ○ a significant increase in antibody titer, ie, at least a 4-fold increase between pre-inoculation and Day 28 titers, where the pre-inoculation titer is ≥ 10<br>• In neutralization assays, seroconversion is defined as:<br>  ○ a significant increase in antibody titer, ie, at least a 4-fold increase between pre-inoculation and Day 28 titers |
| Clinical | Area under the total symptom score-time curve (TSS-AUC) | Area under the total clinical symptom score-time curve (TSS-AUC), as measured by graded symptom scoring system collected 3 times daily; each symptom is graded on a scale of 0 to 3 or 4, where a higher grade represents a higher symptom intensity/impact |
| | Peak total symptom score (TSS) | Maximum total symptoms score (TSS), as measured by graded symptom scoring system collected 3 times daily |
| | Daily maximum TSS | Maximum TSS on each day, measured by graded symptom scoring system collected 3 times daily |
| | Duration (days) of Grade ≥2 symptoms | Duration of time (in days) from the first occurrence of any symptom assigned Grade 2 or higher, to the beginning of the first 24-hour period without any symptom assigned Grade 2 or higher, after the peak TSS |

| Endpoint Type | Endpoint | Definition |
|---|---|---|
| | Time (days) to symptom resolution | Time (in days) from the beginning of the specified time frame until the beginning of a 24-hour period with no symptoms above the baseline maximum TSS, as measured by graded symptom scoring system collected 3 times daily.<br>Baseline maximum is defined as the maximum TSS on Day -1 |
| | Time (days) to peak daily maximum TSS | Time (in days) from the beginning of the specified time frame to the time of the peak daily maximum TSS |
| Combined: virological/ clinical | qRT-PCR-confirmed symptomatic influenza infection | • qRT-PCR-confirmed influenza infection (2 x quantifiable [≥ LLOQ] influenza challenge virus qRT-PCR measurements [reported on ≥2 independent nasopharyngeal samples over 2 days])<br>AND<br>• Total symptoms score (TSS) ≥2 at ≥1 time point following inoculation |
| | qRT-PCR-confirmed moderately severe symptomatic influenza infection | • qRT-PCR-confirmed influenza infection (2 x quantifiable [≥ LLOQ] influenza challenge virus qRT-PCR measurements [reported on ≥2 independent nasopharyngeal samples over 2 days])<br>AND<br>• Any symptom of Grade ≥2 at ≥1 time point following inoculation |
| | qRT-PCR-confirmed febrile influenza infection | • qRT-PCR-confirmed influenza infection (2 x quantifiable [≥ LLOQ] influenza challenge virus qRT-PCR measurements [reported on ≥2 independent nasopharyngeal samples over 2 days])<br>AND<br>• Temperature of ≥37.9°C at ≥1 time point following inoculation |

| Endpoint Type | Endpoint | Definition |
|---|---|---|
| | Quantitative viral culture-confirmed symptomatic influenza infection | • Quantitative viral culture-confirmed influenza infection (1 x quantifiable [≥ LLOQ] influenza challenge virus measurement from quantitative viral culture from a nasopharyngeal sample<br>AND<br>• TSS ≥2 at ≥1 time point following inoculation |
| HAI=hemagglutination inhibition; LLOD=lower limit of detection; LLOQ=lower limit of quantification; PD=pharmacodynamic; qRT-PCR= quantitative reverse transcriptase-polymerase chain reaction; TSS=total symptom score | | |

#### 4.2.1.1 Pharmacodynamic Endpoints

The primary endpoints for Part 2 of this study (MK-4482 challenge study) are virological; this approach was selected based on the rationale that demonstration of antiviral activity (ie, viral load reduction) is reflective of the mechanism of action of the drugs included in the study. Furthermore, viral shedding has been shown to have an association with symptoms, both in terms of magnitude and duration [Fry, A. M., et al 2014].

Reduction in PVL compared to placebo has been selected for the analysis of MK-4482 as PEP, and reduction in the area under the viral load-time curve (VL-AUC) has been selected for the analysis of MK-4482 and OTV as treatment; these selections are based on influenza viral dynamics and anticipated antiviral effects of MK-4482 and OTV when initiated either 12 hours or 2 days post-inoculation (ie, prior to or following predicted PVL, respectively).

Quantitative viral culture (by plaque assay) has been selected as the means of determining viral load, based on the mechanism of action of MK-4482 in halting productive viral replication; qRT-PCR is also included within the secondary virological endpoints. Additional secondary virological endpoints include the duration of quantifiable virus detection; this is intended to complement the clinical endpoints related to time to symptom resolution.

Combined virological/clinical secondary endpoints will also assess the impact of MK-4482 and OTV on the incidence of symptomatic/febrile influenza infection; these are included with the intent of estimating the performance of study drug in a subset of participants with more severe disease.

Exploratory analyses may be performed to define the antiviral activity of MK-4482 relative to the viral dynamics of influenza. Serum and/or nasal immunological biomarkers (Sec. 8.4.5 and 8.10) may be explored for their ability to predict disease severity and/or response to treatment; this will be described separately in a supplemental SAP. Viral sequencing to assess rates of LNS will also be used to explore the exposure-response relationship for NHC in influenza, based on the known mechanism of action.

#### 4.2.1.2 Efficacy Endpoints

Clinical efficacy endpoints are included as secondary and exploratory in this study to provide support to the primary (virology-based) endpoints. Symptom scores, measured from 13 self-reported symptoms on a diary card, will be used to derive a peak symptom score, corresponding to peak illness, and a total symptom score AUC, as a measure of disease burden over time. Additionally, time to symptom resolution will be measured, noting that existing approved antiviral agents have demonstrated a reduction in time to alleviation of symptoms when tested against placebo in randomized clinical trials [Liu, J. W., et al 2021].

In addition to the standard 13-symptom diary card administered 3 times per 24 hours, the FLU-PRO Plus© tool will be administered once every 24 hours (in the evening), and endpoints assessed will be the symptom severity scores (global and by domain). Use of FLU-PRO© (an earlier version of the tool) was assessed based on information from 200 patients with influenza-like illness (28% hospitalized). It has been shown to produce scores that are well defined, reliable, valid, and responsive to change in influenza-positive and influenza-negative adults, demonstrating its utility in clinical trials and epidemiological studies [Powers, J. H. 3rd., et al 2018]. In addition to its demonstration of utility in clinical trials of patients with influenza, the FLU-PRO© has been studied and demonstrated usefulness in a previous influenza HCS. Aligned with FDA PRO-development guidance, the FLU-PRO Plus© can provide additional insight into treatment efficacy and safety in a manner that is more precise and less biased than non-standardized metrics in registrational trials [Coles, C., et al 2019].

Mucus weights will be measured as an objective exploratory endpoint in conjunction with symptom score-based endpoints.

#### 4.2.1.3 Safety Endpoints

Based on available clinical safety data to date, evaluation of safety will be adequately assessed from the following standard safety assessments: VS, 12-lead ECG, laboratory safety tests (blood chemistry, hematology, urinalysis) and AEs. Additional laboratory safety assessments in the setting of the influenza challenge model are also included (coagulation studies, CK, and thyroid function testing). Safety evaluations will be conducted throughout the study at intervals dictated by the viral challenge model and NHC PK properties.

Participants will be domiciled in quarantine conditions for at least 8 days after inoculation with IAV, to allow for a sufficient duration of time to clear the virus. 28 days post-inoculation is deemed an adequate follow-up period for safety following viral inoculation as well as administration of either study drug in this protocol.

#### 4.2.1.4 Pharmacokinetic Endpoints

**Plasma PK for NHC**

Blood samples for the assessment of PK of NHC in plasma will be collected (as described in Sec. 1.3) and used to evaluate standard PK parameters (eg, Cmax, Tmax, AUC0-12, Ctrough) following multiple dose administration of MK-4482. The PK analyses will be

based on only plasma NHC PK (ie, not PBMC NHC-TP). Plasma NHC exposures have been shown to be well correlated with NHC-TP exposures in PBMCs, with plasma NHC AUC being a consistent strong correlate of NHC-TP exposures. Additionally, the t1/2 of NHC-TP in PBMCs was consistent with the terminal t1/2 of NHC in plasma. Based on this, the more readily available NHC exposures can be considered an appropriate surrogate for NHC-TP for the evaluation of exposure-dependency in pharmacometric modeling analyses.

**Plasma PK for Oseltamivir Carboxylate**

A single blood sample for assessment of oseltamivir carboxylate in plasma will be collected near the Tmax (ie, at 4 hours) following the AM dose of study drug administration on Day 2 (as described in Section 8.8.2). These samples will be stored and tested to evaluate plasma oseltamivir carboxylate exposures if deemed necessary by the Sponsor.

#### 4.2.1.5 Planned Exploratory Biomarker Research

##### 4.2.1.5.1 Planned Genetic Analysis

Genetic variation may impact a participant's response to therapy, susceptibility to, severity, and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug ADME, mechanism of action of the drug, disease etiology, and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a sample will be collected for DNA analysis from consenting participants.

DNA samples may be used for research related to the study intervention(s), the disease under study, or related diseases. They may also be used to develop tests/assays including diagnostic tests related to the disease under study, related diseases, and study intervention(s). Genetic research may consist of the analysis of 1 or more candidate genes, the analysis of genetic markers throughout the genome, or analysis of the entire genome. Analysis may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to understand study disease or related conditions.

#### 4.2.1.6 Future Biomedical Research

The Sponsor will conduct FBR on DNA specimens for which consent was provided during this clinical study.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for FBR is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure participants receive the correct dose of the correct drug/vaccine at the correct time. The details of FBR are presented in Appendix 6.

### 4.2.2 Rationale for the Use of Comparator/Placebo

OTV has been selected as a comparator for this study, with its initiation at 48 hours post-inoculation mirroring the MK-4482 Treatment arm. This is in alignment with its approved usage as a treatment of influenza, where it is recommended to be initiated within 2 days of symptom onset; in those participants who develop symptoms in this study, symptom onset is anticipated to occur between 24 and 48 hours post-inoculation. The use of an approved antiviral treatment as a comparator will help to benchmark the performance of MK-4482 in this human challenge model. Additionally, placebo will be used as a direct comparator in the assessments of antiviral activity and symptom resolution in order to evaluate the effects of MK-4482.

## 4.3 Justification for Dose

An 800-mg dose of MK-4482 will be administered Q12H for 5 days in this study, which is the same as the proposed therapeutic dose for adults and was the dose assessed in the pivotal Phase 3 portion of the Phase 2/3 study for the treatment of adults with COVID-19 (P002 Part 2) and in a Phase 3 study of MK-4482 for post-exposure prophylaxis of COVID-19 in adults (P013). This dose is similarly being evaluated in an ongoing human challenge study for the prevention and treatment of RSV in healthy adults (P017).

Preclinical data place the potency of MK-4482 against influenza within the range of the potency against SARS-CoV-2. Comparison of effective dose amounts based on in vitro assays and in vivo preclinical models suggest that similar concentrations of NHC may be effective against both influenza and SARS-CoV-2 infection. In vitro assessments of NHC activity against influenza show a range of EC50 values (0.006-3.2 μM) that overlaps with the range of EC50 values (0.08-2.66 μM) demonstrated against SARS-CoV-2, indicating a similar range of potency, allowing for differences in cell and assay types. As described in Section 2.2.2, in a ferret influenza model, treatment with 7 mg/kg BID MOV was sufficient for maximal therapeutic benefit [Toots, M., et al 2020]. A similar MOV dosing level (5 mg/kg BID) was effective in a ferret model of SARS-CoV-2 infection (Cox 2020). Together these data suggest that the same MK-4482 dose used in the treatment of COVID-19 (800 mg Q12H) should be appropriate for influenza.

PK analyses indicate no difference in NHC exposure between healthy participants and participants infected with SARS-CoV-2. Therefore, the same 800-mg dose administered Q12H for 5 days for patients with SARS-CoV-2 has been selected for evaluation against IAV in this study, as it is expected to achieve exposures that are believed to be efficacious based on the totality of preclinical data.

Of note, multiple doses up to 800 mg MK-4482 Q12H for up to 10.5 days and single doses up to 1600 mg, were generally well tolerated in healthy participants.

The dosing regimen of OTV to be used in this study (75 mg twice daily for 5 days) is the indicated regimen for the treatment of influenza in adults.

## 4.4 Beginning and End-of-Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section 7.3). For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last.

If the study includes countries in the European Economic Area (EEA), the local start of the study in the EEA is defined as First Site Ready (FSR) in any Member State.

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

### 4.4.1 Clinical Criteria for Early Study Termination

There are no prespecified criteria for terminating the study early.

# 5 STUDY POPULATION

As stated in the Code of Conduct for Clinical Trials (Appendix 1.1), this study includes participants of varying age (as applicable), race, ethnicity, and sex (as applicable). The collection and use of these demographic data will follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.

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

## 5.1 Inclusion Criteria

An individual is eligible for inclusion in the study if the individual meets all of the following criteria:

### Type of Participant and Disease Characteristics

1. The participant is in good health based on medical history, physical examination, VS measurements, spirometry, and ECGs performed before inoculation.
   Appendix 9 provides a table of the 12-Lead Electrocardiogram Evaluation Criteria.
2. The participant is in good health based on laboratory safety tests obtained at the screening visit. Appendix 2 provides a table of laboratory safety tests to be performed. Appendix 10 provides an algorithm for the assessment of out-of-range laboratory values.

   The laboratory safety test parameter value(s) for hemoglobin and platelet levels must be ≥LLN, total white cell count must be ≥3000/μL, and absolute neutrophil count must be ≥1500/μL before the participant can be considered eligible for inclusion.

Appendix 10 provides an algorithm for the assessment of out-of-range laboratory values.

### Demographics

3. The participant is an individual of any sex/gender, from 18 years to 55 years of age inclusive, at the time of providing study-specific informed consent.
4. The participant has a total body weight ≥50 kg and Body Mass Index (BMI) ≥18 kg/$m^2$ and ≤35 kg/$m^2$.

### Male Participants

5. Contraception used by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical trials.

Male participants must agree to the following during the intervention period and for at least 28 days after viral challenge (in Part 1) and for at least 90 days after the last dose of study intervention (in Part 2):

- Abstains from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agrees to remain abstinent

OR

- Uses contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause, documented from the site personnel's review of the participant's medical records, medical examination, or medical history interview) as detailed below

Uses a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a POCBP who is not currently pregnant.

Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile- vaginal penetration.

**Female Participants**

6. A participant assigned female sex at birth is eligible to participate if not pregnant or breastfeeding, and at least one of the following conditions applies:

- Is not a POCBP
  OR

- Is a POCBP and:

Uses a contraceptive method that is highly effective (a low user dependency method OR a user dependent hormonal method in combination with barrier method), or is abstinent from penile-vaginal intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 for at least 28 days after viral challenge (in Part 1) and for at least 28 days after the last dose of study intervention (in Part 2). The participant agrees not to donate eggs (ova, oocytes) to others or freeze/store eggs during this period for the purpose of reproduction.

The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Contraceptive use by POCBPs should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions are more stringent than the requirements above, the local label requirements are to be followed.

Has a negative highly sensitive pregnancy test (serum) as required by local regulations) within 24 hours before the first dose of study intervention. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. Additional requirements for pregnancy testing during and after study intervention are in Section 8.5.6.

Abstains from breastfeeding during the study intervention period and for at least 28 days after viral challenge (in Part 1) and for at least 28 days after the last dose of study intervention (in Part 2).

Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a POCBP with an early undetected pregnancy.

**Informed Consent**

7. The participant (or legally acceptable representative) has provided documented informed consent/assent for the study, including for FBR.

**Additional Categories**

8. The participant is serosuitable* to the challenge virus within 90 days prior to study intervention.
    * A participant must be serosuitable to take part in the study, ie, he/she must have no or low pre-existing serum levels of antibodies specific to the challenge agent. This antibody titer cut-off for serosuitability will be described in the AP.
    * Serum levels of pre-existing IAV (A/France/759/21 [H1N1] or the alternative virus eg, A/Perth/16/2009 [H3N2] or A/California 2009-like [H1N1])-specific antibodies will be determined as described in the AP.

## 5.2 Exclusion Criteria

The participant must be excluded from the study if the participant meets any of the following criteria:

**Medical Conditions**

1. The participant has a history of, or has currently active, symptoms or signs suggestive of upper or lower respiratory tract infection within 4 weeks prior to admission to quarantine..
2. The participant has a history of clinically significant endocrine, GI, cardiovascular, hematological, hepatic, immunological, renal, respiratory, genitourinary, or major neurological (including stroke and chronic seizures) abnormalities or diseases. Participants with a remote history of uncomplicated medical events (eg, uncomplicated kidney stones, as defined as spontaneous passage and no recurrence in the last 5 years, or childhood asthma) may be enrolled in the study at the discretion of the investigator. Additionally, participants with a physician-diagnosed mild Irritable Bowel Syndrome not requiring regular treatment can be included at the discretion of the investigator.

3. The participant is mentally or legally incapacitated, has significant emotional problems at the time of prestudy (screening) visit, or expected during the conduct of the study, or has a history of clinically significant psychiatric disorder of the last 5 years. Participants who have had situational depression may be enrolled in the study at the discretion of the investigator. Participants with a history of resolved depression and/or anxiety 1 or more years ago may be included at the discretion of the investigator. Participants with a history of stress related illness, which is not ongoing or requiring current therapy, with good evidence of preceding stressors may also be included at the investigator's discretion. If required, participants will be assessed prior to enrolment with a Patient Health Questionnaire (PHQ-9) and/or Generalized Anxiety Disorder Questionnaire (GAD-7) which must score ≤ 4 on admission.
4. The participant has a history of cancer (malignancy). Exceptions: (1) Adequately treated nonmelanomatous skin carcinoma or carcinoma in situ of the cervix or; (2) Other malignancies that have been successfully treated with appropriate follow up and therefore unlikely to recur for the duration of the study, in the opinion of the investigator and with agreement of the Sponsor (eg, malignancies that have been successfully treated ≥10 years prior to admission to quarantine).
5. The participant has a history of rhinitis (including hay fever) which is clinically active, or history of moderate to severe rhinitis, or history of seasonal allergic rhinitis likely to be active at the time of inclusion into the study and/or requiring regular nasal corticosteroids on an at least weekly basis, within 30 days prior to admission to quarantine. Participants with a history of currently inactive rhinitis (within the last 30 days) or mild rhinitis may be included at the investigator's discretion.
6. The participant has a history of atopic dermatitis/eczema which is clinically severe and/or requiring moderate to large amounts of daily dermal corticosteroids. Participants with mild to moderate atopic dermatitis/eczema, taking small amounts of regular dermal corticosteroids may be included at the investigator's discretion.
7. The participant has a diagnosis of cluster headache/migraine or is receiving prophylaxis against migraine. A participant whose reporting physician has diagnosed migraine may be included provided there are no associated neurological symptoms such as hemiplegia or visual loss. Investigator discretion may also be based on whether or a participant will be receiving study drug (Part 1 versus Part 2.).
8. The participant has an estimated eGFR ≤80 mL/min/1.73 $m^2$ based on the CKD-EPI Equation.

$$\text{eGFR} = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018 \text{ if female} \times 1.159 \text{ if black or African American}$$

At the discretion of the investigator a measured CrCl, as determined by a 24-hour urine collection, may be used in place of, or in conjunction with, the estimate of the eGFR.

Participants who have an eGFR or measured CrCl of up to 10% below either 80 mL/min (for CrCl) or 80 mL/min/1.73 $m^2$ (for eGFR) may be enrolled in the study at the discretion of the investigator.

9. The participant has a lifetime history of anaphylaxis and/or a lifetime history of severe allergic reaction. Significant intolerance to any food or drug in the last 12 months, as assessed by the Investigator.
10. The participant has a positive test(s) for HBsAg, hepatitis C antibodies or HIV.
11. The participant has had major surgery and/or donated or lost 1 unit of blood (approximately 550 mL) within 3 months prior to the prestudy (screening) visit.

**Prior/Concomitant Therapy**

12. The participant uses or anticipates the use of concomitant medications (prescription and/or non-prescription), including vitamins or herbal and dietary supplements from approximately 2 weeks (or 5 half-lives, whichever is longer) prior to the planned date of viral challenge until the poststudy visit. There may be certain medications that are permitted (see Section 6.5). An exception to this criterion would be if, in the opinion of the study physician/Investigator, the medication will not interfere with the study procedures or compromise participant safety. Specifically, the following are excluded:
    - Herbal supplements within 7 days prior to the planned date of viral challenge.
    - Chronically used medications, vitamins, or dietary supplements, including any medications known to be potent inducers or inhibitors of CYP450 enzymes, within 21 days prior to the planned date of viral challenge.
    - Medications or products (prescription or over-the-counter) for symptoms of nasal congestion or respiratory tract infection within 48 hours prior to the planned date of viral challenge and during the inpatient quarantine period.
    - Systemic anti-viral administration within 4 weeks prior to the planned date of viral challenge.
    - Chronic administration (defined as more than 14 continuous days) of an immunosuppressant or other immune-modifying drug within 6 months prior to the planned date of viral challenge and through the Follow-up visit (Day 28).

**Prior/Concurrent Clinical Study Experience**

13. The participant has evidence of receipt of vaccine within the 4 weeks prior to the planned date of viral challenge.
14. The participant intends to receive any vaccine(s) before the last day of follow-up. (Note: no travel restrictions will apply after the Day 28 follow-up visit.)
15. The participant has received any investigational drug within 3 months (or 5 half-lives, whichever is greater) prior to the planned date of viral challenge.
16. The participant has received 3 or more investigational drugs within the previous 12 months prior to the planned date of viral challenge.
17. The participant has had prior inoculation with a virus from the same virus subtype as the challenge virus.

18. The participant has had prior inoculation with a virus from the same virus-family as the challenge virus in the last 12 months
19. The participant has had prior participation in another human viral challenge study with a respiratory virus in the preceding 3 months, taken from the date of viral challenge in the previous study to the date of expected viral challenge in this study.

**Diagnostic Assessments**

20. The participant has a presence of fever, defined as participant presenting with a temperature reading of ≥37.9°C on Day -2, Day -1, and/or pre-Challenge on Day 0.
21. The participant has any of the following: QTc interval ≥470 msec (males) or ≥480 msec (females), a history of risk factors for Torsades de Pointes (eg, heart failure/cardiomyopathy or family history of long QT syndrome), uncorrected hypokalemia or hypomagnesemia, or is taking concomitant medications that prolong the QT/QTc interval.
22. The participant has a confirmed positive test for drugs of abuse and/or cotinine at the Day -2/-1 visit. One repeat test allowed at PI discretion.
23. The participant has a forced expiratory volume in 1 second <80%.

**Other Exclusions**

24. The participant is under the age of legal consent.
25. The participant has smoked ≥10 pack-years at any time (10 pack-years is equivalent to one pack of 20 cigarettes a day for 10 years).
26. The participant has a recent history or presence of alcohol addiction, or excessive use of alcohol (weekly intake in excess of 28 units alcohol; 1 unit being a half glass of beer, a small glass of wine or a measure of spirits).
27. The participant consumes excessive amounts, defined as more than 6 servings of caffeinated beverages or xanthine-containing products (1 serving is approximately equivalent to 120 mg of caffeine) per day.
28. The participant has venous access deemed inadequate for the phlebotomy and cannulation demands of the study.
29. The participant has any significant abnormality altering the anatomy of the nose in a substantial way or nasopharynx that may interfere with the aims of the study and, in particular, any of the nasal assessments or viral challenge. History of nasal polyps is allowed, but large nasal polyps causing current and significant symptoms and/or requiring regular treatments in the last month is exclusionary.
30. The participant has any clinically significant history of epistaxis (large nosebleeds) within the 3 months prior to the Day -2/-1 visit and/or history of being hospitalized due to epistaxis on any previous occasion.
31. The participant has had any nasal or sinus surgery within 3 months prior to the Day -2/-1 visit.
32. The participant is a regular user of cannabis or any illicit drugs, or has a history of drug (including alcohol) abuse within approximately 1 year prior to study-specific screening.

33. The investigator has any concern regarding safe participation in the study, or for any other reason the investigator considers the participant inappropriate for participation in the study.
34. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is investigational site or Sponsor staff directly involved with this study.

## 5.3 Lifestyle Considerations

### 5.3.1 Meals and Dietary Restrictions - Part 2 Only

#### 5.3.1.1 Diet Restrictions

In Part 2, participants will fast from all food and drinks, except water, for at least 8 hours before administration of the AM dose on Day 5, after which rich PK sampling will take place. Water will be restricted 1 hour before and 1 hour after study intervention administration but will be unrestricted at all other times.

On days with sparse PK sampling (ie, trough samples), meals and snacks will be unrestricted in caloric content, composition and timing.

Each study intervention administration will be taken with 250 mL water. Additional water, in increments of 50 mL if needed, may be provided.

#### 5.3.1.2 Fruit Juice Restrictions

In Part 2, participants will refrain from the consumption of grapefruit juice, grapefruits, and grapefruit products beginning approximately 2 weeks before administration of the initial dose of study intervention, throughout the study and until the poststudy visit.

Participants will refrain from the consumption of all fruit juices 24 hours before the study intervention administration at Day 5 AM until 12 hours after drug administration at this time point.

On all other days during the study, the consumption of all fruit juices (except for grapefruit, grapefruit juices, and grapefruit products) is allowed, and consumption of all fruits (except for grapefruit) is not restricted throughout the study.

### 5.3.2 Caffeine, Alcohol, and Tobacco Restrictions – Parts 1 and 2

#### 5.3.2.1 Caffeine Restrictions

The consumption of caffeine or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) should be limited to no more than 6 units per day (1 unit = 120 mg of caffeine) from 48 hours prior to quarantine admission and during quarantine and for 48 hours prior to each study clinic visit.

#### 5.3.2.2 Alcohol Restrictions

Participants will not be allowed to consume alcohol from 72 hours prior to quarantine admission and while in the clinic unit, and for 72 hours prior to each study clinic visit.

#### 5.3.2.3 Tobacco Restrictions

Participants will follow the smoking restrictions (and if applicable, the use of nicotine/nicotine-containing products) defined by the CRU as follows:

Participants must not smoke or use tobacco or nicotine containing products for 72 hours prior to and during quarantine. Participants that are current smokers may be enrolled in the study if, in the opinion of the Investigator, cessation of smoking during quarantine will not lead to withdrawal symptoms which could interfere with the accurate recording on the symptom diary card.

### 5.3.3 Activity Restrictions

Participants must refrain from strenuous exercise for 48 hours prior to and during quarantine and for at least 48 hours prior to each clinic visit (unless it is within the usual activity of the participant) and participants are advised to avoid any new strenuous activities for 1 week prior to clinic visits such as weightlifting or running to avoid potential spurious elevation of clinical laboratory safety parameters.

## 5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized in the study. A minimal set of screen failure information may be included, as outlined in the eCRF entry guidelines. Minimal information may include demography, screen failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements. For individuals who do not meet the criteria for participation in this study (screen failure), the Investigator will decide whether the participant should be permanently excluded from the study or invited back for repeat assessments (i.e., repeat clinical laboratory test) if the initial screening assessments are still within the allowed screening windows or rescreening for a later quarantine, as appropriate. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities.

## 5.5 Participant Replacement Strategy

If a participant discontinues from study intervention OR withdraws from the study a replacement participant may be enrolled if deemed appropriate by the investigator and Sponsor. The replacement participant will generally receive the same intervention or intervention sequence (as appropriate) as the participant being replaced. The replacement participant will be assigned a unique treatment/randomization number.

The study site should contact the Sponsor for the replacement participant's treatment/randomization number.

# 6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies (MK-4482 200-mg capsules and MK-4482 placebo capsules) will be packaged to support enrollment and replacement participants as required. When a replacement participant is required, the Sponsor or designee needs to be contacted before dosing the replacement participant. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

## 6.1 Study Intervention(s) Administered

The study intervention(s) to be used in this study are outlined in Table 3. Table 4 depicts the study administration schedule.

Country-specific requirements are noted in Appendix 7.

Table 3 Study Interventions

| Arm Name | Arm Type | Intervention Name | Intervention Type | Dose Formulation | Unit Dose Strength(s) | Dosage Level(s) | Route of Administration | Treatment Period | Use | IMP or NIMP/AxMP | Sourcing |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Active | Experimental | MK-4482 | Drug | Capsule | 200 mg | 800 mg | Oral | MK-4482 PEP Q12H x 5 days<br><br>MK-4482 Treatment: Q12H x 5 days | Test Product | IMP | Sponsor |
| Placebo | Placebo | Placebo | Drug | Capsule | N/A | N/A | Oral | Matched Placebo: Q12H x 7 days<br><br>MK-4482 Treatment: Q12H Day 5 PM and Day 6<br><br>MK-4482 Treatment: Q12H Day 0 PM and Day 1 | Placebo | IMP | Sponsor |
| Placebo | Placebo | Placebo | Drug | Capsule | N/A | N/A | Oral | Oseltamivir Treatment: Q12H Day 0 PM and Day 1 | Placebo | IMP | Sponsor |

| Arm Name | Arm Type | Intervention Name | Intervention Type | Dose Formulation | Unit Dose Strength(s) | Dosage Level(s) | Route of Administration | Treatment Period | Use | IMP or NIMP/AxMP | Sourcing |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Comparator | Active Comparator | Oseltamivir | Drug | Capsule | 75 mg | 75 mg | Oral | Oseltamivir Treatment: Q12H x 5 days | Comparator | IMP | Sourced locally by the site |
| Virus Inoculation | N/A | Influenza A Virus* | Virus (Challenge Agent) | N/A | Approximately 5 to 7 $TCID_{50}$* | Approximately 5 to 7 TCID50* | Intranasal | Single Administration | Challenge Agent | AxMP | Site |

EEA=European Economic Area; IMP=investigational medicinal product; NIMP/AxMP=noninvestigational/auxiliary medicinal product, PEP=post-exposure prophylaxis.
The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

* The Influenza A/France/759/21 [H1N1] challenge virus used in Part 1 will be prepared to have an inoculum concentration of between approximately 5 and 7 Log10 tissue culture infective dose 50% (TCID50/mL). The Influenza A challenge virus used in Part 2 will either be Influenza A/France/759/21 [H1N1] (inoculum concentration of between approximately 5 and 7 Log10 TCID50/mL) or an alternative virus eg, A/Perth/16/2009 [H3N2] or A/California 2009-like [H1N1]; the inoculum concentration for an alternative virus is provided in Appendix 11, and final details of the virus will be outlined in the Analytical Plan.

Table 4 Study Administration Schedule

| | Day 0 | | Day 1 | | Day 2 | | Day 3 | | Day 4 | | Day 5 | | Day 6 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | AM | PM | AM | PM | AM | PM | AM | PM | AM | PM | AM | PM | AM | PM |
| MK-4482 PEP | | MK-4482 | MK-4482 | MK-4482 | MK-4482 | MK-4482 | MK-4482 | MK-4482 | MK-4482 | MK-4482 | MK-4482 | PBO(MK) | PBO(MK) | PBO(MK) |
| MK-4482 Tx | | PBO(MK) | PBO(MK) | PBO(MK) | MK-4482 | MK-4482 | MK-4482 | MK-4482 | MK-4482 | MK-4482 | MK-4482 | MK-4482 | MK-4482 | MK-4482 |
| OTV Tx | | PBO(OTV) | PBO(OTV) | PBO(OTV) | OTV* | OTV* | OTV* | OTV* | OTV* | OTV* | OTV* | OTV* | OTV* | OTV* |
| PBO | | PBO(MK) | PBO(MK) | PBO(MK) | PBO(MK) | PBO(MK) | PBO(MK) | PBO(MK) | PBO(MK) | PBO(MK) | PBO(MK) | PBO(MK) | PBO(MK) | PBO(MK) |

OTV=oseltamivir; PBO(MK)=placebo to match MK-4482; PBO(OTV)=placebo to match oseltamivir; PEP=post-exposure prophylaxis; Tx=treatment

*At each administration of OTV, participants will receive 1 capsule of OTV + 3 capsules of PBO(OTV)

All supplies indicated in Table 2 will be provided per the "Sourcing" column depending on local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc).

Refer to Section 8.1.8 for details regarding administration of the study intervention.

## 6.2 Preparation/Handling/Storage/Accountability

### 6.2.1 Dose Preparation

There are no specific calculations or evaluations required to be performed to administer the proper dose to each participant. The rationale for selection of doses to be used in this study is in Section 4.3.

### 6.2.2 Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

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

## 6.3 Measures to Minimize Bias: Randomization and Blinding

### 6.3.1 Intervention Assignment

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

Sample allocation schedules are shown in Table 5 and Table 6.

Table 5 Sample Allocation Schedule for Part 1

| Number of Participants | Treatment |
|---|---|
| 20 | Viral inoculation on Day 0 |

Table 6 Sample Allocation Schedule for Part 2

| Intervention[a] | Approximate Number of Participants[b] | Treatment |
|---|---|---|
| MK-4482 PEP | 35 | 800 mg MK-4482 Q12H |
| MK-4482 Tx | 35 | 800 mg MK-4482 Q12H |
| OTV Tx | 35 | 75 mg OTV Q12H |
| Placebo | 35 | PBO Q12H |

OTV = oseltamivir, PEP = post-exposure prophylaxis, Q12H = every 12 hours, Tx = treatment
[a] Participants will be randomly assigned to one of four interventions, which will be dosed in a blinded fashion. In order to maintain the blind, all participants will receive 4 capsules at each dose administration and will be blindfolded during dosing.
[b]. The number of participants to be enrolled in Part 2 will be confirmed following the review of Part 1 data.

### 6.3.2 Stratification

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

### 6.3.3 Blinding

A double-blinding technique will be used. MK-4482, placebo, and OTV will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or delegated unblinded study-site personnel. Dosing will be carried out by an unblinded dosing team and participants will be blindfolded during dose administration (see Section 4.1 for further details). The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration or clinical evaluation of the participants are unaware of the intervention assignments.

## 6.4 Study Intervention Compliance

Interruptions from the protocol-specified treatment plan require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

## 6.5 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the time periods specified by this protocol. If there is a clinical indication for any medications or vaccinations specifically prohibited, discontinuation from study intervention may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

Listed below are specific restrictions for concomitant therapy or vaccination:

- Receipt of blood or blood products, or loss (including blood donations) of 550 mL or more of blood within the 3 months prior to the planned date of viral challenge or planned during the 3 months after the Follow-up visit.
- Herbal supplements within 7 days prior to the planned date of viral challenge.
- Chronically used medications, vitamins, or dietary supplements, including any medications known to be potent inducers or inhibitors of CYP450 enzymes, within 21 days prior to the planned date of viral challenge.
- Medications or products (prescription or over-the-counter) for symptoms of nasal congestion or respiratory tract infection for 48 hours prior to viral challenge and during the inpatient quarantine period.
- Systemic anti-viral administration within 4 weeks prior to the planned date of viral challenge.
- Chronic administration (defined as more than 14 continuous days) of an immunosuppressant or other immune-modifying drug within 6 months prior to the planned date of viral challenge and through the Follow-up visit (Day 28).

Paracetamol/acetaminophen may be used for minor ailments without prior consultation with the Sponsor. Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates

- Dosage information including dose and frequency

The Sponsor Clinical Director should be contacted if there are any questions regarding concomitant or prior therapy.

### 6.5.1 Rescue Medications and Supportive Care

No rescue or supportive medications are specified for use in this study.

## 6.6 Dose Modification

The suggested doses may be adjusted downward at the discretion of the sponsor based upon newly available safety, tolerability, and/or PK data from this study or other studies within the program.

### 6.6.1 Stopping Rules

The following stopping rules will be used during the conduct of this study.

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

1. An individual participant reports an SAE considered related to the study intervention by the investigator.
2. Any unexpected virus-related SAE or unexpected virus-related AEs of clinical concern have been reported following Human Viral Inoculation (expectedness will be assessed by referring to the inoculation virus dossier). Clinical concern will be determined at the discretion of the investigator.

## 6.7 Intervention After the End of the Study

There is no study-specified intervention after the end of the study.

## 6.8 Clinical Supplies Disclosure

The emergency unblinding call center will use the intervention allocation/randomization schedule for the study to unblind participants and to unmask study intervention identity. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.11). The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

See Section 8.1.11 for a description of the method of unblinding a participant during the study, should such action be warranted.

## 6.9 Standard Policies

Not applicable for this study.

# 7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

## 7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study. As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3 and Section 8.1.9, or if available, a PCL.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.9.

A participant must be discontinued from study intervention, but continue to be monitored in the study, for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant's treatment assignment has been unblinded by the investigator, MSD subsidiary, or through the emergency unblinding call center.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- The participant has a positive urine drug screen at any time during the course of the study prior to the final follow up visit. The drug screen can be confirmed by a recheck at the discretion of the investigator after discussion with the Sponsor.

## 7.2 Participant Withdrawal From the Study

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

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

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from FBR, are outlined in

Section 8.1.10. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

## 7.3 Lost to Follow-up

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

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

# 8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical (or dental) decisions must be made by an investigator who is a qualified physician (or dentist when appropriate).
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be used for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.
- The maximum amount of blood collected from each participant over the duration of the study will not exceed the volume mentioned in Appendix 8.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

## 8.1 Administrative and General Procedures

### 8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent from each potential participant (or their legally acceptable representative) prior to participating in this clinical study or FBR. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent is in place.

#### 8.1.1.1 General Informed Consent

Informed consent given by the participant or their legally acceptable representative must be documented on a consent form. The form must include the study protocol number, study protocol title, dated signature, and agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent discussion.

A copy of the signed and dated informed consent form should be given to the participant (or their legally acceptable representative) before participation in the study.

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

If the investigator recommends continuation of study intervention beyond disease progression, the participant or their legally acceptable representative will be asked to provide documented informed consent.

Specifics about the study and the study population are to be included in the study informed consent form.

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

#### 8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the FBR consent to the participant, or the participant's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent before performing any procedure related to FBR. A copy of the informed consent will be given to the participant before performing any procedure related to FBR.

### 8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator, who is a qualified physician, to ensure that the participant qualifies for the study.

### 8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study-site contact information (including direct telephone numbers) to be used in the event of an emergency. The participants will be quarantined from the time the study specific informed consent is signed (Day -2/Day-1) until

discharge from the site (Day 8). The investigator or qualified designee will provide the participant with a participant identification card at the time of discharge from the inpatient quarantine. At the time of intervention allocation/randomization, site personnel will add the treatment/randomization number to the participant identification card.

The participant identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

### 8.1.4 Medical History

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

### 8.1.5 PHQ-9 and GAD-7 Questionnaire

PHQ-9 and GAD-7 questionnaires will be used at the discretion of the investigator to assess participants' eligibility in terms of ability to tolerate isolation in the quarantine unit.

### 8.1.6 Prior and Concomitant Medications Review

#### 8.1.6.1 Prior Medications

The investigator or qualified designee will review before medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 14 days before starting the study.

#### 8.1.6.2 Concomitant Medications

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

### 8.1.7 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur before randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be reused for different participants.

### 8.1.8 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a randomization number. The randomization number identifies the participant for all procedures occurring after randomization. Once a randomization number is assigned to a participant, it can never be reassigned to another participant.

A single participant cannot be assigned more than 1 randomization number.

### 8.1.9 Study Intervention Administration

In Part 2, study medication will be administered by unblinded study staff, as described in the pharmacy manual.

#### 8.1.9.1 Timing of Dose Administration

In Part 2, the first dose of MK-4482 or placebo will be administered in the PM on Day 0, approximately 12 hours post-inoculation. All subsequent doses of MK-4482, OTV, or placebo will be given in the morning and evening (ie, Q12H) on Days 1 through Day 6, at approximately the same time each day.

### 8.1.10 Discontinuation and Withdrawal

The investigator or study coordinator must notify the Sponsor when a participant has been discontinued/withdrawn from the study. If a participant discontinues for any reason at any time during the course of the study and/or intervention, the participant may be asked to return to the clinic (or be contacted) for a poststudy visit as per the number of days described in Section 8.12.5 to have the applicable procedures conducted. However, the investigator may decide to perform the poststudy procedures at the time of discontinuation or as soon as possible after discontinuation. If the poststudy visit occurs prior to the safety follow-up time frame as specified in Section 8.5, the investigator should perform a follow-up telephone call at the end of the follow-up period (Section 8.5) to confirm if any AEs have occurred since the poststudy clinic visit. Any AEs that are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 8.5.

#### 8.1.10.1 Withdrawal From Future Biomedical Research

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

If the medical records for the study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

### 8.1.11 Participant Blinding/Unblinding

STUDY INTERVENTION IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY FOR THE WELFARE OF THE PARTICIPANT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND.

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically qualified designee, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Before contacting the emergency unblinding call center to request unblinding of a participant's intervention assignment, the investigator who is qualified physician should make reasonable attempts to enter the intensity of the AEs observed, the relation to study intervention, the reason thereof, etc, in the medical record. If it is not possible to record this assessment in the medical record before the unblinding, the unblinding should not be delayed.

If unblinding has occurred, the circumstances around the unblinding (eg, date, reason, and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible.

Once an emergency unblinding has taken place, the investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

Participants whose treatment assignment has been unblinded by the investigator or medically qualified designee and/or nonstudy treating physician must be discontinued from study intervention, but should continue to be monitored in the study.

### 8.1.12 Domiciling

Participants will report to the CRU on Day -2/Day-1 before the scheduled day of study intervention administration on Day 0 and remain in the unit until Day 8. At the discretion of the investigator, participants may be requested to remain in the CRU longer.

Participants may be permitted to leave the unit, for emergency situations or if this is the wish of the participant, during the domiciling period. Leaving the CRU early during the quarantine period will be strongly discouraged, due to potential risks to the participant and his/her contacts, in particular vulnerable people, as outlined in Section 8.14.3. The CRU will notify the Sponsor and the decision how to monitor the participant will be at the discretion of the investigator after discussion with the Sponsor.

### 8.1.13 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably

calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

## 8.2 Serosuitability Assessment

A participant must be serosuitable to take part in the study, ie, he/she must have no or low pre-existing serum levels of antibodies specific to the challenge agent. Participant serosuitability will be determined within 90 days prior to challenge virus inoculation (Day 0) to determine participant eligibility; this will be conducted under a generic screening protocol and serosuitability criteria. At baseline and at follow-up, a sample will be taken to check for seroconversion. Serum levels of pre-existing influenza-specific antibodies to the challenge virus will be determined using HAI for influenza.

## 8.3 Intranasal Administration of the Challenge Virus

The challenge agent used in Part 1 of this study is A/France/759/21 [H1N1], and in Part 2 is either A/France/759/21 [H1N1] or an alternative strain eg, A/Perth/16/2009 [H3N2] or A/California 2009-like [H1N1].

The challenge agent stock was manufactured under current GMP. The challenge agent stock has undergone quality testing performed during manufacturing (identity, appearance, sterility, infectivity, and contaminants) according to predetermined specifications, and has subsequently also passed an extensive panel of adventitious agent testing. The challenge agent is stored in a secure -80ºC freezer (normal temperature range -60°C to -90°C).

Inoculum vials containing the challenge agent will be used for intranasal inoculation of each participant. The inoculum will be prepared and/or provided according to the AP and administered in accordance with site SOPs.

All administrations will be made by a member of the study staff and witnessed by a second study staff member. The exact time of challenge agent inoculation will be recorded in the administration log. Accurate records will be kept of when and how much inoculum is prepared and used. The oversight process will be signed off prior to administration of the challenge agent. Any noncompliance or problems with the inoculation will be recorded in the participant's source notes and reported to the Investigator.

Following challenge agent inoculation, participants will be closely observed specifically for potential allergic reactions and any AEs for the following 24 hours. Post inoculation, participants will lie flat for 10 minutes then sit up with nose pegs on for 20 minutes. Participants will continue to be monitored throughout the clinical phase of the study.

## 8.4 Efficacy Assessments

Compliance with the efficacy and safety assessments (along with study treatment use) is essential, and any noncompliance noted by the investigator or designee should result in consultation with the participant on corrective measures needed to ensure compliance.

### 8.4.1 Symptom Diary Card

Participants will report and assess the severity of any challenge agent-related signs and symptoms 3 times per day during quarantine, at the same time each day (±1 hour), using the SDC. This information will be collected using a paper form.

The following symptoms in the 13-item symptom questionnaire will be graded on a scale of 0 to 3 (Grade 0: no symptoms; Grade 1: just noticeable; Grade 2: clearly bothersome from time to time but does not interfere with me doing my normal daily activities; Grade 3: quite bothersome most or all of the time, and it stops me participating in activities); shortness of breath and wheeze have an additional grade, ie, Grade 4: symptoms at rest.

- Runny nose
- Stuffy nose
- Sneezing
- Sore throat
- Earache
- Malaise/tiredness
- Headache
- Muscle and/or joint ache
- Chilliness/feverishness
- Cough
- Chest tightness
- Shortness of breath
- Wheeze

Additional to the categorical SDC, a visual analogue scale diary card using a 100 mm scale, with the same symptoms, will be completed by the participants.

Between 10 and 13 of the 13 items in the SDC will be used for the primary analysis; the selected items will be summarized in the sSAP. Those items not included in the primary analysis may be explored separately.

**SDC: Participant Common Cold Perception Questions**

Two additional common cold-related questions will be answered by the participant within the SDC each morning. The responses to these questions will be analyzed in an exploratory manner. The first question asks the participant's perception of whether they have a cold or not, the second asks the participant's perception of improvement/worsening of the cold.

1. Do you have a cold: Yes/No

If the participant selects Yes to having a cold, then the second 7-point Likert scale "global change since yesterday" question is completed by the participant, as below:

1. Compared to yesterday, I feel that my cold is:

    - Very much better
    - Somewhat better
    - A little better
    - The same
    - A little worse
    - Somewhat worse
    - Very much worse

### 8.4.2 FLU-PRO Plus© Questionnaire

The FLU-PRO Plus© tool will be administered once every 24 hours, in the evening before bedtime, considering the prior 24-hour period. The FLU-PRO© is a patient-reported outcome measure developed to assess symptoms of viral respiratory illness in adults. The measure contains 32 items in six domains evaluating the severity of symptoms in the nose (4 items), throat (3 items), eyes (3 items), chest/respiratory (7 items), gastrointestinal (4 items), and body/systemic (11 items). A higher score indicates more severe symptoms. There is a global score and scoring by domain.

An adaptation, FLU-PRO Plus©, is intended to assess a broader array of viral respiratory tract infections and considers an additional body system, senses (taste and smell). This measure can yield both FLU-PRO© scores as well as the new FLU-PRO Plus© scores. Data from the FLU-PRO Plus© will be analyzed based on multiple time points, in addition to 1-item patient global impression questions, intended to serve as anchor for the psychometric analyses to estimate responder definitions (ie, meaningful changes) used for score interpretation. The FLU-PRO Plus© will be completed first, followed by the patient global impression questions.

### 8.4.3 Nasal Discharge Collection from Paper Tissues

Each participant will be given pre-weighed packets of paper tissues. Participants will be asked to place single tissues used for nose blowing or sneezing into a specified collection bag (for that participant only).

A daily 24-hour paper tissue collection will take place throughout the quarantine period. Distribution of paper tissues and collection bags will start on Day -1, with the first collection on Day 0. Thereafter, distribution and collection of tissues will occur daily at the same time each day (±1 hour) until discharge from quarantine.

24-hour paper tissue collections will be analyzed to determine the following over the quarantine period:

- 24-hour nasal discharge weight
- The number of paper tissues used for nose blowing or sneezing over each 24-hour period

### 8.4.4 Nasopharyngeal Swabs

Nasopharyngeal swabs will be performed to collect samples of epithelial lining fluid for:

- Respiratory pathogen screen
- Virological assessments
- Pre-discharge viral test (if determined by the Investigator to be needed)

On entry to quarantine, a nasopharyngeal swab will be collected and tested to detect the presence of a set of respiratory pathogens, including SARS-CoV-2, that could potentially contraindicate a person's participation in the study. The methodology to be used to conduct the respiratory pathogen screen will be documented in the AP. Additional nasopharyngeal swabs may be collected if the results from the first test were invalid to support study eligibility prior to challenge agent inoculation, or if a community-acquired infection is suspected during quarantine.

Any additional screening tests will be conducted at the discretion of the Investigator.

Viral titer may be determined by qRT-PCR and/or a viral culture assay to investigate the following parameters:

- Viral load
- Infectivity status and rate
- Viral dynamics (e.g., duration, peak, time to peak)

Where required, a rapid viral antigen test or PCR-based test will be used to determine the presence of influenza in a nasopharyngeal swab sample taken prior to discharge from the quarantine unit on Day 8. The rapid viral antigen test will be performed at the discretion of the Investigator and only if indicated for a clinical or other reason. Additional tests may be performed at the discretion of the Investigator.

### 8.4.5 Nasal Sample for Immunology

Nasal sampling using either a nasal swab or nasosorption will be performed as outlined in the SoA for the exploratory evaluation of mucosal antibodies and inflammatory markers. Sample collection, storage, and shipment instructions for nasal samples will be provided in the Study Operations Manual.

## 8.5 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood volumes drawn/collected by visit and by sample type per participant, can be found in Appendix 8.

Planned time points for all safety assessments are provided in the SoA.

### 8.5.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard. Height (recorded at screening only) and weight will also be measured and recorded. Investigators should pay special attention to clinical signs related to previous serious illnesses.

A brief directed physical examination, including nasal exam, will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard.

Symptom-directed physical examinations will be conducted as appropriate by the Investigator and may include (as applicable) examination of the eyes, ears, nose, throat, and respiratory system/chest (via stethoscope). Based upon the presence or absence of clinical signs and symptoms, Investigator discretion will be used to determine the requirement to perform certain ongoing assessments.

Assessment and grading of any upper respiratory tract (nasal discharge, otitis, pharyngitis, sinus tenderness) and lower respiratory tract findings (abnormal breath sounds externally [e.g., stridor, wheezing] and on chest auscultation [rhonchi, crepitations, or other]) will be performed, as applicable. Physician reported assessments of challenge agent-related illness will be graded in accordance with its intensity and documented in the source data.

Following challenge agent inoculation, additional symptoms that are not available in the list of symptoms of the symptom diary card and are deemed to be clinically significant (in the opinion of the Investigator) will be captured as AEs (for more details see Section 8.6).

Following challenge agent inoculation all unexpected (in the opinion of the Investigator) symptom-directed physical examination findings will be captured as AEs, along with all other occurrences that meet the criteria for an AE.

**BMI**

BMI equals a person's weight in kilograms divided by height in meters squared ($BMI = kg/m^2$). BMI will be rounded to the nearest whole number according to the standard convention of 0.1 to 0.4 round down and 0.5 to 0.9 round up.

Body weight and height will be obtained with the participant's shoes off and jacket or coat removed.

### 8.5.2 Vital Signs

Vital signs assessments will be recorded according to the study site's SOPs:

- Tympanic temperature, heart rate, respiratory rate, $O_2$ saturation, and blood pressure will be assessed.
- BP and HR measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Peripheral arterial oxygen saturation will be assessed using pulse oximetry.
- VS are to be taken before blood collection for laboratory tests.

#### 8.5.2.1 Resting Vital Signs

**Vital Sign Measurements (Heart Rate and Blood Pressure)**

Participants should be resting in a quiet setting without distractions, and in position for at least 10 minutes before having VS measurements obtained - during generic screening, the supine position will be used, and for all other time points, the semirecumbent position will be used. VS will include HR, systolic and diastolic BP, RR, and body temperature at time points indicated in the SoA. The correct size of the BP cuff and the correct positioning on the participant's arm is essential to increase the accuracy of BP measurements.

Upon admission to the CRU on Day -2/-1, HR and BP will be single measurements used to assess for participant eligibility. These may be repeated at the discretion of the study investigator.

The pre-inoculation (baseline) HR and BP on Day 0 will be triplicate measurements, obtained at least 1 minute apart within 3 hours prior to inoculation. The median of these three measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed). Post-inoculation VS measurements will be single measurements, and in Part 2 are to be taken within 3 hours prior to the AM dose of study drug.

In Part 2 participants will rest semirecumbent from dosing until 4 hours following the AM dose on Days 2 and 5, except to stand for study-related procedures, if required, per the SoA.

**Body Temperature**

Body temperature (tympanic) will be measured. The same method must be used for all measurements for each individual participant and should be the same for all participants. Temperature is to be monitored as outlined in the SoA, but may be monitored more frequently during quarantine, if appropriate.

Following challenge agent inoculation, pyrexia (temperature ≥37.9oC) will be expected and presumed to represent infection consequent to vial challenge and will not be additionally

captured as an AE unless it meets the definition of an AE and is deemed to be clinically significant (in the opinion of the Investigator) to be classed as an AE.

Following challenge agent inoculation, all unexpected (in the opinion of the Investigator) pyrexia will be captured as an AE, along with all other occurrences that meet the criteria for an AE.

### 8.5.3 Electrocardiograms

- 12-lead ECGs will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and QTc intervals. Refer to Appendix 9 for evaluation and potentially significant findings.

Special care must be taken for proper lead placement by qualified personnel. Skin should be clean and dry before lead placement. Participants may need to be shaved to ensure proper lead placement. Female participants may need to remove interfering garments.

Participants should be resting in position for at least 10 minutes before each ECG measurement – during generic screening, the supine position will be used, and for all other time points, the semirecumbent position will be used.

The correction formula to be used for QTc is Fridericia.

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

ECGs taken on Day -2/-1 will be triplicate measurements. The median of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed). All other ECG measurements will be single measurements.

During the treatment period, if a participant demonstrates an increase in QTc interval ≥60 msec compared with median predose baseline measurement, the ECG will be repeated twice within 5 minutes. The median value of the QTc interval from the 3 ECGs will represent the value at that time point. If the median QTc interval increase from baseline for any postdose time point is ≥60 msec, the participant will continue to be monitored by repeat 12-lead ECGs every 15 minutes for at least 1 hour or until the QTc interval is within 60 msec of baseline. If prolongation of the QTc interval ≥60 msec persists, a consultation with a study cardiologist may be appropriate and the Sponsor should be notified.

During the treatment period, if a participant demonstrates a QTc interval ≥500 msec on a postdose ECG, the ECG will be repeated twice within 5 minutes. The median value of the QTc interval from the 3 ECGs will represent the value at that time point. If the median QTc interval is ≥500 msec, the Sponsor should be notified, and the ECGs should be reviewed by a

cardiologist. The participant should be telemetry monitored (until the QTc interval is <500 msec) or should be considered for transfer to a location where closer monitoring and definitive care (eg, a CCU or ICU) is available.

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

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

A cardiologist will be consulted by the investigator as needed to review ECG tracings with significant abnormalities.

### 8.5.4 Spirometry

Spirometry will be performed according to the study site's SOPs. Height at screening will be used as the baseline measurement for all spirometry assessments.

Spirometry should meet the American Thoracic Society/European Respiratory Society guidelines criteria [Graham, B. L., et al 2019]. For FEV1 and forced vital capacity (FVC), the highest value from a minimum of 3 technically satisfactory attempts will be considered. For FEV1 and FVC the highest and the second-highest value should not exceed more than 150 mL or 5% (whichever is greater). If the difference is larger, up to 8 technically acceptable measurements will be made with repeatability assessed after each additional attempt. If after 8 technically acceptable attempts the difference remains greater than 150 mL or 5% (whichever is greater) the highest values will be reported, and an operator comment will be made to the source data. Values for FEV1 and FVC will be assessed and reported as the highest values regardless of curve.

Predicted values will be calculated according to the formula of the Report of the Global Lung Function Initiative, European Respiratory Society Task Force Lung Function Reference Values [Quanjer, P. H., et al 2012].

Spirometry may be repeated at any time in the event of respiratory signs or symptoms (repeated coughing, bradypnea, tachypnoea, rales, and rhonchi) or respiratory difficulties.

A 15% drop in a spirometry value (compared to baseline and confirmed by a repeat on the same day) may be judged a Grade 1 (mild) AE. However, due to variability in participants' ability to perform these tests with adequate technique, the Investigator will use his/her clinical judgement to assess whether abnormal spirometry readings are consistent with a true drop and whether an AE should be raised. The Investigator will use his/her clinical judgement to assign severity grades above Grade 1, based on evaluation of clinical signs and symptoms. If a spirometry reading on repeat assessment has returned to normal an AE will not be raised.

### 8.5.5 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation In the study or within 14 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

### 8.5.6 Pregnancy Testing

- Pregnancy testing:

Pregnancy testing requirements for study inclusion are described in Sections 1.3 and 5.1.

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

### 8.5.7 Photograph of Rash

Photographs of the rash are highly recommended to be taken immediately, along with any additional information that may assist the investigator to evaluate the skin reaction, skin eruption, or rash occurrence in determining etiology and study intervention relationship.

## 8.6 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators need to document if an SAE was associated with a medication error, misuse, or abuse.

Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.5.3. The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity, and causality.

### 8.6.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before intervention allocation/randomization, must be reported by the investigator under any of the following circumstances:

- if the participant is receiving placebo run-in or other run-in treatment,
- if the event causes the participant to be excluded from the study,
- if it is the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, placebo, or a procedure.

From the time of intervention allocation/randomization through 22 days after cessation of intervention, all AEs, SAEs, and other reportable safety events must be reported by the investigator.

Additionally, any SAE brought to the attention of an investigator any time outside the period specified in the previous paragraph also must be reported immediately to the Sponsor if the event is considered related to study intervention.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 7.

Exception: A positive pregnancy test at the time of initial screening is not a reportable event unless the participant has received study intervention.

Table 7 Reporting Periods and Time Frames for Adverse Events and Other Reportable Safety Events

| **Type of Event** | **Reporting Period: Consent to Randomization/Allocation** | **Reporting Period: Randomization/Allocation through Protocol-specified Follow-up Period** | **Reporting Period: After the Protocol-specified Follow-up Period** | **Time Frame to Report Event and Follow-up Information to Sponsor** |
|---|---|---|---|---|
| NSAE | Report if:<br>– due to protocol-specified intervention<br>– causes exclusion<br>– participant is receiving placebo run-in or other run-in treatment | Report all | Not required | Per data entry guidelines |
| SAE | Report if:<br>– due to protocol-specified intervention<br>– causes exclusion<br>– participant is receiving placebo run-in or other run-in treatment | Report all | Report if:<br>– drug/vaccine related.<br>(Follow ongoing to outcome) | Within 24 hours of learning of event |
| Pregnancy/Lactation Exposure | Report if:<br>– participant has been exposed to any protocol-specified intervention (eg, procedure, washout, or run-in treatment including placebo run-in)<br>Exception: A positive pregnancy test at the time of initial screening is not a reportable event. | Report all | Previously reported<br>– Follow to completion/termination; report outcome | Within 24 hours of learning of event |
| ECI (require regulatory reporting) | Report if:<br>– due to intervention<br>– causes exclusion | Report<br>– potential DILI<br>– require regulatory reporting | Not required | Within 24 hours of learning of event |
| ECI (do not require regulatory reporting) | Report if:<br>– due to intervention<br>– causes exclusion | Report<br>– non-DILI ECIs and those not requiring regulatory reporting | Not required | Within 5 calendar days of learning of event |

| Type of Event | **Reporting Period:** Consent to Randomization/Allocation | **Reporting Period:** Randomization/Allocation through Protocol-specified Follow-up Period | **Reporting Period:** After the Protocol-specified Follow-up Period | Time Frame to Report Event and Follow-up Information to Sponsor |
|---|---|---|---|---|
| Cancer | Report if:<br>– due to intervention<br>– causes exclusion | Report all | Not required | Within 5 calendar days of learning of event (unless serious) |
| Overdose | Report if:<br>– receiving placebo run-in or other run-in medication | Report all | Not required | Within 24 hours of learning of event |
| DILI=drug-induced liver injury; ECI=event of clinical interest; NSAE=nonserious adverse event; SAE=serious adverse event. | | | | |

### 8.6.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

### 8.6.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

### 8.6.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

### 8.6.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding (spontaneously reported to the investigator or their designee) that occurs in a participant during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy.

Any pregnancy complication will be reported as an AE or SAE.

The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing fetus will be born with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

Pregnancy outcomes of ectopic pregnancy, spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

### 8.6.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

The following events do not qualify as AEs for this study:

1. Typical/normal/solicited viral infection symptoms on symptom diary cards.

2. Procedure-related events may be noted during the study while conducting nasal sampling (collection of nasopharyngeal swabs or other nasal samples), specifically:

- Nasal discomfort/irritation
- Nasal abrasions
- Nasal epistaxis
- Sneezing
- Watery eyes

When mild in nature and as expected in the opinion of the Investigator or delegated physician, these events will not be reported as AEs.

3. Asymptomatic bruising following venipuncture, or removal of an intravenous cannula.

4. Dry lips and skin if solely due to the air-conditioning in the quarantine unit, with or without the use of emollients to maintain skin integrity.

### 8.6.7 Events of Clinical Interest

Selected serious and nonserious AEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study include:

1. An overdose of Sponsor's product, as defined in Section 8.7.
2. Potential DILI events defined as an elevated AST or ALT laboratory value that is greater than or equal to 3× the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2× the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2× the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*
   *Note: These criteria are based on available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study-site guidance for assessment and follow-up of these criteria can be found in the Investigator Study File Binder (or equivalent).

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

## 8.7 Treatment of Overdose

For purposes of this study, an overdose will be defined as any dose of any drug administered as part of the study exceeding the dose prescribed by the protocol. It is up to the investigator or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the Sponsor.

The Sponsor does not recommend specific treatment for an overdose. Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Sponsor Clinical Director based on the clinical evaluation of the participant.

## 8.8 Pharmacokinetics

The decision as to which plasma samples collected will be measured for evaluation of PK will be collaboratively determined by the Sponsor. If indicated, these samples may also be measured and/or pooled for assay in an exploratory manner for metabolites and/or additional pharmacodynamic markers. Blood samples collected may be stored and further analysis may be performed, if required.

### 8.8.1 Blood Collection for Plasma NHC

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

### 8.8.2 Blood Collection for Plasma Oseltamivir Carboxylate

A single sample will be drawn at 4 hours following the AM dose of study drug on Day 2 in all participants. These samples will be stored and only tested if deemed necessary by the Sponsor.

## 8.9 Pharmacodynamics

The virologic endpoints (as described in Sec. 3) will be used to evaluate any PK/pharmacodynamics relationships for NHC. Blood samples collected may be stored and further analysis may be performed, if required.

## 8.10 Immunological Assessments

In addition to serum testing for the determination of serosuitability (Sec. 8.2), serum will be collected for the following analyses:

- Assessment of seroconversion (based on HAI and/or neutralization assays) at Day 28
- Serum immunological biomarker (cytokine/chemokine) responses may be evaluated in an exploratory manner.

Additionally, mucosal antibodies and inflammatory markers may be explored in nasal samples (Sec. 8.4.5).

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

## 8.11 Biomarkers

Collection of samples for other biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all participants as specified in the SoA:

- Blood for genetic analysis

### 8.11.1 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for FBR if the participant provides documented

informed consent for FBR. If the planned genetic analysis is not approved, but future biomedical research is approved, this sample will be collected for the purpose of FBR.

Sample collection, storage, and shipment instructions for planned genetic analysis samples will be in the Operations/Laboratory Manual.

## 8.12 Future Biomedical Research Sample Collection

If the participant provides documented informed consent for FBR, the following specimens will be obtained as part of FBR:

- Leftover DNA for future research

## 8.13 Health Economics Medical Resource Utilization and Health Economics

This section is not applicable. Health Economics OR Medical Resource Utilization and Health Economics are not evaluated in this study.

## 8.14 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

### 8.14.1 Screening

Participants will be screened under a generic screening process. Participants who fulfill inclusion and exclusion criteria for this study through a generic screening process, including being serosuitable within 90 days prior to viral challenge and having normal or not clinically significant laboratory safety data within 56 days prior to viral challenge, will be invited for admission to the quarantine unit on Day -2/-1.

Upon admission on Day -2/-1, a protocol-specific consent form will be signed, and eligibility will be confirmed prior to allocation/randomization on Day 0. On Day 0, after all pre-inoculation procedures have been completed, participants will be assigned a unique allocation number associated with a specific treatment as defined by a computer-generated allocation schedule.

Participants on Day 0 who have an acute illness or fever prior to the inoculation may be rescheduled as long as their Day 1 visit falls within the screening window (within 90 days for serosuitability and 56 days for laboratory safety data prior to admission to quarantine).

### 8.14.2 Intranasal IAV Inoculation Period

On Day 0, participants will be inoculated with IAV according to the study site's SOPs. Further details of the inoculum will be provided in the AP. The study site will be responsible for recording the lot number, manufacturer, and expiry date of applicable supplies related to IAV administration.

To reduce the risk of passing the Challenge Virus to others, participants will be asked to avoid contact with vulnerable people for 2 weeks after they leave quarantine. For the purposes of this protocol, a vulnerable individual is as follows:

1. Elderly individuals ≥65 years old;
2. Children ≤2 years old;
3. Anyone who lives in a nursing home;
4. Anyone with a low resistance to infection or who takes drugs that lower their resistance;
5. Anyone who is having or is about to have drug treatment for cancer (chemotherapy);
6. Anyone who has chronic obstructive pulmonary disease (COPD), emphysema or other severe lung disease;
7. Anyone who has heart disease such as heart failure; has had a heart attack or heart surgery;
8. Anyone with cerebral palsy, epilepsy, who has seizures or who has had a stroke.

### 8.14.3 Study Drug Intervention Period – Part 2

Participants will be dosed with study drug commencing Day 0 PM at the study site as set forth in the SoA and Section 6.

### 8.14.4 Participants Discontinued From Study Intervention but Continuing to be Monitored in the Study

At any point if a participant discontinues from treatment but continues to be monitored in the study, all or a subset of study procedures specified in the SoA may be completed at the discretion of the investigator and with Sponsor agreement. The subset of study procedures completed will be communicated in a PCL.

### 8.14.5 Poststudy

Participants will be required to return to clinic approximately 28 days after the administration of IAV. If the poststudy visit occurs earlier than 28 days post-inoculation, a subsequent follow-up telephone call should be made at Day 28 to determine if any AEs have occurred since the poststudy clinic visit.

### 8.14.6 Critical Procedures Based on Study Objectives: Timing of Procedure

For this study, the nasopharyngeal swab for virology is the critical procedure.

At any postdose time point, the nasopharyngeal swab for virology needs to be collected as close to the exact time point as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible. Study procedures can be performed before or after the prescribed/scheduled time.

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

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

The following variance in procedure conduct times will be permitted.

- Nasopharyngeal swab sampling: to be conducted 2X per day at the same times each day (+/- 1 hour)
- Tissue collection (for mucus production analysis): to be 1X per day at the same time each day (+/- 1 hour)
- Symptom reporting (SDC): to be conducted 3X per day at the same times each day (+/- 1 hour)
- FLU-PRO Plus© Questionnaire: to be completed once per day (in the evening) at the same time each day (+/- 1 hour)
- Dosing of study drug: first dose to be administered 12 hours (+/- 30 min) post-inoculation. Subsequent doses to be administered every 12 hours (+/- 1 hour)
- PK Collection as outlined in Table 8.

Table 8 PK Collection Windows

| **Plasma NHC or OTV PK Collection** | **Collection Window** |
|---|---|
| Predose (Day 0 PM) | Within 3 hr prior to first dose |
| Predose (all other days) | Within 30 min prior to the next dose |
| 0 to <1 h | 5 min |
| 1 to <12 h | 10 min |
| 12 to <24 h | 15 min |
| 24 to <48 h | 1 h |
| 48 to 72 h | 2 h |
| PK collection windows are +/- relative to the AM dose on the respective day, with the exception of the Predose Day 0 sampling, which occurs prior to the PM dose. | |

- Pre-inoculation standard safety evaluations: VS and ECG within 3 hours prior to inoculation; laboratory safety tests and physical examination within 24 hours prior to inoculation

- Post-inoculation standard safety evaluations: VS, ECG, laboratory safety tests, and physical examination

Starting from Day 1, post-inoculation safety evaluations may be obtained within +/-a hour of the theoretical sampling time

Day 28 follow-up visit may be conducted within ±3 calendar days.

### 8.14.7 Study Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters

This protocol is written with some flexibility to accommodate the inherent dynamic nature of early phase clinical studies. Modifications to the dose, dosing regimen, and/or clinical or laboratory procedures currently outlined may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants.

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

- Switch from A/France/759/21 [H1N1] to alternative challenge virus (eg, A/Perth/16/2009 [H3N2] or A/California 2009-like [H1N1]) for Part 2
- Change in A/France/759/21 [H1N1] viral inoculum titer for Part 2
- Change in sample size for Part 2 (within an anticipated range of 25 to 50 per intervention group)
- Increase in duration of quarantine period (Part 1 or 2)
- Omission of discretionary safety assessments in Part 2
- Decrease in the dose of the study intervention(s)
- Decrease in the duration of study intervention administration (eg, number of days)
- Instructions to take study intervention with or without food or drink may also be modified based on newly available data
- Modification of the PK/PD sample processing and shipping details based on newly available data

The PK and/or PD sampling scheme currently outlined in the protocol may be modified during the study based on newly available data. These collected samples may also be assayed in an exploratory manner for metabolites and/or additional PD markers.

The timing of procedures for assessment of safety procedures (eg, vital signs, ECG, safety laboratory tests, etc.) currently outlined in the protocol may be modified during the study based on newly available data. Additional laboratory safety tests may be added to blood samples previously drawn to obtain additional safety information.

- Additional blood samples may be taken for laboratory safety tests or other tests, such as measurement for PK or PD analysis. The total blood volume withdrawn from any single participant will not exceed the maximum allowable volume during his/her participation in the entire study (Appendix 8).
- Additional noninvasive, painless procedures that are already specified in this protocol may be performed based on newly available data.
- An additional 24 hours residence in the CRU and up to 2 additional outpatient visits per period will be permitted, in the event of a technical failure, and/or if extra blood samples, or extra PD measurements, are needed.

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

# 9 KEY STATISTICAL CONSIDERATIONS

This section outlines the statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized, but prior to unblinding, will be documented in the SAP and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

## 9.1 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this study will be conducted by, or under the direct auspices of, the Early Clinical Development Statistics Department in collaboration with the Quantitative Pharmacology and Pharmacometrics Department and Translational Medicine Departments of the Sponsor. If, after the study has begun, changes are made to the statistical analysis plan stated below, then these deviations to the plan will be listed, along with an explanation as to why they occurred, in the CSR.

## 9.2 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.

No hypotheses in Part 1.

Part 2

Primary Hypotheses:

Hypothesis (Post-exposure prophylaxis [PEP]): MK-4482 (800 mg Q12H for 5 days), initiated 12 h following intranasal inoculation of the influenza challenge virus reduces the peak viral load (as determined by quantitative viral culture) compared to placebo.

Hypothesis (Treatment): MK-4482 (800 mg Q12H for 5 days), initiated 2 days following intranasal inoculation of the influenza challenge virus reduces the viral load AUC (as determined by quantitative viral culture) compared to placebo.

## 9.3 Analysis Endpoints

<u>Primary Endpoints:</u>

Part 1:

• Day 1 PM to planned discharge, Day 2 PM to planned discharge:

- Quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR)-confirmed influenza infection

Safety: Viral challenge to Follow-up Visit

- Adverse events (AEs) related to viral challenge

Part 2:

PEP (MK-4482) Day 1 PM to planned discharge:

- Peak viral load (PVL) (by quantitative viral culture)

Treatment (MK-4482) First dose of study drug to planned discharge:

- Area under the viral load-time curve (VL-AUC) (by quantitative viral culture)

Secondary Endpoints:

Part 1:

Day 1 PM to planned discharge, Day 2 PM to planned discharge:

- Quantitative viral culture-confirmed influenza infection
- VL-AUC (qRT-PCR and quantitative viral culture)
- PVL (qRT-PCR and quantitative viral culture)
- Duration of quantifiable influenza (qRT-PCR and quantitative viral culture)

Day 1 AM to planned discharge, Day 2 middle of day to planned discharge:

- Area under the total symptom score-time curve (TSS-AUC)
- Peak total symptom score (TSS)
- Daily maximum TSS
- Duration (days) of Grade ≥2 symptoms
- Time (days) to symptom resolution
- Time (days) to peak daily maximum TSS

Part 2:

PEP (MK-4482) – Virology: Day 1 PM to planned discharge:

Symptoms and temperature Day 1 AM to planned discharge:

- VL-AUC (qRT-PCR and quantitative viral culture)
- PVL (qRT-PCR)
- qRT-PCR-confirmed influenza infection
- qRT-PCR-confirmed symptomatic influenza infection

- qRT-PCR-confirmed moderately severe symptomatic influenza infection
- qRT-PCR-confirmed febrile influenza infection
- Quantitative viral culture-confirmed influenza infection
- Quantitative viral culture-confirmed symptomatic influenza infection
- Duration of quantifiable influenza (qRT-PCR and quantitative viral culture)
- Time (days) to confirmed negative test (qRT-PCR and quantitative viral culture)
- Time (days) to peak viral load (qRT-PCR and quantitative viral culture)

Treatment (MK-4482 and oseltamivir) – first dose study drug to planned discharge:

- VL-AUC (qRT-PCR and quantitative viral culture)
- PVL (quantitative viral culture and qRT-PCR)
- Duration of quantifiable influenza (qRT-PCR and quantitative viral culture)
- Time (days) to confirmed negative test (qRT-PCR and quantitative viral culture)
- Time (days) to peak viral load (qRT-PCR and quantitative viral culture)

PEP (MK-4482) – Day 1 AM to planned discharge:

Treatment (MK-4482 and oseltamivir) – first dose study drug to planned discharge:

- TSS-AUC
- Peak TSS
- Daily maximum TSS
- Duration (days) of Grade ≥2 symptoms
- Time (days) to symptom resolution
- Time (days) to peak daily maximum TSS

• Safety

PEP (MK-4482) and Treatment (MK-4482) – from first dose of study drug to Follow-up Visit:

- All AEs

Viral challenge to Follow-up Visit:

- AEs related to viral challenge
- Concomitant medication use

• Pharmacokinetics:

PEP (MK-4482) and Treatment (MK-4482):

- NHC Cmax, Tmax, t1/2, AUC0-12hr, AUC0-last, Ctrough following multiple dose administration of MK-4482

Tertiary/Exploratory Endpoints:

Part 2:

- Number of seroconversions by Day 28 post inoculation

Treatment (MK-4482 and oseltamivir) – first dose of study drug to planned discharge:

- qRT-PCR-confirmed influenza infection
- qRT-PCR-confirmed symptomatic influenza infection
- qRT-PCR-confirmed moderately severe symptomatic influenza infection
- qRT-PCR-confirmed febrile influenza infection
- Occurrence viral culture-confirmed influenza infection
- Quantitative viral culture-confirmed symptomatic influenza infection

PEP (MK-4482) – Day 1 PM to planned discharge;

Treatment (MK-4482) – Day 2 PM to planned discharge:

- Symptom severity score (total and domains) by FLU-PRO Plus© questionnaire

PEP (MK-4482) – Day 1 AM to planned discharge;

Treatment (MK-4482) - Day 2 AM - Day 8 AM:

- Total weight of mucus produced
- Total number of tissues used by participants
- Exploratory assays related to respiratory viral infection and immunology (blood and nasal samples)

• LNS quantitation by viral sequencing of nasal samples.

• Germline genetic variation and association to clinical data collected in this study.

## 9.4 Analysis Populations

Full Analysis Set (FAS) Population

The FAS will serve as the primary population for the PEP portion for the evaluation of pharmacodynamics and efficacy. The FAS population consists of all randomized participants who received 1 dose of the correct clinical material corresponding to the treatment group the participants were randomized into and who received the viral inoculation.

Full Analysis Set – Infected (FAS-I) Population

The FAS-I will serve as the primary population for the treatment portion for the evaluation of pharmacodynamics and efficacy. For the treatment portion, only those that are virus infected participants in the FAS will be included in the pharmacodynamics and efficacy analysis.

Safety Analysis Population

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

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

PK Analysis Population

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

## 9.5 Statistical Methods

### 9.5.1 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of AEs and other relevant parameters, including laboratory test results, vital signs, and ECG measurements.

### 9.5.2 Statistical Methods for Efficacy Analyses

Methods:

Part 1

Primary

The peak viral load (on the log10 scale) from Part 1 determined by viral quantitative culture (plaque assay) will be summarized. Geometric means with corresponding 95% confidence intervals (CI) will be reported.

VL-AUC (on the log10 scale) from Part 1 determined by viral quantitative culture (plaque assay) will be summarized. Geometric means with corresponding 95% confidence intervals (CI) will be reported. The infectivity rate will be calculated.

The infectivity rate will be calculated.

Part 2

Primary

**PEP**

Only placebo and PEP (MK-4482) will be included in the model.

Peak viral load (on the log10 scale) from Part 2 determined by viral quantitative culture (plaque assay) will be analyzed using a linear model with treatment group as a fixed categorical effect. The model will estimate the variance of each treatment group separately.

The mean difference in peak viral load between MK-4482 (PEP; 'early' administration) and placebo and the corresponding 2-sided 95% CI will be computed based on the model.

**Treatment**

Only placebo and Tx (MK-4482) will be included in the model. For both panels, only the participants with virus infection will be included.

VL-AUC (on the log10 scale) from Part 2 determined by viral quantitative culture (plaque assay) will be analyzed using a linear model with treatment group as a fixed categorical effect. The model will estimate the variance of each treatment group separately.

The mean difference in VL-AUC between MK-4482 (Treatment; 'late' administration) and placebo and the corresponding 2-sided 95% CI will be computed based on the model.

The primary hypothesis for PEP and treatment will be tested separately. The primary hypothesis will be supported if the upper limit of the two-sided 95% CI for the difference in mean peak viral load (PEP) or VL-AUC (Treatment) between MK-4482 and placebo is <0 (indicating a reduction).

For both the PEP and treatment arm, if the assumption of normality of log10 peak viral load/VL-AUC is not met, an alternative method, such as Wilcoxon-Rank-Sum test will be applied.

Secondary

**OTV**

Only placebo and OTV Tx will be included in the model.

VL-AUC (on the log10 scale) from Part 2 determined by viral quantitative culture (plaque assay) will be analyzed using a linear model with treatment group as a fixed categorical effect. The model will estimate the variance of each treatment group separately.

The mean difference in VL-AUC between OTV (Treatment; 'late' administration) and placebo and the corresponding 2-sided 95% CI will be computed based on the model.

If the assumption of normality of log10 peak viral load/VL-AUC is not met, an alternative method, such as Wilcoxon-Rank-Sum test will be applied.

Details for analyses of the numerous secondary and exploratory endpoints will be included in a supplemental statistical analysis plan (sSAP).

### 9.5.3 Statistical Methods for Pharmacokinetics Analyses

The following (non-model-based) descriptive statistics will be provided for all PK parameters: N (number of participants with non-missing data), arithmetic mean, standard deviation, arithmetic percent CV (calculated as 100 x standard deviation/arithmetic mean), median, minimum, maximum, geometric mean, and geometric percent CV (calculated as 100 x sqrt( exp(s2) - 1), where s2 is the observed variance on the natural log-scale).

## 9.6 Interim Analyses

Prior to the start of Part 2, an analysis for Part 1 will be performed to characterize the viral load/time profile of the H1N1 influenza challenge virus and to evaluate the infectivity rate of the H1N1 influenza challenge virus in healthy adult participants. If the infectivity rate is smaller than expected or variability in PVL or AUC is larger than expected, the sample size and power calculations may be re-estimated for Part 2.

## 9.7 Multiplicity

The study has only 1 primary hypothesis for PEP and Treatment arm respectively which will each be addressed separately and at the alpha level at 0.05 2-sided level; therefore, there is no multiplicity adjustment being applied.

## 9.8 Sample Size and Power Calculations

The sample size for Part 1 was determined based on the Moore et al 2011 paper and prior work on the SARS-CoV-2 study. 20 participants are deemed adequate to evaluate the performance of the H1N1 challenge virus.

The assumed CV in PVL and VL-AUC from viral quantitative culture were obtained from previous published and unpublished influenza challenge studies using the influenza A/Perth/16/2009 [H3N2] (as an estimate for what will be observed with the new H1N1 virus) conducted by hVIVO. Following the completion of Part 1 of the study (sentinel cohort), the required sample size will be re-estimated; depending on the outcome of this re-estimate, Part 2 may be conducted without changes, or a change may be implemented (update the sample size or the A/Perth/16/2009 [H3N2] virus substituted for the new H1N1). The current design proposes a sample size of 35 per arm which allows for a potential evaluable dropout rate of 5 (~14% of 35), which is adequate to demonstrate the treatment effect sizes described below.

For PEP: A sample size of 30 per group would give ~81% power to detect a decrease in PVL of 60% (on the log10 scale) in the MK-4482 group vs. the placebo group assuming a CV in PVL of 0.806 with a 2-sided alpha=0.05 test.

For Treatment: With a sample size of 18 that test positive per group, there is ~82.7% power to detect a decrease in VL-AUC of 55% (on the log10 scale) in the MK-4482 group vs. the placebo group assuming a CV in VL-AUC of 0.552 with a 2-sided alpha=0.05 test. Considering the infection rate of 61.6%, a sample size of 30 per group will maintain 80% power.

For viral load, the estimates of CV for PEP and Treatment incorporate the following imputation approach: a value of 0.5 x log10 LLOQ is imputed for detected but not quantifiable values, and a value of 0.25 x log10 LLOQ is imputed for undetectable values; this approach avoids the impact of several zero values on the AUC in particular.

# 10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## 10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

### 10.1.1 Code of Conduct for Interventional Clinical Trials

**Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)**

## I. Introduction

### A. Purpose

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD), through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, planning, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with MSD's global standards, local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH GCP) E6 and ICH General Considerations for Clinical Studies E8, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

### B. Scope

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

## II. Scientific Issues

### A. Trial Conduct

#### 1. Trial Design

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

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. Input may be considered from a broad range of stakeholders, including patient advocacy groups/patients representing the trial population, caregivers, and healthcare providers to ensure operational feasibility. Trial design also includes

proactive identification of critical to quality factors utilizing a risk-based approach. Plans are then developed to assess and mitigate risks to those factors as appropriate during the trial. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

**2. Site Selection**

MSD's clinical trials are conducted globally in many different countries and in diverse populations, including people of varying age, race, ethnicity, gender, and accounting for other potential disease related factors. MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial. Individuals involved in trial conduct receive training commensurate with their role prior to their becoming involved in the trial.

Where appropriate, and in accordance with regulatory authority guidance, MSD will make concerted efforts to raise awareness of clinical trial opportunities in various communities. MSD will seek to engage underrepresented groups and those disproportionately impacted by the disease under study. MSD will support clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

**3. Site Monitoring/Scientific Integrity**

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

## B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

## III. Participant Protection

### A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations and ICH Guidelines. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

### B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Trial designs include procedures and systems for the identification, monitoring, and reporting of safety concerns. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

During trial planning, the need for an independent Data Monitoring Committee (DMC) is assessed. DMC review of data accumulated during the conduct of the trial is integral to the well-being of trial participants.

### C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

**D. Genomic Research**

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

**E. Trial Results**

At the time of providing informed consent and in accordance with local laws and regulations, participants should be informed about the plans for availability of trial results.

**IV. Financial Considerations**

**A. Payments to Investigators**

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

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on medical record review and medical evaluation to identify potentially eligible participants.

**B. Clinical Research Funding**

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

**C. Funding for Travel and Other Requests**

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc) will be consistent with local guidelines and practices.

**V. Investigator Commitment**

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

### 10.1.2 Financial Disclosure

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

financial disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

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

### 10.1.3 Data Protection

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her 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.

#### 10.1.3.1 Confidentiality of Data

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

#### 10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked before transmission to the Sponsor.

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

#### 10.1.3.3 Confidentiality of IRB/IEC Information

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

### 10.1.4 Committees Structure

This section is not applicable.

### 10.1.5 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

### 10.1.6 Compliance with Study Registration and Results Posting Requirements

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

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

### 10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol, generally accepted standards of GCP (eg, ICH GCP: Consolidated Guideline and other generally accepted standards of GCP), and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Trials.

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

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

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

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

For investigators located in countries with serious breach reporting requirements, investigator will promptly report to the Sponsor any serious breach or suspected serious breach that occurs in compliance with those requirements. Unless more specifically defined in the applicable requirements, a serious breach is any breach of the applicable clinical trial regulation or of the clinical trial protocol which is likely to affect to a significant degree: (i) the safety or rights of a trial participant, or (ii) the reliability and robustness of the data generated in the clinical trial.

### 10.1.8 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

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

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

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

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

### 10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

### 10.1.10 Study and Site Closure

The Sponsor or its designee may stop the study or study-site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

## 10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 9 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 9 Protocol-required Safety Laboratory Assessments

| **Laboratory Assessments** | **Parameters** | | | |
|---|---|---|---|---|
| Hematology | Platelet Count<br>RBC Count<br>Hemoglobin<br>Hematocrit | RBC Indices:<br>MCV<br>MCH<br>Reticulocytes | | WBC count with Differential:<br>Neutrophils<br>Lymphocytes<br>Monocytes<br>Eosinophils<br>Basophils |
| Chemistry | BUN | Potassium | AST/SGOT | Total bilirubin (and direct bilirubin, if total bilirubin is above the ULN) |
| | Albumin | Bicarbonate | Chloride | Phosphorous |
| | Creatinine | Sodium | ALT/SGPT | Total Protein |
| | Glucose (fasted – except at screening, admission, and follow-up) | Calcium | Alkaline phosphatase | C-reactive protein |
| Routine Urinalysis | • Specific gravity<br>• pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick<br>• Microscopic examination (if blood or protein is abnormal) | | | |
| Pregnancy Testing | • Highly sensitive serum or urine hCG pregnancy test (as needed for WOCBP) | | | |
| Other Screening Tests | • FSH (as needed in WONCBP only)<br>• Urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids, and benzodiazepines)<br>• Serology (HIV antibody, HBsAg, and hepatitis C virus antibody)<br>• Breath alcohol test<br>• Coagulation (PT/aPTT)<br>• Cardiac Enzymes (CK and Troponin)<br>• Thyroid Function Test | | | |

ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CK=creatine kinase; FSH=follicle-stimulating hormone; HBsAg=hepatitis B surface antigen; hCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; PT=prothrombin time; RBC=red blood cell; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; ULN=upper limit of normal; WBC=white blood cell; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential

Notes: Laboratory safety tests (hematology and chemistry) will be performed after approximately an 8-hour fast, except on the day of admission and follow up. Screening safety tests and any repeat hematology tests to confirm out of range values do not need to be fasted.

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

## 10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

### 10.3.1 Definitions of Medication Error, Misuse, and Abuse

**Medication Error**

This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

**Misuse**

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the product information.

**Abuse**

This corresponds to the persistent or sporadic intentional, excessive use of a medicinal product for a perceived psychological or physiological reward or desired nontherapeutic effect.

### 10.3.2 Definition of AE

**AE definition**

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- Note: For purposes of AE definition, study intervention includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol-specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

**Events meeting the AE definition**

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."
- Signs or symptoms following challenge agent inoculation that are unexpected (in the opinion of the Investigator) post-inoculation (ie, they are not included on the SDC) will be captured as AEs. Additionally, challenge agent-related signs or symptoms that are considered by the investigator to be clinically significant will be captured as AEs.

**Events NOT meeting the AE definition**

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgical procedure(s) planned prior to informed consent to treat a preexisting condition that has not worsened.
- Refer to Section 8.6.6 for protocol-specific exceptions.

- Signs or symptoms following challenge agent inoculation that are expected (ie, are included on the list on the SDC) will be presumed to represent infection consequent to challenge agent inoculation, and will not be additionally captured as AEs unless they meet the definition of an AE and are deemed to be clinically significant (in the opinion of the investigator).

### 10.3.3 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

**An SAE is defined as any untoward medical occurrence that, at any dose:**

a. Results in death

b. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a preexisting condition that has not worsened is not an SAE.) A preexisting condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

d. Results in persistent or significant disability/incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

In offspring of participant taking the product regardless of time to diagnosis.

f. Other important medical events

Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

### 10.3.4 Additional Events Reported

**Additional events that require reporting**

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.

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

### 10.3.5 Recording AE and SAE

**AE and SAE recording**

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

**Assessment of intensity/toxicity**

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

**Assessment of causality**

**Follow-up of AE and SAE**

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.

- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

### 10.3.6 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

**AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool**

- The primary mechanism for reporting to the Sponsor will be the EDC tool.

Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).

If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.

Reference Section 8.4.1 for reporting time requirements.

- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

**SAE reporting to the Sponsor via paper CRF**

- If the EDC tool is not operational, facsimile transmission or secure email of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

## 10.4 Appendix 4: Medical Device and Drug–Device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

Not applicable.

## 10.5 Appendix 5: Contraceptive Guidance

### 10.5.1 Definitions

**Participants of Childbearing Potential (POCBP)**

A participant assigned female sex at birth is considered fertile following menarche and capable of becoming pregnant until becoming postmenopausal unless permanently sterile (see below):

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Participants assigned female sex at birth who are in the following categories are not capable of becoming pregnant and, therefore, not considered POCBP:

- Premenarchal
- Premenopausal with 1 of the following:

Documented hysterectomy

Documented bilateral salpingectomy

Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Müllerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

  - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in participants assigned female sex at birth who are not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.

Participants assigned female sex at birth who are on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal 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.

### Participants of Nonchildbearing Potential (PONCBP)

Participants assigned female sex at birth who are in the following categories are not capable of becoming pregnant and, therefore, are considered PONCBP:

- Premenopausal with 1 of the following:

Documented hysterectomy

Documented bilateral salpingectomy

Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Müllerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

  - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in participants assigned female sex at birth not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.

Participants assigned female sex at birth on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

### 10.5.2 Contraceptive Requirements

| **Contraceptives allowed during the study include:** |
|---|
| **Highly Effective Contraceptive Methods That Have Low User Dependency**[a]<br>*Failure rate of <1% per year when used consistently and correctly.* |
| • Progestogen-only contraceptive implant[b,c]<br>• IUS[b,d]<br>• Nonhormonal IUD<br>• Bilateral tubal occlusion (Tubal occlusion includes tubal ligation) |
| • Azoospermic partner (vasectomized or secondary to medical cause, confirmed by medical history) – All sexual partner(s) of the POCBP must be azoospermic. The participant must provide verbal confirmation of partner azoospermia during Medical History. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. |
| **Highly Effective Contraceptive Methods That Are User Dependent**[a]<br>*Failure rate of <1% per year when used consistently and correctly.* |
| • Combined (estrogen- and progestogen-containing) hormonal contraception[b,c]<br>- Oral<br>- Intravaginal<br>- Transdermal<br>- Injectable |
| • Progestogen-only hormonal contraception[b,c]<br>- Oral<br>- Injectable |
| **Sexual Abstinence**<br>• Sexual abstinence is considered a highly effective method only if defined as refraining from penile-vaginal intercourse with a partner capable of producing sperm, during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant. |
| [a] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly)<br>[b] Penile/external condoms must be used in addition to the POCBP's hormonal contraception<br>[c] If locally required, in accordance with CTFG guidelines, acceptable contraceptives are limited to those which inhibit ovulation<br>[d] IUS is a progestin releasing IUD<br><br>Note: Tubal occlusion includes tubal ligation |

## 10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

### 1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

### 2. Scope of Future Biomedical Research[3, 4]

The specimens consented and/or collected in this study as outlined in Section 8.11 will be used in various experiments to understand:

The biology of how drugs/vaccines work

Biomarkers responsible for how a drug/vaccine enters and is removed by the body

Other pathways with which drugs/vaccines may interact

The biology of disease

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

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

### 3. Summary of Procedures for Future Biomedical Research[3, 4]

a. Participants for Enrollment
All participants enrolled in the clinical study will be considered for enrollment in future biomedical research.

b. Informed Consent
Informed consent for specimens (ie, DNA, RNA, protein, etc) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

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

c. eCRF Documentation for Future Biomedical Research Specimens
Documentation of participant consent for future biomedical research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)
Collection of specimens for future biomedical research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for future biomedical research, these will usually be obtained at a time when the participant is having blood drawn for other study purposes.

**4. Confidential Participant Information for Future Biomedical Research[3, 4]**

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participants' clinical information with future test results. In fact, little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like sex, age, medical history, and intervention outcomes is critical to understanding clinical context of analytical results.

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

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number that does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

**5. Biorepository Specimen Usage[3, 4]**

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

**6. Withdrawal From Future Biomedical Research[3, 4]**

Participants may withdraw their consent for FBR and ask that their biospecimens not be used for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox

(clinical.specimen.management@MSD.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to study use only. If specimens were collected from study participants specifically for FBR, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

If the medical records for the study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

**7. Retention of Specimens[3, 4]**

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

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

**8. Data Security[3, 4]**

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

**9. Reporting of Future Biomedical Research Data to Participants[3, 4]**

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

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

## 10. Future Biomedical Research Study Population[3, 4]

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

## 11. Risks Versus Benefits of Future Biomedical Research[3, 4]

For future biomedical research, risks to the participant have been minimized and are described in the future biomedical research informed consent.

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

## 12. Questions

Any questions related to the future biomedical research should be emailed directly to clinical.specimen.management@MSD.com.

## 13. References

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618
2. International Council on Harmonisation [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html
3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

## 10.7 Appendix 7: Country-specific Requirements

Not applicable.

## 10.8 Appendix 8: Blood Volume Table

| Parts 1 and 2 | Screening | Treatment and Inoculation Period | Poststudy | Total Collections | mL Per Collection | Total mL/ Test |
|---|---|---|---|---|---|---|
| Screening & Admission Laboratory Safety Test (chemistry and hematology) | 1 | - | - | 1 | 7.0 | 7.0 |
| Coagulation Testing (PT/aPTT) | 1 | - | - | 1 | 2.7 | 2.7 |
| Routine Safety Laboratory Test | - | 7 | 1 | 8 | 5.5 | 44 |
| FSH (for WONCBP only, if applicable) (blood from chemistry sample) | 1 | - | - | 1 | - | - |
| Serum β-hCG for WOCBP only, if applicable) (blood from chemistry sample) | 1 | - | - | 1 | - | - |
| HIV/Hepatitis Screen (at the discretion of the investigator) (blood from chemistry sample) | 1 | - | - | 1 | - | - |
| Blood - Serum Markers Humoral Immunity | 1 | - | 1 | 2 | 5 | 10 |
| Blood - Serum Exploratory Immunological Biomarkers | - | 9 | 1 | 10 | 5 | 50 |
| Blood for Plasma NHC Assay[b] | - | 12 | - | 12 | 3 | 36 |
| Blood for Plasma OTV Assay[b] | | 1 | | 1 | 3 | 3 |
| Blood for Planned Genetic Analysis | - | 1 | - | 1 | 8.5 | 8.5 |
| | Total Blood Volume per Participant in Part 1[a] | | | | | 122.2 mL |
| | Total Blood Volume per Participant in Part 2[a] | | | | | 161.2 mL |

aPTT=activated partial thromboplastin time; β-hCG=beta human chorionic gonadotropin; FSH=follicle stimulating hormone; HIV-human immunodeficiency virus; NHC=N-hydroxycytidine; PT=prothrombin time; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential;

[a] If additional pharmacokinetic/pharmacodynamic analysis is necessary, additional blood (up to 50 mL) may be obtained. If additional safety analysis is required, additional blood may be obtained, but not to exceed a total blood volume of 550 mL for the study (including blood collected for PK/PD).

[b] Part 2 only

## 10.9 Appendix 9: 12-Lead Electrocardiogram Evaluation Criteria

| | Screen Failure Criteria | Potentially Significant Postrandomization Findings |
|---|---|---|
| **RHYTHM** | | |
| Sinus Tachycardia | >110 bpm | HR >110 bpm and HR increase of ≥25 bpm from baseline |
| Sinus Bradycardia | <40 bpm | HR <40 bpm and HR decrease of ≥5 bpm from baseline |
| Sinus Pause/Arrest | >2.0 seconds | >2.0 seconds |
| Atrial Premature Complex | >1 beat | ≥3 beats |
| Ventricular Premature Complex | All | ≥3 beats |
| Ectopic Atrial Rhythm | None | None |
| Junctional Rhythm | Junctional Rhythm with HR <40 bpm | Junctional Rhythm with HR <40 bpm |
| Idioventricular Rhythm | All | All |
| Atrial Fibrillation | All | All |
| Atrial Flutter | All | All |
| Supraventricular Tachycardia | All | All |
| Ventricular Tachycardia | All | All |
| **AXIS** | | |
| Left Axis Deviation | RBBB With LAHB | New Onset LAHB |
| Right Axis Deviation | RBBB With LPHB | New Onset LPHB |
| **CONDUCTION** | | |
| 1st Degree AV Block | PR ≥230 ms | PR ≥230 ms + Increase of >15 ms; or PR Increase of >25% |
| 2nd Degree AV Block | Mobitz Type II | Mobitz Type II |
| 3rd Degree AV Block | All | All |
| LBBB | All | All |
| RBBB | RBBB With LAHB/LPHB as Defined Above | New Onset RBBB (Not Including Rate-related) |
| ICRBBB (QRS <120 ms) | No Exclusion | Nothing |
| Short PR/Preexcitation Syndrome | Delta Wave + PR <120 ms | Delta Wave + PR <120 ms |
| Other Intraventricular Conduction Delay | QRS ≥130 ms | QRS ≥130 ms + Increase of ≥10 ms |
| **QTc (B or F)** | | |
| Male | QTc ≥470 ms | QTc ≥500 ms or Increase of ≥60 ms From Baseline |
| Female | QTc ≥480 ms | QTc ≥500 ms or Increase of ≥60 ms From Baseline |
| **HYPERTROPHY** | | |
| Atrial Abnormalities | Definite Evidence of P Mitrale or P Pulmonale | Definite Evidence of *P. Mitrale* or *P. Pulmonale* |
| Ventricular Abnormalities | Voltage Criteria for LVH Plus Strain Pattern | Voltage Criteria for LVH Plus Strain Pattern |
| **MYOCARDIAL INFARCTION** | | |
| Acute or Recent | All | All |
| Old | All | All |

| | **Screen Failure Criteria** | **Potentially Significant Postrandomization Findings** |
|---|---|---|
| **ST/T MORPHOLOGY** | | |
| ST Elevation Suggestive of Myocardial Injury | In 2 or more contiguous leads | In 2 or more contiguous leads |
| ST Depression Suggestive of Myocardial Ischemia | In 2 or more contiguous leads | In 2 or more contiguous leads |
| T-wave Inversions Suggestive of Myocardial Ischemia | In 2 or more contiguous leads | In 2 or more contiguous leads |
| Nonspecific ST-T Changes (In 2 or More Leads) | No exclusion | In 2 or more contiguous leads |
| **PACEMAKER** | **All** | **All** |

AV=atrioventricular; bpm=beats per minute; HR=heart rate: ICRBBB=incomplete right bundle branch block; LAHB=left anterior hemiblock; LPHB=left posterior hemiblock; LVH=left ventricular hypertrophy; mm=millimeter; ms=milliseconds, PR=pulse rate; QTcB=QT correction using Bazett's formula; QTcF=QT correction using Fredericia formula; RBBB=right bundle branch block; ST/T=ST-segment/T wave.
Baseline is defined as Predose Day 1.

## 10.10 Appendix 10: Algorithm for Assessing Out of Range Laboratory Values

For all laboratory values obtained at screening:

A. If all protocol-specified laboratory values are normal, the participant may enter the study.
B. If a protocol-specified laboratory value is outside the parameter(s) outlined in the inclusion/exclusion criteria (including a repeat if performed), the participant will be excluded from the study.
C. If ≥1 protocol-specified laboratory value not specified in the inclusion/exclusion criteria is outside the normal range, the following choices are available:
    a. The participant may be excluded from the study.
    b. The participant may be included in the study if the abnormal value(s) is NCS (the investigator must annotate the laboratory value "NCS" on the laboratory safety test source document).
    c. The participant may be included in the study if the abnormality is consistent with a pre-existing medical condition which is not excluded per protocol (eg, elevated eosinophil count in a participant with asthma or seasonal allergies), the medical condition should be annotated on the laboratory report.

OR

    d. The abnormal test may be repeated (refer items a. and b. below for continuation of algorithm for repeated values).
        i. If the repeat test value is within the normal range, the participant may enter the study.
        ii. If the repeat test value is still abnormal, the study investigator will evaluate the potential participant with a complete history and physical examination, looking especially for diseases that could result in the abnormal laboratory value in question. If such diseases can be ruled out, and if the abnormal laboratory value is not clinically relevant, then the participant may enter the study.
D. If there is any clinical uncertainty regarding the significance of an abnormal value, the participant will be excluded from the study.

## 10.11 Appendix 11: Alternative Challenge Viruses for Part 2 – Summary

In the event that the challenge virus used in Part 1 (Influenza A/France/759/21 [H1N1]) is not deemed suitable to be studied in Part 2, an alternative challenge virus will be selected, eg, A/Perth/16/2009 [H3N2] or A/California 2009-like [H1N1]. An overview of these two alternative options is provided below. Final details of the challenge virus will be outlined in the Analytical Plan.

### A/Perth/16/2009 [H3N2]

The influenza A/Perth/16/2009 [H3N2] challenge virus strain used in the majority of studies to date has been given to over 400 healthy participants by hVIVO. The virus has been well tolerated with no virus-related SAEs occurring in any of the participants inoculated to date. Furthermore, the challenge virus has been shown to induce measurable disease profiles with clear distinction from non-infected participants, and study participants have approximately 60% to 75% chance of becoming infected following the administration of the virus. Typical influenza illness is characterized by an abrupt onset of rhinitis, nasal stuffiness, fever, malaise, myalgia (muscle aches), and sore throat. In healthy adults, the illness usually resolves without any treatment, with relief of symptoms occurring naturally within 3 to 5 days. The disease profiles of the challenge agent are consistent with the mild to moderate disease profiles expected with wild-type challenge viruses in healthy adult participants [Fragaszy, E. B., et al 2017]. In summary, the influenza A/Perth/16/2009 [H3N2] challenge virus is considered safe, well tolerated, and induces appropriate disease pathogenesis to be an effective viral challenge agent in the human viral challenge studies.

Table 10 Study Challenge Agent Details: A/Perth/16/2009 [H3N2]

| | |
|---|---|
| **Challenge Agent Name** | Influenza A/Perth/16/2009 [H3N2] Virus |
| **Type** | Virus |
| **Dose Formulation** | Ampoule, liquid |
| **Unit Dose Strength(s)** | ~$10^{5.5}$ tissue culture infective dose (50%) ($TCID_{50}$) |
| **Dosage Level(s)** | A single dose of virus will be administered on Day 0. Dose volume and delivery method will be provided in the analytical plan (AP) |
| **Route of Administration** | Intranasal |
| **Use** | Infectious challenge agent |
| **Investigational Medicinal Product** | Auxiliary Medicinal Product (AxMP) |
| **Sourcing** | Provided centrally by hVIVO |
| **Packaging and Labelling** | The details of the challenge agent provision will be provided in the AP |
| **Current/Former Name(s) or Alias(es)** | Not applicable |

### A/California 2009-like [H1N1]

The influenza A/California/2009-like [H1N1] challenge virus has been used by several groups globally over the last 7 years and has helped assess influenza disease and therapies [Watson, J. M., et al 2015] [Sloan, S. E., et al 2020] hVIVO has safely inoculated 62 participants with the Influenza A/California/2009-like [H1N1] challenge virus. The virus has been well tolerated with no virus-related SAEs occurring in any of the participants inoculated to date. Furthermore, the challenge virus has been shown to induce measurable disease profiles with clear distinction from non-infected participants, and study participants have approximately 40% to 60% chance of becoming infected following the administration of the virus. Typical influenza illness is characterized by an abrupt onset of rhinitis, nasal stuffiness, fever, malaise, myalgia (muscle aches), and sore throat. In healthy adults, the illness usually resolves without any treatment, with relief of symptoms occurring naturally within 3 to 5 days. The disease profiles of the challenge agent are consistent with the mild to moderate disease profiles expected with wild-type challenge viruses in healthy adult participants [Fragaszy, E. B., et al 2017]. In summary, the influenza A/California/2009-like [H1N1)] challenge virus is considered safe, well tolerated, and induces appropriate disease pathogenesis to be an effective viral challenge agent in the human viral challenge studies.

Table 11 Study Challenge Agent Details: A/California 2009-like [H1N1]

| | |
|---|---|
| **Challenge Agent Name** | Influenza A/California/2009-like [H1N1] Virus |
| **Type** | Virus |
| **Dose Formulation** | Ampoule, liquid |
| **Unit Dose Strength(s)** | ~$3.5x10^6$ tissue culture infective dose (50%) ($TCID_{50}$) |
| **Dosage Level(s)** | A single dose of virus will be administered on Day 0.<br>Dose volume and delivery method will be provided in the analytical plan (AP) |
| **Route of Administration** | Intranasal |
| **Use** | Infectious challenge agent |
| **Investigational Medicinal Product** | AxMP |
| **Sourcing** | Provided centrally by hVIVO |
| **Packaging and Labelling** | The details of the challenge agent provision will be provided in the AP |
| **Current/Former Name(s) or Alias(es)** | Not applicable |

## 10.12 Appendix 12: Abbreviations

| Abbreviation | Expanded Term |
|---|---|
| ADME | absorption, distribution, metabolism, and excretion |
| AE | adverse event |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| AP | analytical plan |
| APaT | All-Participants-as-Treated |
| AR | adverse reaction |
| ART | antiretroviral therapy |
| AST | aspartate aminotransferase |
| AUC | area under the curve |
| bid | twice daily |
| BMI | body mass index |
| BP | blood pressure |
| CHS | cough hypersensitivity syndrome |
| CI | confidence interval |
| Cmax | maximum plasma concentration |
| CKD-EPI | Chronic Kidney Disease Epidemiology Collaboration |
| CL | clearance |
| CrCl | creatinine clearance |
| CR | complete response |
| CRF | Case Report Form |
| CRU | clinical research unit |
| C-SSRS | Columbia-Suicide Severity Rating Scale |
| CSR | Clinical Study Report |
| CT | computed tomography |
| CTMS | Clinical Trial Management System |
| DDI | drug-drug interaction |
| DILI | drug-induced liver injury |
| DNA | deoxyribonucleic acid |

| Abbreviation | Expanded Term |
|---|---|
| ECG | electrocardiogram |
| ECI | event of clinical interest |
| eCRF | electronic Case Report Form |
| eCTA | exploratory Clinical Trial Application |
| EDC | electronic data collection |
| eGFR | estimated glomerular filtration rate |
| ELISA | enzyme-linked immunosorbent assay |
| EMA | European Medicines Agency |
| ePROs | electronic patient-reported outcomes |
| FDA | Food and Drug Administration |
| FDAAA | Food and Drug Administration Amendments Act |
| FIH | first in human |
| FSH | follicle-stimulating hormone |
| GAD-7 | Generalized Anxiety Disorder 7 Questionnaire |
| GCP | Good Clinical Practice |
| GMP | Good Manufacturing Practice |
| GI | gastrointestinal |
| HAI | haemagglutination inhibition |
| HBcAb | hepatitis B core antibody |
| HBsAg | hepatitis B surface antigen |
| HBV | hepatitis B virus |
| hCG | human chorionic gonadotropin |
| HCS | human challenge study |
| HCV | hepatitis C virus |
| HIV | human immunodeficiency virus |
| HR | heart rate |
| HRT | hormone replacement therapy |
| IAV | influenza A virus |
| IB | Investigator's Brochure |
| IBV | influenza B virus |

| Abbreviation | Expanded Term |
|---|---|
| ICF | Informed Consent Form |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| ICMJE | International Committee of Medical Journal Editors |
| ICU | intensive care unit |
| IEC | Independent Ethics Committee |
| Ig | immunoglobulin |
| IND | Investigational New Drug |
| IRB | Institutional Review Board |
| IUD | intrauterine device |
| IUS | intrauterine hormone-releasing system |
| IV | intravenous |
| IVD | in vitro diagnostic |
| LAM | lactational amenorrhea method |
| LLN | lower limit of normal |
| LLOQ | lower limit of quantitation |
| mAb | monoclonal antibody |
| MAD | maximum administered dose |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MERS-CoV | Middle East respiratory syndrome coronavirus |
| MRI | magnetic resonance imaging |
| mRNA | messenger RNA |
| NCS | not clinically significant |
| NDA | New Drug Application |
| NHC | N-hydroxycytidine |
| NHC-TP | N-hydroxycytidine triphosphate |
| NOAEL | no observed adverse effect level |
| OTC | over the counter |
| OTV | oseltamivir |
| PCL | Protocol Clarification Letter |
| PCR | polymerase chain reaction |

| Abbreviation | Expanded Term |
|---|---|
| PD | Pharmacodynamics |
| PEP | post-exposure prophylaxis |
| PHQ-9 | Patient Health Questionnaire 9 |
| PK | pharmacokinetic |
| po | orally |
| POCBP | person of childbearing potential |
| PP | per-protocol |
| PRO | patient-reported outcome |
| PVL | Peak viral load |
| QP2 | Department of Quantitative Pharmacology and Pharmacometrics |
| qRT-PCR | quantitative reverse transcription polymerase chain reaction |
| RNA | ribonucleic acid |
| RR | respiratory rate |
| RSV | respiratory syncytial virus |
| SAC | Scientific Advisory Committee |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SARS-CoV | severe acute respiratory syndrome coronavirus |
| SARS-CoV-2 | SARS-associated coronavirus-2 |
| SD | standard deviation |
| SDC | symptom diary card |
| SGOT | serum glutamic oxaloacetic transaminase |
| SGPT | Serum glutamic pyruvic transaminase |
| SLAB | Supplemental laboratory test(s) |
| SmPC | summary of product characteristics |
| SoA | schedule of activities |
| SOC | standard of care |
| SOP | Standard Operating Procedures |
| sSAP | supplemental Statistical Analysis Plan |
| SUSAR | suspected unexpected serious adverse reaction |

| Abbreviation | Expanded Term |
|---|---|
| SVR12 | sustained viral response |
| TCID50 | tissue culture infective dose (50%) |
| Tmax | time to maximum plasma concentration |
| Tx | treatment |
| t½ | half life |
| UDS | urine drug screen |
| ULN | upper limit of normal |
| VL | viral load |
| VL-AUC | area under the viral load-time curve |
| VS | vital signs |
| WBC | white blood cell |
| WPAI | Work Productivity and Activity Impairment |
| WOCBP | woman/women of childbearing potential |
| WONCBP | woman/women of nonchildbearing potential |

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