Janssen Research & Development *

Clinical Protocol

A Phase 3 Randomized, Double-blind, Placebo-controlled, Multi-center Study to Evaluate the Efficacy and Safety of Pimodivir in Combination With the Standard-of-care Treatment in Adolescent, Adult, and Elderly Non-hospitalized Subjects With Influenza A Infection who Are at Risk of Developing Complications

Protocol 63623872FLZ3002; Phase 3
AMENDMENT 1

JNJ-63623872-ZCD Pimodivir

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This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	11 Sep 2017
Amendment 1	08 Feb 2018

Amendments are listed beginning with the most recent amendment.

Amendment 1 (08 February 2018)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The overall reason for the amendment is to implement the recommendations from specific Health Authorities.

Rationale: To meet the request of specific Health Authorities, superiority evaluation of pimodivir in combination with oseltamivir (OST)-containing standard-of-care (SOC) treatment compared to placebo in combination with OST-containing SOC treatment was added.

SYNOPSIS
2.1 Objectives and Endpoints
11.3 Sample Size Determination
11.4 Efficacy Analyses

Rationale: An interim analysis was added to re-estimate sample size and assess futility.

SYNOPSIS
11.11 Interim Analysis

Rationale: Based on Health Authority feedback, the power was estimated using a rank-based approach.

SYNOPSIS
11.3 Sample Size Determination

Rationale: Safety follow-up and monitoring for hepatic dysfunction were updated to optimize the general safeguards and practices in clinical studies. The hepatic-related exclusion and the hepatic-related discontinuation criteria were updated as well. The potential risks section was updated accordingly.

SYNOPSIS
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Rationale: Based on Health Authority feedback, time to resolution of fever was added as a secondary objective and endpoint.

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Rationale: Based on Health Authority feedback, the hemagglutinin gene (if applicable) was included in addition to neuraminidase and polymerase acidic protein (PA) genes in the comprehensive sequence analysis. PA and polymerase basic protein 1 genes of virus from all subjects who meet criteria for reduced response or viral rebound will be sequenced as well.

SYNOPSIS
9.3.1 Viral Sequencing

Rationale: Based on Health Authority feedback, a secondary objective and endpoint were added on time to resolution of each of the individual influenza-related symptoms as assessed by the Flu-iiQ™.

SYNOPSIS
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Rationale: Based on Health Authority feedback, secondary endpoints based on Modules 2, 3, and 4 of the Flu-iiQ™ questionnaire were moved to exploratory endpoints.

SYNOPSIS
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Rationale: Based on Health Authority feedback, shipping and storage of leftovers from the local virology samples for further testing at the central lab was added to account for the performance of the point-of-care influenza diagnostic tests.

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9.1.2 Screening Phase

Rationale: Based on Health Authority feedback, the type of pregnancy testing was added (ie, urine or serum).

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Rationale: Analysis of virologic response by baseline resistance was deleted as objective/endpoint, as well as the pharmacokinetic/pharmacodynamic analyses endpoint, because they reflect an analysis and not a study endpoint.

SYNOPSIS
2.1 Objectives and Endpoints

Rationale: Clarifications were made throughout the protocol.

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Rationale: Minor grammatical, formatting, or spelling changes were made throughout the protocol.

SYNOPSIS

A Phase 3 Randomized, Double-blind, Placebo-controlled, Multi-center Study to Evaluate the Efficacy and Safety of Pimodivir in Combination With the Standard-of-care Treatment in Adolescent, Adult, and Elderly Non-hospitalized Subjects With Influenza A Infection who Are at Risk of Developing Complications

Pimodivir (formerly known as VX-787 and JNJ-63623872) is a non-nucleotide inhibitor of the polymerase basic protein 2 (PB2) subunit of the influenza A virus polymerase complex and is currently in Phase 3 development as treatment for influenza A infection.

OBJECTIVES AND HYPOTHESIS

Objectives

Primary Objective

The primary objective is to evaluate superiority of pimodivir in combination with standard-of-care (SOC) treatment compared to placebo in combination with SOC treatment, with respect to the time to resolution of influenza-related symptoms.

Secondary Objectives

The secondary objectives are:

- To investigate the safety and tolerability of pimodivir in combination with SOC treatment compared to placebo in combination with SOC treatment.
- To evaluate superiority with respect to the hospital admission rate 28 days after initiation of treatment in the pimodivir in combination with SOC treatment arm, compared to the placebo in combination with SOC treatment arm.
- To evaluate superiority with respect to the incidence of complications associated with influenza after the start of study treatment in the pimodivir in combination with SOC treatment arm, compared to the placebo in combination with SOC treatment arm.
- To investigate time to resolution of each of the 10 individual influenza-related symptoms as assessed by the PRO measure Flu-iiQ^{TM}.
- To investigate the time to return to daily activities as assessed by the subject in the pimodivir in combination with SOC treatment arm, compared to the placebo in combination with SOC treatment arm.
- To investigate the time to resolution of fever in the pimodivir in combination with SOC treatment arm, compared to the placebo in combination with SOC treatment arm.
- To investigate all-cause mortality in the pimodivir in combination with SOC treatment arm, compared to the placebo in combination with SOC treatment arm.
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- To assess the pharmacokinetics (PK) of pimodivir and to explore the PK/pharmacodynamic (PD) relationships of pimodivir for efficacy and safety.
- To investigate the acceptability (taste and swallowability) of the pimodivir formulation in adolescents.
- To investigate the emergence of viral resistance against pimodivir detected by genotyping and/or phenotyping.

- To evaluate superiority with respect to time to viral negativity in the pimodivir treatment arm compared to the control arm by quantitative real time polymerase chain reaction (qRT-PCR) and viral culture.
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Endpoints

Primary Endpoint

The primary endpoint is the time to resolution of influenza-related symptoms as assessed by the PRO measure Flu-iiQ™. The resolution of influenza-related symptoms is defined as the beginning of the 24-hour period that the 7 primary influenza symptom scores (cough, sore throat, headache, nasal congestion, feeling feverish, body aches and pains, fatigue) are at most mild or at least back to previous level of symptom severity in case the subject reported the symptom as pre-existing.

Secondary Endpoint

The secondary endpoints are:

- Safety and tolerability based on assessment of adverse events (AEs), clinical laboratory assessments, 12-lead electrocardiograms (ECGs) and vital signs.
- The hospital admission rate 28 days after treatment initiation.
- Incidence of complications associated with influenza after the start of study treatment.

  A blinded Adjudication Committee (AC) will be established to adjudicate AEs on predefined criteria for complications (pulmonary versus extrapulmonary, major versus minor, as well as infectious versus non-infectious complications). The AC will receive data on AEs, including medical assessments (eg chest X-ray results, lab results) and concomitant therapy of cases selected from the AEs. Details will be provided in an AC charter.

- Time to resolution of each of the 10 individual influenza-related symptoms as assessed by the PRO measure Flu-iiQ™. The resolution of each influenza-related symptom is defined as the beginning of the 24-hour period when the influenza symptom score is at most mild or at least back to the previous level of symptom severity in case the subject reported the symptom as pre-existing.
- Time to return to daily activities as assessed by the subject.
- Time to resolution of fever. Resolution of fever is defined as a body temperature <37.0°C during a period of 24 hours without the use of antipyretics.
- All-cause mortality.
- PK parameters of pimodivir (ie, plasma concentration just prior to the beginning or at the end of a dosing interval [C_{trough}], C_{max}, t_{max}, and AUC_{12h}), as determined by population PK analysis.
- The acceptability of the pimodivir formulation in adolescents, as measured by a taste and swallowability questionnaire.
- The emergence of viral resistance against pimodivir detected by genotyping and/or phenotyping.
- Time to viral negativity by qRT-PCR and viral culture.
- Viral load over time by qRT-PCR and viral culture.
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Exploratory Endpoints

- Time to resolution of impact of influenza on daily activities, emotions and others, as defined by the Flu-iiQ^{TM} questionnaire (Modules 2, 3, and 4).

Hypothesis

The time to resolution of the 7 primary influenza-related symptoms, as assessed by a PRO measure (Flu-iiQ^{TM}), with pimodivir in combination with SOC treatment is statistically superior to treatment with placebo in combination with SOC treatment in subjects with influenza A infection who are at risk of developing complications.

OVERVIEW OF STUDY DESIGN

This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of pimodivir in combination with SOC treatment versus placebo in combination with SOC treatment in adolescent (13 to 17 years), adult (18 to 65 years), and elderly (>65 to ≤85 years) non-hospitalized subjects with influenza A infection who are at risk of developing complications.

A target of 720 subjects will be randomly assigned in this study with 360 subjects planned per treatment arm. The aim is to enroll a minimum of 72 adolescent subjects in this study in selected countries and study sites consistent with local regulations. The target population of the study are influenza-infected, non-hospitalized subjects who, due to their age (>65 to 85 years of age) or underlying comorbidities (regardless of age), are at increased risk of developing influenza-related complications. The randomization will be stratified by type of baseline SOC (including or not including influenza antiviral treatment), and time since onset of symptoms (first administration of study drug ≤48 hours or >48 hours since onset of influenza symptoms). The study population should consist of at least 60% of subjects with first administration of study drug ≤48 hours since onset of influenza symptoms.

Subjects who meet all eligibility criteria will be randomized in a 1:1 ratio to receive 1 of the following 2 treatments:

- Treatment Arm 1: pimodivir 600 mg twice daily (bid) for 5 days + SOC treatment*
- Treatment Arm 2: pimodivir placebo bid for 5 days + SOC treatment*

*SOC treatment will be determined by the investigator based on local practice, and may include influenza antivirals and/or supportive care only. The choice to use influenza antivirals as part of the SOC should be made before randomization. The influenza antiviral should be started no later than Day 2 morning (up to noon). An influenza antiviral as part of the SOC cannot be changed (eg, switching one influenza antiviral for another) during the treatment period, with the exception that an influenza antiviral may be discontinued in the case of a suspected AE.

Study drugs will be taken orally.

The study will consist of a screening/baseline visit, a double-blind treatment period of 5 days, and a follow-up period of 23 days after the last dosing day. The entire study duration for each subject will be 28 days. The study is considered complete with the completion of the last study assessment for the last subject participating in the study.

When subjects are hospitalized during the course of the study, the reason for hospitalization should be recorded and every effort should be made by the investigator to perform all the assessments as indicated in the TIME AND EVENTS SCHEDULE, if practically feasible.

An Independent Data Monitoring Committee (IDMC) will be commissioned for this study to monitor efficacy and safety data on a regular basis.

SUBJECT POPULATION

Study drug treatment should be started as soon as possible after the start of the influenza infection. Screening will occur before randomization and the first administration of study drug.

Key Inclusion Criteria

- Male or female, 13 to 85 years of age, inclusive. Note: Adolescent subjects (13-17 years) will be enrolled in selected countries and study sites consistent with local regulations.
- Present to the clinic with symptoms suggestive of a diagnosis of acute influenza and have at least 1 respiratory symptom and at least 1 systemic symptom, both scored as at least "moderate" if the symptom did not pre-exist before influenza onset, or scored worse than usual if the symptom pre-existed as determined by subject's ratings on Module 1 of the Flu-iiQ^{TM} and the Pre-existing Symptom Questionnaire in the ePRO device. Symptoms must include the following by category: respiratory symptoms: cough, sore throat, nasal congestion; systemic symptoms: headache, body aches or pain, feverishness, fatigue.
- Tested positive for influenza A infection after the onset of symptoms, using a rapid influenza diagnostic test (RIDT) or, if available, a PCR-based molecular diagnostic assay.
- Not be in need of hospitalized medical care at screening. Emergency room or hospital observation status for <24 hours is not considered hospitalization as long as a determination of the need for hospitalization has not been made.
- Enrollment and initiation of study drug treatment ≤72 hours after onset of influenza symptoms.
- Subjects 13 to 65 years of age, inclusive must also have at least one of the following:
  - Cardiovascular or cerebrovascular disease (including congenital heart disease, chronic heart failure, coronary artery disease, or stroke; excluding isolated hypertension).
  - Chronic lung disease (eg, asthma, chronic obstructive lung disease [COPD] or cystic fibrosis).
  - Weakened immune system due to disease or medication (eg, subjects with human immunodeficiency virus [HIV], cancer, or chronic liver or kidney disease, or subjects taking chronic systemic steroids).

Key Exclusion Criteria

- Received more than 1 dose of influenza antiviral medication (eg, oseltamivir [OST] or zanamivir), or any dose of ribavirin within 2 weeks, prior to first study drug intake, or received intravenous (IV) peramivir more than 1 day prior to screening.
- Unwilling to undergo regular nasal mid-turbinate (MT) swabs or has any physical abnormality which limits the ability to collect regular nasal MT specimens.
- Unstable angina pectoris or myocardial infarction within 30 days prior to screening (inclusive).
- Presence of clinically significant heart arrhythmias, uncontrolled, unstable atrial arrhythmia, or sustained ventricular arrhythmia, or risk factors for Torsade de Pointes syndrome.
- Known severe hepatic impairment (Child Pugh C cirrhosis) or chronic hepatitis C infection undergoing hepatitis C antiviral therapy.
- Severely immunocompromised in the opinion of the investigator (eg, known cluster of differentiation 4+ [$CD4^+$] count <200 cells/mm^3, absolute neutrophil count <750/mm^3, first course of chemotherapy completed within 2 weeks prior to screening, history of stem cell transplant within 1 year prior to screening, history of a lung transplant).

DOSAGE AND ADMINISTRATION

During the treatment period, all subjects will receive 1 of the following 2 dose regimens:

- Pimodivir 600 mg bid on Days 1 through 5 + SOC treatment
- Pimodivir placebo bid on Days 1 through 5 + SOC treatment

No post-study medication is provided as part of this protocol.

EFFICACY EVALUATIONS

Patient-reported Outcomes

The impact of influenza infection and its treatment (efficacy and safety) on patient-reported symptoms and functioning will be evaluated at the time points specified in the TIME AND EVENTS SCHEDULE using the Flu-iiQ™ questionnaire, the Patient Global Impression of Severity (PGIS) questionnaire, the Patient Global Impression of Change (PGIC), and the European Quality of Life (EuroQol) 5 Dimensions (EQ-5D) questionnaire. Time to resolution of influenza-related symptoms, ie, the proposed primary endpoint, will be based on the patients' ratings on 7 items from the symptoms domain of the Flu-iiQ™ (cough, sore throat, headache, nasal congestion, feeling feverish, body aches and pains, fatigue). These questionnaires will be programmed onto the electronic PRO (ePRO) device.

Return to daily activities will be assessed once daily by means of the subject's response to the question 'Over the past 24 hours, how much has influenza (flu) interfered with your ability to carry out your daily activities?' and the associated scale:

1. Not at all
2. A little bit
3. Somewhat
4. Quite a bit
5. Very much

Viral Kinetics (Nasal MT Swabs)

Influenza viral load will be quantified in nasal MT swab samples taken at scheduled times throughout the study as indicated in the TIME AND EVENTS SCHEDULE. Nasal MT swabs will be analyzed centrally using qRT-PCR and viral culture. Influenza A subtype will be determined from the baseline sample.

Hospital Admission

The hospital admission rate will be determined 28 days after initiation of study drug administration.

RESISTANCE EVALUATIONS

Viral Sequencing

Nasal MT swabs will be collected at the time points specified in the TIME AND EVENTS SCHEDULE and will be used for sequence analysis of the PB2 region of the influenza polymerase gene, and of neuraminidase (and hemagglutinin, if applicable) genes for subjects using a neuraminidase inhibitor as part of their SOC. For subjects who meet criteria for reduced virologic response or viral rebound, the acidic protein and PB1 regions of the influenza polymerase will be sequenced as well. Exploratory sequencing of other regions of the influenza virus genome may also be performed.

Phenotyping

Nasal MT swabs will be used for the analysis of phenotypic resistance against pimodivir (and other antivirals if applicable) at the time points specified in the TIME AND EVENTS SCHEDULE.

PHARMACOKINETIC EVALUATIONS

Sparse PK sampling for the measurement of plasma concentrations of pimodivir will be performed at the time points specified in the TIME AND EVENTS SCHEDULE.

PHARMACOKINETIC/PHARMACODYNAMIC EVALUATIONS

A population PK and PK/PD analysis of plasma concentration-time data of pimodivir will be performed using the nonlinear mixed-effects modeling approach. The relationship between the PK and PD (clinical outcomes, safety parameters, and antiviral activity) after repeated oral administration of pimodivir will be explored.

TASTE AND SWALLOWABILITY

A taste and swallowability questionnaire will be completed by adolescent subjects within approximately 15 minutes after the first and last intake the pimodivir or placebo tablet.

SAFETY EVALUATIONS

Safety and tolerability will be evaluated throughout the study from signing of the informed consent form (ICF/assent form) onwards until the last study-related activity. The evaluations of safety and tolerability will include monitoring of AEs, clinical laboratory tests, ECGs, and vital signs measurements, and (symptom-directed) physical examinations at the time points specified in the TIME AND EVENTS SCHEDULE.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

Adverse events and laboratory abnormalities will be graded according to the WHO Toxicity Grading Scale.

A blinded Adjudication Committee (AC) will be established to adjudicate AEs on predefined criteria for complications (pulmonary versus extrapulmonary, major versus minor, as well as infectious versus non-infectious complications). The AC will receive data on AEs, including medical assessments (eg chest X-ray results, lab results) and concomitant therapy of cases selected from the AEs. Details will be provided in an AC charter.

BIOMARKER EVALUATIONS

At the time points specified in the TIME AND EVENTS SCHEDULE, a blood sample will be collected for exploratory analyses of biomarkers (host RNA). In addition, leftovers from MT nasal swabs or blood samples may be used for other biomarker analyses (eg, proteins including cytokines).

Samples can only be used for research related to safety, PK, and efficacy of the influenza treatment, or influenza disease. They may also be used to develop tests/assays related to influenza treatment, or influenza disease.

Analyses of biomarkers may be conducted at the sponsor’s discretion and may be reported separately from this study.

PHARMACOGENOMICS EVALUATIONS

A pharmacogenomic blood sample may be collected for future exploratory pharmacogenomic analyses (where local regulations permit). This pharmacogenomic sample collection is optional. The sample will be collected only from subjects who consent separately to this component of the study. Pharmacogenomic samples will be analyzed if it is hypothesized that this may help understand the clinical outcomes.

Samples can only be used for research related to safety, PK, and efficacy of the influenza treatment, or influenza disease. They may also be used to develop tests/assays related to influenza treatment, or influenza disease.

Pharmacogenomics analyses may be conducted at the sponsor's discretion and may be reported separately from this study.

STATISTICAL METHODS

The primary analysis will be performed when all randomized subjects have completed the final study visit or discontinued earlier.

Sample Size Calculation

The study will aim to enroll 720 subjects, with 360 subjects per treatment arm.

The sample size is based on the primary endpoint of time to resolution of influenza-related symptoms. Time to resolution of influenza-related symptoms, ie, the proposed primary endpoint, will be based on the subjects' ratings on 7 items from the symptoms domain of the Flu-iiQ™ (cough, sore throat, headache, nasal congestion, feeling feverish, body aches and pains, and fatigue).

For the sample size, it is assumed that the recovery time is distributed similar to the time of symptom recovery in uncomplicated influenza, albeit with a somewhat longer average time to recovery due to the increased risk for complications and the increased time to recover for this population.

An underlying log-logistic distribution of the recovery time is assumed with a scale parameter of 0.55 and an intercept of 5.0 (in hours). Using the Gehan-Wilcoxon test to analyze the data and based on the assumption that the time to recovery is improved with 25%, a sample size of 600 subjects (randomized 1:1) will have an estimated power of 90% as based on 10,000 simulations. It is expected that approximately 15% of the total enrolled subjects may not be influenza A positive, resulting in a total of 720 subjects to be enrolled.

To assess the effect of different distributional assumptions, recovery times were simulated for a trial with a sample size of 600 patients, based on the log-logistic model and separately also based on the log-normal distribution, assuming that the time to recovery is reduced by 25% in the pimodivir with SOC treatment arm compared to the placebo with SOC treatment arm, and that the subjects are randomized in a 1:1 ratio between the 2 treatment groups. To consider the variability in the intercept and scale parameters, different values for the 2 parameters were applied. A trial was simulated 10,000 times.

Based on the Gehan-Wilcoxon test and Accelerated Failure Time model, power is at least 88% and above 90% in most scenarios.

Efficacy Analyses

The efficacy endpoints will be analyzed on the Intent-to-Treat-infected (ITT-i) Set, consisting of all subjects who were randomized, treated and had a confirmed influenza A infection, and will be analyzed by randomized treatment.

Descriptive statistics will be used for all efficacy endpoints and will be tabulated by treatment arm and stratification factors (type of baseline SOC and time since onset of symptoms).

Subgroup analyses will be performed by, but might not be limited to, region and age group.

As a confirmatory strategy, to account for multiplicity in the statistical evaluation of the most important efficacy endpoints, hierarchical testing will be applied to control for overall Type I error. The following endpoints are included in the confirmatory strategy:

1. Time to resolution of the 7 primary influenza-related symptoms (cough, sore throat, headache, nasal congestion, feeling feverish, body aches and pains, fatigue), ie, primary endpoint
2. Incidence of complications associated with influenza after the start of study treatment
3. Hospital admission rates 28 days after treatment initiation

First, the primary endpoint will be tested for superiority of pimodivir in combination with SOC over placebo in combination with SOC at the 2-sided 5% significance level. If superiority is shown on the primary endpoint, the first secondary endpoint in the sequence as indicated above will be tested for superiority at the same significance level. If superiority is shown for this secondary endpoint, the second (and last) secondary endpoint in sequence will be tested. In case superiority is not shown for an endpoint, no further endpoints in the sequence will be tested for superiority. For the primary endpoint, the results from the Gehan-Wilcoxon test will be used in the hypothesis testing. For the secondary endpoints, incidence of complications associated with influenza after the start of study treatment and hospital admission rates 28 days after treatment initiation, the results of the logistic regression will be used.

Primary Endpoint

Time to resolution of the 7 primary influenza-related symptoms is defined as the time from initiation of study treatment to when all symptoms are considered resolved for at least 24 hours. A symptom is considered resolved, depending on pre-existence of the symptom:

- The symptom is pre-existing:
  - The symptom is considered resolved if post-baseline severity is equal or lower than the pre-existing severity
- The symptom is not pre-existing:
  - The symptom is considered resolved if its severity is scored at most mild post-baseline

The primary efficacy analysis of the time to resolution of the 7 primary influenza-related symptoms (cough, sore throat, headache, nasal congestion, feeling feverish, body aches and pains, fatigue) will consist of a stratified Gehan-Wilcoxon test (using the randomization stratification factors, ie, type of baseline SOC and time since onset of symptoms as strata). Kaplan‑Meier curves, overall and by stratum, and a stratified log-rank test for time to symptom resolution will also be provided. Additionally, the data will be analyzed using an accelerated failure time model. Also, a Cox proportional hazards model will be applied. Both models will be adjusted for stratification factors and baseline symptom domain score.

Secondary Endpoints

The incidence of hospital admissions 28 days after treatment initiation will be analyzed using a logistic regression. Stratification factors will be added as covariates to the model.

Return to daily activities will be assessed once daily by means of the question 'Over the past 24 hours, how much has influenza (flu) interfered with your ability to carry out your daily activities?' The responses will be dichotomized: 'Not at all' and 'A little bit' will be considered as returned to daily activities and 'Somewhat', 'Quite a Bit' and 'Very much' will be considered as not having returned to daily activities. "Time to return to daily activities" is defined as the time from initiation of study treatment to when return

to daily activities is reached for at least 24 hours. This endpoint will be analyzed analogously to the primary endpoint.

Time to resolution of fever will be analyzed analogously to the primary endpoint.

The incidence of treatment-emergent adjudicated complications will be analyzed using a logistic regression. Stratification factors will be added as covariates to the model.

The time to viral negativity, by qRT-PCR and viral culture, will be analyzed analogously to the primary endpoint. The viral load over time will be analyzed using mixed effects modeling. Stratification factors will be added as covariates to the model. Additional predictive baseline covariates may be added.

Exploratory Endpoints

Time to resolution of impact of influenza on daily activities, emotions, and others, as defined by the Flu-iiQ^{TM} questionnaire (Modules 2, 3, and 4), is the time at which all scores within each module are reported as "no difficulty" (Module 2), "not at all" (Module 3), and "not at all concerned" (Module 4), respectively, and will be analyzed analogously to the primary endpoint. Each module will be evaluated separately.

Other Analyses

Descriptive statistics by day of assessment will be provided for PGIS and PGIC questionnaires. The EQ-5D total scores and EQ-5D visual analog scale (VAS) 'thermometer' scores will be evaluated at each time point.

The PGIS and PGIC questionnaire responses may be used as anchors to perform responder analyses for selected PROs. The anchor-based analysis, if performed, will be defined and described in a separate report.

For the EQ-5D questionnaire a post-hoc analysis plan will be developed when the economic model structure is finalized, and results of this analysis will be reported separately.

Resistance Analyses

Development of resistance against pimodivir (and other antivirals in the SOC if applicable) will be determined by viral sequencing and phenotypic testing. All baseline samples as well as the last evaluable post-baseline samples will be analyzed. Additional genotypic and phenotypic testing might be requested by the sponsor virologist.

The presence of baseline polymorphisms potentially affecting virologic response will be analyzed. The incidence of emerging mutations as well as changes in drug susceptibility (fold change in 50% of the effective concentration [EC_{50}] value) will be described and compared between treatment arms. Results of the resistance analysis may be reported in a separate report.

Biomarker Analyses

Statistical approaches to explore correlations between clinical outcome and blood biomarkers vary and depend on the different data types of the applied technology platforms, as well as on the extent of observed differences between subjects. Analyses will be conducted at the sponsor's discretion and may be reported separately from this study.

Pharmacogenomic Analyses

Pharmacogenomic samples may be used for research related to pimodivir or influenza A. They may also be used to develop tests/assays related to pimodivir or influenza A. Pharmacogenomic research may consist of the analysis of one or more candidate genes or of the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate) in relation to pimodivir clinical endpoints. Results of pharmacogenomic analysis will be reported in a separate report.

Pharmacokinetic Analyses

Population PK analysis of plasma concentration-time data of pimodivir will be performed using nonlinear mixed-effects modeling. Data may be combined with those of other selected studies (ie, Phase 1 and 2 studies) to support a relevant structural model. Available baseline subject characteristics (eg, demographics, body weight, laboratory variables, race) will be tested as potential covariates affecting PK parameters. The results of the population PK analysis will be reported in a separate report.

Pharmacokinetic/Pharmacodynamic Analyses

The PK/PD relationship of pimodivir exposure (area under the plasma concentration-time curve from time of dosing to 12 hours postdose [AUC_{12h}], maximum plasma concentration [C_{max},], or plasma concentration just prior to the beginning or at the end of a dosing interval [C_{trough}]) with selected efficacy (eg, time to resolution of influenza symptoms, change in viral load from baseline and in other virologic response parameters) and safety (including AEs and laboratory abnormalities) parameters will be explored. If there is any visual trend in graphical analysis, suitable models will be applied to describe the exposure-effect relationships. Results will be described in a separate report.

Taste and Swallowability

Taste and swallowability questionnaire results (collected for adolescents who take pimodivir or placebo tablets) will be summarized per tablet intake (first and last intake of the study drug) by means of frequency tabulations. For overall taste, a dichotomization will be made for the overall question, categorizing ‘bad’ and ‘almost acceptable’ versus ‘acceptable’ and ‘good’. For the swallowability, a dichotomization will be made of ‘slightly difficult’ or worse versus ‘neither difficult nor easy’ or better. The number of subjects (%) will be presented by category.

Safety Analyses

All safety endpoints will be evaluated on the Safety population, consisting of all subjects who received at least one dose of study drug and will be analyzed by actual treatment received. Safety will be evaluated by means of AEs (including influenza complications), clinical laboratory tests, ECGs, vital signs, and (symptom-directed) physical examinations. The safety analysis will be performed using descriptive statistics for the safety population and for each study phase separately (treatment, follow-up, and combined). Descriptive statistics and frequency tabulations will be provided.

Interim Analysis

An interim analysis will be implemented to re-estimate the study sample size and to perform an assessment of futility. The maximum total number of subjects that may be enrolled in the study will be approximately 1,080. This interim analysis will be implemented through an IDMC, providing recommendations to a Sponsor Committee. Only the IDMC and the independent Statistical Support Group will be unblinded to the data. Details will be specified in the IDMC charter.

Details on the statistical decision rules will be provided in a separate Modeling and Simulation Report. The interim analysis will be conducted at the end of the first influenza season when between 360 and 540 subjects have been enrolled or during the season when 540 subjects have been enrolled.

TIME AND EVENTS SCHEDULE

Note: When subjects are hospitalized during the course of the study, the reason for hospitalization should be recorded and every effort should be made by the investigator to perform all the assessments as indicated in the Time and Events Schedule, if practically feasible.

Phase	**Screening**	**Treatment[a]**					**Follow-up[a]**						
Day	**0-1[b]**	**1**	**2**	**3[c]**	**4[c]**	**5**	**6[d]**	**7-9**	**10 +/-1 Day**	**11-13**	**14 +/-1 Day**	**15-27**	**28 +/-1 Day**
	Screening / Baseline		**Phone Follow-up**		**Phone Follow-up**	**Phone Follow-up**						**Phone Follow-up[f]**	**Safety Follow-up Visit / Final Study Visit[a] On-site**
Clinic or home visit	X	X		X			X		X		X		X
Screening/Administrative/Safety													
ICF/assent form	X												
Inclusion/exclusion criteria[dd]	X[g]												
Medical and surgical history, demographics, influenza vaccination status, substance use	X												
Pre-existing Symptom Questionnaire[h,dd]	X												
Physical exam	X												
Symptom-directed physical exam				X			X		X		X		X
Height and body weight	X[i]												
12-lead ECG[j]	X												X
Pregnancy test (female subjects of childbearing potential)	X[k]			X									X
Randomization / Administration													
Randomization	X												
Administration of study drug[l]		X	X	X	X	X							
Virology													
Nasal swab for local virology testing[m]	X[n]												
Nasal MT swab for central testing[o]	X			X[p]			X[p]		X		X		
Efficacy / Safety													
Vital signs[q]	X			X			X						X
Temperature as measured by subject[aa]	X	2x daily on Day 1 through Day 14											
Influenza symptoms and impact (Flu-iiQ™)[r,cc,dd]	X	2x daily on Day 1 through the Final Study Visit / Safety Follow-up Visit[bb]											
Assessment of daily activities resumption[s,cc]	X		1x daily on Day 2 through the Final Study Visit / Safety Follow-up Visit[bb]										
PGIS[t,cc]	X		1x daily on Day 2 through the Final Study Visit / Safety Follow-up Visit[bb]										
PGIC[u,cc]							X[bb]				X[bb]		X[bb]

Phase	Screening	Treatment[a]					Follow-up[a]						
Day	0-1[b]	1	2	3[c]	4[c]	5	6[d]	7-9	10 +/-1 Day	11-13	14 +/-1 Day	15-27	28 +/-1 Day
	Screening / Baseline		Phone Follow-up		Phone Follow-up	Phone Follow-up						Phone Follow-up[f]	Safety Follow-up Visit / Final Study Visit[a] On-site
EQ-5D[u,cc]	X						X[bb]				X[bb]		X[bb]
Hematology, chemistry	X[v,w]			X[w]			X[w]				X[w]		X[w]
Urinalysis	X			X			X				X		X
Blood biomarker sampling (host RNA)	X			X									
Pharmacogenomic sampling (host DNA)[x]				X									
Pharmacokinetics[y]				X[p]			X[p]						
Taste and swallowability[z]		X				X							
Adverse events recording	X	X	X	X	X	X	X		X		X	X	X
Prestudy and concomitant medication recording	X	X	X	X	X	X	X		X		X	X	X

Abbreviations: DNA: deoxyribonuclocleic acid; ECG: electrocardiogram; EQ-5D: European Quality of Life 5 Dimensions; Flu-iiQ™: Influenza Intensity and Impact Questionnaire; ICF: informed consent form; RNA: ribonucleic acid; MT: mid-turbinate; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity.

a. Subjects who prematurely discontinue study drug treatment for any reason (except withdrawal of consent) will be asked to continue with their remaining study visits and assessment schedule. Subjects who withdraw consent during the treatment or follow-up phase will be offered an optional Safety Follow-up Visit. The optional Safety Follow-up Visit will occur the day of consent withdrawal or the day after and will consist of the same assessments as at the Final Study Visit (Day 28), with optional PRO completion.
b. Screening/baseline assessments start at signing of the ICF/assent form and can continue the next calendar day if needed. All screening/baseline procedures should take place prior to the first study drug intake.
c. The Day 3 visit may be performed on Day 4. In that case, the phone follow-up initially planned on Day 4 should be performed on Day 3.
d. The Day 6 visit may be performed on Day 7, although efforts should be made to respect the initial Time and Events Schedule.
e.
f. During this period, at minimum one phone contact should be established with the subject to document potential adverse events (AEs) and concomitant medications (the need for a face-to-face visit, at-home or on-site, is at the investigator's discretion).
g. Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that they no longer meet all eligibility criteria, they should be excluded from participation in the study.
h. This questionnaire will be administered as a baseline assessment after the subject completes the Flu-iiQ™.
i. Height and body weight are only to be measured at screening if not already available in the subject's chart (weight data should not be more than 1 month old).
j. Subjects should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital signs measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECGs, vital signs, blood draw. An ECG recorded within 1 calendar day before signing of the ICF/assent form can be used in lieu of the baseline ECG requirement.

k. The result of a prior urine or serum pregnancy test that occurred within 1 calendar day before signing of the ICF/assent form can be used in lieu of the baseline requirement.
l. Depending on the time of screening/enrollment, subjects will receive 1 dose (evening) or 2 doses (morning and evening) of study drug on Day 1. For subjects who receive only 1 dose of pimodivir or placebo on Day 1 (evening), dosing should continue until the morning of Day 6 so that all subjects receive 10 doses in total.
m. Local virology testing can be done via a polymerase chain reaction (PCR)-based or other rapid molecular diagnostic assay or a rapid influenza diagnostic test (RIDT). It is recommended to use MT swabs for local virology testing, although nasopharyngeal (NP) swabs are allowed if required by local procedures. Nasal swabs for local virology testing should be obtained from the left and right nostrils (from both nostrils if feasible, but from only one nostril otherwise) and pooled into the same collection tube. If available, leftovers from the local virology samples (with the exception of "earlier sample", see footnote n) will be shipped to and stored at the central lab for further testing, regardless of local influenza test result.
n. The results of an earlier sample collected and tested positive for influenza A infection after the onset of symptoms, using a RIDT or, if available, a PCR-based or other rapid molecular diagnostic assay, can be used in lieu of the local virology testing at screening. This sample is used to determine eligibility.
o. Central virology testing: Nasal MT swabs should be obtained from the left and the right nostrils and pooled into the same collection tube. The samples will be collected at screening/baseline and on Days 3, 6, 10, and 14. The screening/baseline sample needs to be collected predose, as close as possible, to the first dose. Sampling should be done at approximately the same time (±4 hours) on each sampling day. Leftovers from nasal MT swabs collected for virology testing may be used for protein biomarker analysis.
p. At the time points where both nasal MT swabs and pharmacokinetic (PK) samples are obtained, these samples should be obtained as close together in time as possible.
q. Vital signs include body temperature, pulse rate, respiratory rate, and blood pressure.
r. The Flu-iiQ^{TM} questionnaire will be completed twice daily throughout the study; it will be programmed onto the electronic PRO (ePRO) device.
s. Questionnaire (Return to daily activities) to be completed at screening/baseline (as close as possible to first study drug intake) and then once daily onto the ePRO device.
t. Questionnaire PGIS to be completed from screening/baseline (as close as possible to the first study drug intake) and then once daily throughout Final Study Visit/Safety Follow-up Visit.
u. Questionnaire EQ-5D to be completed at screening/baseline (as close as possible to the first study drug intake); Questionnaires EQ-5D and PGIC to be completed on Day 6, 14, and 28 onto the ePRO device.
v. Follicle-stimulating hormone (FSH) will be tested at screening for female subjects who are amenorrheic for 12 months or less.
w. If feasible, safety blood samples will be collected after fasting for at least 10 hours.
x. The pharmacogenomic sample should preferably be collected at the specified time point, however if necessary it may be collected at a later time point without constituting a protocol deviation.
y. Sparse PK sampling will be performed as follows (if practically feasible):
On Day 3: at any time during the visit (date and time of last drug intake before PK sampling will be recorded).
On Day 6: preferentially as close as possible to 12h after the last dose of study drug (ie, the evening dose on Day 5). If treatment was started in the evening of Day 1, PK sampling will be performed on Day 6 before the last drug intake. The date and time of the evening drug intake on Day 5 will be recorded. In case the Day 6 visit is performed on Day 7 (footnote d), the PK sample should be taken as early as possible during the visit (date and time of the last study drug intake before PK sampling will be recorded). Leftovers from samples collected for PK testing may be used for protein biomarker analysis.
z. The taste and swallowability questionnaire should only be completed by adolescent subjects for pimodivir or placebo. The questionnaire should be completed within approximately 15 minutes after the first and last intake of the pimodivir or placebo tablet. For subjects who receive the last dose of pimodivir or placebo on Day 6 (see footnote l), the questionnaire should be completed on Day 6.

aa. In case of antipyretic use, temperature should be taken whenever possible at least 4 hours after antipyretic medication. Temperature at baseline should be measured after randomization and ePRO completion, but before the first dose. Oral temperature will be measured and recorded in the ePRO device by the subject twice daily until Day 14 by all subjects at sites where appropriate forms and translations are available and approved
bb. PRO completion compliance should be assessed daily by the site staff via the ePRO web platform. Reasons for missing assessment should be documented on the web platform by the site after discussion with the subject.
cc. PRO assessments will be completed by all subjects at sites where appropriate PROs and translations are available and approved.
dd. Assessment of inclusion criterion n°2 (flu symptoms severity) must be performed through the evaluation of the subject's answers to Pre-existing Symptom Questionnaire and Flu-iiQ^{TM} Module 1 questions programmed on the ePRO device (before randomization).

ABBREVIATIONS

AC	Adjudication Committee
ADL	activities of daily living
ADR	adverse drug reaction
AE	adverse events
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{∞}	area under the plasma concentration-time curve from time of dosing extrapolated to infinity
AUC_{12h}	area under the plasma concentration-time curve from time of dosing to 12 hours postdose
AUC_{24h}	area under the plasma concentration-time curve from time of dosing to 24 hours postdose
AUC_{last}	area under the plasma concentration-time curve from time of dosing to time of last observation
bid	twice daily
BUN	blood urea nitrogen
C_{0h}	predose plasma concentration
CI	confidence interval
$CD4^{+}$	cluster of differentiation 4^{+}
CDC	Centers of Disease Control and Prevention
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
COPD	chronic obstructive lung disease
CPK	creatine phosphokinase
C_{trough}	plasma concentration just prior to the beginning or at the end of a dosing interval
CYP	cytochrome P450
DBP	diastolic blood pressure
DDI	drug-drug interaction
EC_{50}	50% effective concentration
ECG	electrocardiogram
eCRF	electronic case report form
eDC	electronic data capture
ePRO	electronic patient-reported outcome
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
HMG CoA	3-hydroxy-3-methylglutaryl-coenzyme A
IB	Investigator's Brochure
IC_{50}	50% inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IWRS	interactive web response system
LS	least squares
M2	matrix 2
MCH	mean corpuscular hemoglobin
MedDRA	Medical Dictionary for Regulatory Activities
MESH	measured solutions for health
MT	mid-turbinate

NAI	neuraminidase inhibitor
NAP	not applicable
NOAEL	no observed adverse effect level
NP	nasopharyngeal
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OC	oral contraceptive
OST	oseltamivir
PB2	polymerase basic protein 2
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	pharmacokinetic(s)
PQC	Product Quality Complaint
PRO	patient-reported outcome
PT	prothrombin time
qRT-PCR	quantitative real time polymerase chain reaction
QTc	corrected QT interval
QTcB	QT interval corrected for heart rate according to Bazett's correction
QTcF	QT interval corrected for heart rate according to Fridericia's correction
RBC	red blood cell
RBV	ribavarin
RIDT	rapid influenza diagnostic test
RNA	ribonucleic acid
SAE	serious adverse events
SBP	systolic blood pressure
SOC	standard of care
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2term}$	terminal elimination half-life
TCID50	50% tissue culture infective dose
TEAE	treatment-emergent adverse event
t_{max}	time to reach C_{max}
TQT	thorough QT
ULN	upper limit of normal
vp	viral particles
vs	versus
WBC	white blood cell
WHO	World Health Organization

DEFINITIONS OF TERMS

Electronic source system (eSource)	Contains data traditionally maintained in a hospital or clinic record to document medical care or data recorded in an electronic case report form (eCRF) as determined by the protocol. Data in this system may be considered source documentation.
Study drug	Pimodivir or placebo only

1. INTRODUCTION

Pimodivir (formerly known as VX-787 and JNJ-63623872) is a non-nucleotide inhibitor of the polymerase basic protein 2 (PB2) subunit of the influenza A virus polymerase complex and is currently in Phase 3 development as treatment for influenza A infection.

For the most comprehensive nonclinical and clinical information regarding pimodivir, refer to the latest version of the Investigator's Brochure (IB) for pimodivir.[9]

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.1. Background

Both seasonal and pandemic influenza are a significant cause of morbidity and mortality worldwide. For example, the 2009 H1N1 influenza pandemic in the United States was responsible for an estimated approximately 61 million cases, 274,000 hospitalizations, and over 12,500 deaths.[14] Because the efficacy of the current annual hemagglutinin-based or modified live influenza virus vaccines depends on accurately predicting the viral strains prior to each influenza season or pandemic and because vaccines are not provided universally, there remains annually a significant burden of disease due to influenza.[13]

Accordingly, several antiviral drugs have been developed for the treatment of influenza. These drugs have been shown to shorten the duration and reduce the severity of symptoms if taken early after the onset of symptoms (within 24 to 48 hours). They can also be taken as prophylaxis against infection. The 2 main classes of antiviral drugs used against influenza are the neuraminidase inhibitors (NAIs), such as Tamiflu® (oseltamivir [OST]), Rapivab™ (peramivir), and Relenza® (zanamivir), and the viral matrix 2 (M2) protein inhibitors, such as Symmetrel® (amantadine) and Flumadine® (rimantadine). Unfortunately, these drugs have several limitations. Influenza strains have emerged that show resistance to both of these classes of drugs, especially the M2 protein inhibitors. In addition, these drugs need to be administered no later than 24 to 48 hours after infection, and therefore many patients are not eligible for therapy when they present for treatment. Further, none of these antiviral agents have been able to demonstrate a clinical benefit to those with the greatest unmet medical need, specifically those patients who are hospitalized or at high risk of complications due to influenza. Given these considerations, there remains a need for better therapeutic options for the treatment of influenza.

A desired profile of a novel influenza antiviral includes: (1) rapid onset of protective effects leading to an expanded treatment window; (2) better activity in patients with high viral load; (3) inhibition of both production and release of virus; (4) maintenance of potency against neuraminidase and M2 inhibitor resistant viral strains; (5) safe and well tolerated. Pimodivir, an inhibitor of the viral replication complex, potentially meets all of these criteria.

Clinical Studies

At the time of protocol writing, data were available from 12 completed clinical studies: nine Phase 1 studies and three Phase 2 studies (*note: for one Phase 2 study, the clinical study*

report is not final yet). In addition, two Phase 1 studies were still ongoing. Refer to the IB for more details.[9]

Human Pharmacokinetics

After oral administration of pimodivir as a capsule or tablet formulation in healthy adult subjects, pimodivir was absorbed with a median time to reach the maximum plasma concentration (t_{max}) of 2 to 4 hours, with some subjects exhibiting multiple peaks suggestive of enterohepatic recycling. Concomitant food (a high-fat meal) has no effect on the oral bioavailability (based on area under the plasma concentration-time curve from time of dosing extrapolated to infinity [AUC_{∞}]) of pimodivir when administered as either capsule or tablet. However, the maximum plasma concentration (C_{max}) was decreased by 9% for the capsule formulation and increased by 53% for the tablet formulation when compared to fasted conditions. The absolute bioavailability of the tablet was approximately 46%.

Results from a ^{14}C-pimodivir human mass balance study (Study 63623872FLZ1007) showed that unchanged pimodivir is the major circulating entity (about 86%) in plasma with an acylglucuronide (J4) as a minor metabolite (about 3%). Fecal elimination was the main excretion pathway for pimodivir (83% to 89% of the administered dose); renal elimination is a minor excretion pathway.

Pimodivir plasma concentrations exhibit biphasic kinetics, eliminated from plasma initially at a more rapid rate, followed by a slower terminal elimination phase. The mean terminal phase elimination half-life ($t_{1/2term}$) ranged from approximately 13 to 28 hours following single doses of pimodivir.

Study 63623872FLZ2001 was a Phase 2b, randomized, double-blind, placebo-controlled, parallel-group, multicenter study of 2 dose levels of pimodivir administered as monotherapy and as 1 dose level of pimodivir in combination with OST for the treatment of acute uncomplicated seasonal influenza A in adult subjects. Pimodivir concentrations appeared to reach steady-state between Days 3 and 4, with no evidence of a pharmacokinetic (PK) drug interaction between pimodivir and OST.

Study 63623872FLZ2002 was a randomized, double-blind, placebo-controlled, parallel-group, multicenter Phase 2b study to evaluate the effect of pimodivir 600 mg twice daily (bid) vs placebo, both in combination with OST 75 mg bid in adult (aged 18 to ≤64 years) and elderly (aged 65 to ≤85 years) hospitalized subjects with influenza A infection. The geometric mean ratios (95% confidence interval [CI]) of the pimodivir PK parameters at Day 3 of elderly adults (65 to ≤85 years) vs non-elderly adults (18 to ≤64 years) showed that PK of pimodivir was comparable between elderly and non-elderly adults.

Drug-drug Interactions With Pimodivir

Pimodivir has a low potential to reversibly inhibit cytochrome P450 (CYP)1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4. Its potential to inactivate CYP3A4 in a time dependent manner also was assessed and determined to be low. In human hepatocytes, pimodivir did not induce

CYP1A2 or 3A4 enzyme expression or activity. Taken together, these data suggest a low potential for drug-drug interactions (DDIs) with coadministered CYP substrates.

Pimodivir was evaluated as a potential substrate and inhibitor of organic anion transporting polypeptide 1 (OATP1B1) in stably transfected human embryonic kidney-293 cells overexpressing OATP1B1. Pimodivir was found to inhibit OATP1B1 with a 50% inhibitory concentration (IC_{50}) of 0.6 μM. Pimodivir was also determined to be a substrate of OATP1B1. In vitro, pimodivir is an inhibitor of OATP1B1, OATP1B3, organic anion transporter (OAT) 1 and OAT3.

A clinical DDI study with pitavastatin (OATP1B1 and OATP1B3 substrate) was completed (Study 63623872FLZ1004). Based on the ratios of the least squares (LS) means, C_{max} and AUC from time of dosing to time of last observation (AUC_{last}) of pitavastatin were 1.20-fold and 1.44-fold higher, respectively, after coadministration of pitavastatin with pimodivir compared to the administration of pitavastatin alone. These changes are not considered clinically relevant interactions and no dose adjustment is necessary.

Pimodivir 600 mg bid administered alone or in combination with OST 75 mg bid for 5 days in healthy volunteers (Study 63623872FLZ1001) resulted in generally comparable values for pimodivir predose analyte concentrations (C_{0h}) on Days 3, 4, and 5, indicating that near steady-state conditions had been achieved between Day 3 and 4. For pimodivir administered alone vs in combination with OST, minimum plasma concentration (C_{min}), and AUC from time of dosing to 12 hours postdose (AUC_{12h}) of pimodivir were comparable, while mean pimodivir C_{max} was 30% higher when administered in combination with OST, compared with administration of pimodivir alone. The median t_{max} of pimodivir was 3.0 hours when pimodivir was administered alone and 1.5 hours when administered in combination with OST. For OST administered alone vs in combination with pimodivir, OST AUC_{12h} and OST carboxylate (also referred to as OST acid) C_{min}, C_{max}, and AUC_{12h} were comparable. Oseltamivir mean C_{min} was 10% higher and C_{max} was 5% lower when administered in combination with pimodivir, compared with OST administered alone. Following doses of 600 mg of pimodivir bid for 10 days, mean C_{max} and AUC_{12h} of pimodivir were, respectively, 1.2-fold and 1.8-fold higher on Day 10 compared with Day 1.

A clinical DDI study with ethinylestradiol and norethindrone, provided as the commercially available oral contraceptive (OC) tablet Ovysmen®, was completed (Study 63623872FLZ1009). The coadministration of ethinylestradiol and norethindrone with pimodivir did not result in a PK DDI, and therefore pimodivir may be dosed with OCs without special considerations.

In Study 63623872FLZ1006, the influence of food intake on the bioavailability of pimodivir was investigated. Single administration of 600 mg of pimodivir taken under fasted or under fed conditions resulted in a similar AUC_{last} and AUC_{∞}, as the 90% CIs of the LS means were completely within the 80% to 125% boundaries. C_{max} was 45% higher under fed conditions compared to fasted conditions. The 90% CI of the LS means ratio of C_{max} fell outside the 80% to 125% boundaries (112.97% to 185.18%).

Clinical Efficacy

Refer to the IB for detailed info on the Phase 2a challenge study (Study VX11-787-101).[9]

In Study 63623872FLZ2001 (community study), subjects received one of the 4 treatments for a total of 5 days: (1) pimodivir placebo bid + OST placebo bid, (2) pimodivir 300 mg bid + OST placebo bid, (3) pimodivir 600 mg bid + OST placebo bid, or (4) pimodivir 600 mg bid + OST 75 mg bid. Results from Study 63623872FLZ2001 showed that pimodivir was effective in decreasing viral loads (by quantitative real time polymerase chain reaction [qRT-PCR]) in subjects with a confirmed influenza A infection.

- The results showed an average change of AUC viral load (95% CI) (by qRT-PCR) vs placebo treatment of -3.6 (-7.1; -0.1), -4.5 (-8.0; -1.0), and -8.6 (-12; -5.1) day*log10 copies/mL for the pimodivir 300 mg bid, pimodivir 600 mg bid, and pimodivir 600 mg bid + OST 75 mg bid treatment groups, respectively. The average change in AUC viral load of pimodivir 600 mg bid + OST 75 mg bid vs pimodivir 600 mg bid treatment was -4.1 (-7.4; -0.7) day*log10 copies/mL. The primary analysis showed a statistically significant dose-response relationship of reduction in AUC viral load vs pimodivir dose.
- The results showed an average change on the AUC of viral load (95% CI) (by viral culture) vs placebo treatment of -2.1 (-2.9; -1.3), -2.1 (-2.8; -1.3), and -2.0 (-2.8; -1.2) $\log_{10}$ 50% tissue culture infective dose ($TCID_{50}$)/mL for the pimodivir 300 mg bid, pimodivir 600 mg bid, and pimodivir 600 mg bid + OST 75 mg bid treatment groups, respectively. The AUC viral load of pimodivir 600 mg bid + OST 75 mg bid and pimodivir 600 mg bid treatment was similar (0.1 [-0.7; 0.8]).
- There was a reduction of time to viral negativity vs placebo treatment of 13%, 18%, and 31% for the pimodivir 300 mg bid, pimodivir 600 mg bid, and pimodivir 600 mg bid + OST 75 mg bid treatment groups, respectively. The time to viral negativity was statistically significantly shorter for the pimodivir 600 mg bid and pimodivir 600 mg bid + OST 75 mg bid treatment groups compared to placebo treatment.
- There was an estimated reduction in time to resolution of the 7 primary influenza symptoms vs placebo of 13% and 17% for the pimodivir 600 mg bid and pimodivir 600 mg bid + OST 75 mg bid treatment groups, respectively, and an estimated increase in time to resolution of the influenza symptoms vs placebo of 7% for the pimodivir 300 mg bid treatment group. The differences in time to resolution compared to placebo treatment were not statistically significant for active treatment groups. However, given that the study was finalized at the interim analysis for early success on virologic response, the sample sizes per arm were relatively small, and clinical outcome comparisons had reduced power to show differences.

In Study 63623872FLZ2002 (hospital study), adult (aged 18 to ≤64 years) and elderly (aged 65 to ≤85 years) hospitalized subjects with influenza A infection received pimodivir 600 mg bid + OST 75 mg bid or pimodivir placebo bid + OST 75 mg bid, for a total of 7 days. The following results were observed:

- Viral Kinetics
  - The difference (95% CI) in viral titer (by culture) AUC of pimodivir 600 mg bid + OST 75 mg bid treatment vs placebo bid + OST 75 mg bid treatment

was -0.5 (-2.0, 1.0) log_{10} $TCID_{50}$/mL*day. For subjects that were treated within 72 hours from onset of symptoms, the difference (95% CI) in AUC was -1.2 (-4.2, 1.8) log_{10} $TCID_{50}$/mL*day. For subjects that were treated within 96 hours from onset of symptoms, the difference (95% CI) in AUC was -0.9 (-3.0, 1.3) log_{10} $TCID_{50}$/mL*day.

- Based on viral titer (by culture), the median time to viral negativity was 1.1 and 1.3 days for the pimodivir 600 mg bid + OST 75 mg bid and placebo bid + OST 75 mg bid treatment groups, respectively, as estimated from an accelerated failure time model. For subjects that were treated within 72 hours from onset of symptoms, the median time to viral negativity was 1.2 and 1.8 days for the pimodivir 600 mg bid + OST 75 mg bid and placebo bid + OST 75 mg bid treatment groups, respectively, as estimated via the accelerated failure time analysis. For subjects that were treated within 96 hours from onset of symptoms, the median time to viral negativity was 1.2 and 1.6 days for the pimodivir 600 mg bid + OST 75 mg bid and placebo bid + OST 75 mg bid treatment groups, respectively, as estimated via the accelerated failure time analysis.
- The difference (95% CI) in viral load (by qRT-PCR) AUC of pimodivir 600 mg bid + OST 75 mg bid treatment vs placebo bid + OST 75 mg bid treatment was 0.7 (-3.0, 4.3) log_{10} viral particles (vp)/mL*day. For subjects that were treated within 72 hours from onset of symptoms, the difference (95% CI) in AUC was -2.2 (-8.0, 3.7) log_{10} vp/mL*day. For subjects that were treated within 96 hours from onset of symptoms, the difference (95% CI) in AUC was -0.9 (-5.4, 3.6) log_{10} vp/mL*day.

- Ordinal Scale at Day 8

  Overall, treatment with either placebo bid + OST 75 mg bid or pimodivir 600 mg bid + OST 75 mg bid resulted in a similar improvement in clinical status at Day 8, as expressed by a common odds ratio (95% CI) of 1.03 (0.43; 2.47). For subjects treated within 72 hours from onset of influenza symptoms, the estimated reduction of 0.60 in the odds, as expressed by a common odds ratio (95% CI) of 0.40 (0.09; 1.71), reflects an improvement in clinical outcome of 60%, with pimodivir 600 mg bid + OST 75 mg bid treatment compared to placebo bid + OST 75 mg bid treatment at Day 8. For subjects treated within 96 hours from onset of influenza symptoms, the estimated reduction of 0.50 in the odds, as expressed by a common odds ratio (95% CI) of 0.50 (0.16; 1.56), reflects an improvement in clinical outcome of 50%, with pimodivir 600 mg bid + OST 75 mg bid treatment compared to placebo bid + OST 75 mg bid treatment at Day 8.

- Influenza-related Complications

  Overall, the incidence of influenza-related complications was 7.9% (5/63) and 15.6% (5/32) in the pimodivir 600 mg bid + OST 75 mg bid and placebo bid + OST 75 mg bid treatment groups, respectively. For subjects treated within 72 hours from onset of influenza symptoms, the incidence of influenza-related complications was 4.8% (1/21) and 26.7% (4/15) in the pimodivir 600 mg bid + OST 75 mg bid and placebo bid + OST 75 mg bid treatment groups, respectively. For subjects treated within 96 hours from onset of influenza symptoms, the incidence of influenza-related complications was 5.9% (2/34) and 23.8% (5/21) in the pimodivir 600 mg bid + OST 75 mg bid and placebo bid + OST 75 mg bid treatment groups, respectively.

- Time to Clinical Endpoints
  - Median times to clinical endpoints were shorter for treatment with pimodivir 600 mg bid + OST 75 mg bid compared to placebo bid + OST 75 mg bid for resolution of 7 primary influenza symptoms (cough, sore throat, headache, nasal stuffiness, feverishness or chills, muscle or joint pain, and fatigue) (22%), return to usual activity (24%) and return to usual health (22%). A 13% longer time to hospital discharge was estimated for the pimodivir 600 mg bid + OST 75 mg bid treatment group compared to the placebo bid + OST 75 mg bid treatment group.
  - For subjects treated within 72 hours from onset of symptoms, results for resolution of 7 primary influenza symptoms, return to usual health results and hospital discharge were similar to the overall study population, whereas the median time to return to usual activity was estimated to be 61% shorter for pimodivir 600 mg bid + OST 75 mg bid treatment compared to placebo bid + OST 75 mg bid treatment.
  - For subjects treated within 96 hours from onset of symptoms, results for resolution of 7 primary influenza symptoms, return to usual health results and hospital discharge showed relatively minimal differences between the pimodivir 600 mg bid + OST 75 mg bid compared to placebo bid + OST 75 mg bid, whereas the median time to return to usual activity was estimated to be 26% shorter for the pimodivir 600 mg bid + OST 75 mg bid treatment.

Resistance

Population sequence analyses of the PB2 segment in subjects in Study VX11-787-101 identified a variant (PB2 M431I) that was observed in multiple subjects (N=4). This amino acid change confers a 57-fold decrease in sensitivity to pimodivir in in vitro studies but the virus had reduced replication capacity compared to wild type strains. Additional variants at 3 PB2 positions that had previously been associated with mutations that cause a decrease in sensitivity to pimodivir in vitro (S324C, K376R, and M431L/R/V) were also observed in single pimodivir-treated subjects. Emergence of variants was not coincident with viral rebound, and all subjects subsequently cleared virus after treatment.

In the Phase 2b study 63623872FLZ2001, genotypic and phenotypic changes in the influenza A viral variants obtained from the nasal swab samples of subjects were investigated. This first exploratory analysis was focused on the baseline and the last virus-positive post-baseline samples, which were analyzed using population sequencing of the PB2 and neuraminidase genes as well as phenotypic susceptibility testing in cell culture. The Full Analysis Set consisted of 223 subjects that were randomized, treated, and had a confirmed influenza A infection. Sequencing of the baseline samples was successful in 206/223 (92%) subjects and did not show any mutation at PB2 positions of interest. In addition, baseline phenotypic resistance to pimodivir, defined as a fold change in 50% of the effective concentration (EC_{50}) >4.0, was not observed (data available for 180/223 [81%] subjects).

Emergence of mutations at positions of interest occurred in 9 subjects, of which only 1 subject in the pimodivir + OST combination treatment group. These mutations included S324K, S324N, S324R, F325L, S337P, K376N, K376R, and N510K. Emergence of phenotypic resistance to

pimodivir was observed in 9 subjects. Seven of these 9 subjects also had emerging known PB2 position mutations, one subject had no genotypic data available, and one subject harbored T378S, a newly identified resistance mutation in PB2. No emergent-phenotypic resistance was observed in the combination arm. Virologic breakthrough was not observed in any of these subjects. Overall, a high correlation between the presence of PB2 mutations at positions of interest and the emergence of phenotypic resistance to pimodivir was observed. The PB2 mutation T378S was associated with high-level phenotypic resistance to pimodivir and represented a newly identified position of interest. The list of PB2 positions of interest was updated for subsequent analyses to contain the following 13 amino acid substitutions: Q306, F323, S324, F325, S337, H357, F363, K376, T378, F404, Q406, M431, and N510.

Resistance data from Study 63623872FLZ2002 are not yet available.

Clinical Safety

Up to 15 June 2017, 634 subjects had been exposed to pimodivir, which included 277 healthy subjects, 72 subjects inoculated with influenza, and 285 subjects naturally infected with influenza, in the Phase 1, Phase 2a, and Phase 2b studies, respectively. Administration of pimodivir was generally safe and well tolerated. In these studies, 1 serious adverse event (SAE) of hypersensitivity was reported and considered to be at least possibly related to pimodivir by the investigator. Refer to the IB for more details.[9]

Based on the data available up to 15 June 2017, only headache and diarrhea were seen consistently in healthy subjects. In the pooled analysis of the Phase 1 and Phase 2a studies, on the list of events that occurred in at least 10% of subjects, the overall incidence of headache was comparable following single doses of pimodivir (9.1%) and placebo (8.7%); the overall incidence was also comparable following multiple doses of pimodivir (12.8%) and placebo (11.9%). The overall incidence of diarrhea was higher following single doses of pimodivir (9.8%) than following single doses of placebo (2.9%) and was increased following multiple doses of pimodivir (18.1%) compared with multiple doses of placebo (2.4%). The investigator reported term for the diarrhea cases were “loose stools”, “diarrhea” and “acute diarrhea”. The severity was recorded as mild, with 1 exception of a case reported as “diarrhea” of moderate severity in a subject receiving pimodivir 600 mg bid.

In accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)-E14 guideline, the thorough QT (TQT) study (Study 63623872FLZ1005) was negative and study sensitivity was shown by moxifloxacin control, demonstrating that pimodivir induces no corrected QT (QTc) interval prolongation of regulatory concern.

Results from Phase 2b Study 63623872FLZ2001 (community study) showed that pimodivir was generally safe and well tolerated:

- The most common treatment-emergent adverse event (TEAE) was diarrhea: 5.6%, 6.8%, 27.0%, and 17.8% of subjects in the placebo, pimodivir 300 mg bid, pimodivir 600 mg bid, and pimodivir 600 mg bid + OST 75 mg bid treatment groups, respectively. The majority of

the diarrhea cases were mild, with 1 case of diarrhea indicated as severe (in the pimodivir 600 mg bid treatment group).

- No subjects died and for 2 subjects 1 treatment-emergent SAE was reported: an SAE of moderate increased alanine aminotransferase (ALT) in the pimodivir 600 mg bid treatment group (doubtfully related according to the investigator, started on Day 14 and was reported resolved 21 weeks later), and an SAE of severe thrombocytopenia in the placebo group (possibly related according to the investigator, started on Day 63 and was reported resolved 5 weeks later).

Results from Phase 2b Study 63623872FLZ2002 (hospital study) showed that overall, safety was similar for the pimodivir 600 mg bid + OST 75 mg bid treatment group compared with placebo bid + OST 75 mg bid treatment group. Overall, TEAEs were reported in 75.0% of subjects in the pimodivir 600 mg bid + OST 75 mg bid treatment group compared with 71.4% of subjects in the placebo bid + OST 75 mg bid treatment group. The most common TEAE was diarrhea, reported in 20.3% and 11.4% of subjects in the pimodivir 600 mg bid + OST 75 mg bid treatment group and placebo bid + OST 75 mg bid treatment group, respectively. The diarrhea cases were transient in nature and of mild to moderate severity.

- One subject in the pimodivir 600 mg bid + OST 75 mg bid treatment group died at Day 8 after experiencing multiple SAEs, all reported to be doubtfully or not related to treatment. Serious AEs were reported in 17.2% and 11.4% of subjects in the pimodivir 600 mg bid + OST 75 mg bid treatment group and placebo bid + OST 75 mg bid treatment group, respectively. One SAE of hypersensitivity was reported to be possibly related to pimodivir 600 mg bid + OST 75 mg bid treatment.

1.2. Standard-of-care

Currently available influenza antiviral therapies used as standard-of-care (SOC) treatment include NAIs and, less commonly, adamantanes. The NAIs OST (oral), zanamivir (inhaled), and peramivir (intravenous, IV) are used as de-facto SOC treatment as recommended by the Centers of Disease Control and Prevention (CDC) and the World Health Organization (WHO). Adamantanes, such as rimantadine, are no longer recommended for antiviral treatment of currently circulating influenza A virus strains due to widespread resistance.[2] Reports of ribavirin (RBV) use have been published although this drug has not been approved for influenza treatment. Worldwide treatment of influenza is however diverse and not standardized. As such, local SOC treatment may include any of the above antivirals as well as supportive care.

1.3. Overall Rationale for the Study

Although generally a self-limited disease, infection with influenza A can cause significant morbidity and mortality, especially in certain patient populations such as those at the extremes of age.

Pimodivir is being developed for the treatment of patients who are hospitalized due to or at high risk of complications from influenza A, who have the highest unmet medical need. As a therapeutic option intended for global use, studying pimodivir in combination with the SOC accounts for worldwide differences in the treatment of this population. In the instances where

pimodivir is administered with a NAI SOC option, an additive effect of pimodivir over NAI administration alone will be explored in high-risk subjects. Accordingly, the study design allows subjects to gain any potential benefits of the current SOC therapies, while assessing the benefit of pimodivir given in combination.

The purpose of the current study is to therefore evaluate the additional benefit of pimodivir in combination with SOC treatment over placebo in combination with SOC treatment following a 5-day 600 mg bid therapy in adolescent (13 to 17 years), adult (18 to 65 years), and elderly (>65 to ≤85 years) non-hospitalized subjects with influenza A infection who are at risk of developing complications.

1.4. Benefits and Risks Management

1.4.1. Known Benefits of Pimodivir

The clinical benefit of pimodivir remains to be established.

1.4.2. Potential Benefits of Pimodivir

Results from pimodivir clinical studies may be useful in developing a new therapy for influenza A infection.

The dose regimen of 600 mg bid is expected to result in antiviral activity and subjects may benefit from participating in this study.

1.4.3. Known Risks of Pimodivir

At the time of protocol writing, 634 subjects had been exposed to pimodivir, with 277 healthy subjects, 72 subjects inoculated with influenza, and 285 subjects naturally infected with influenza, in the Phase 1, Phase 2a, and Phase 2b studies, respectively. In these studies, 1 SAE of hypersensitivity was reported and considered to be at least possibly related to pimodivir by the investigator.

Adverse drug reactions:

A formal adverse drug reaction (ADR) identification process was conducted on the clinical safety data of Study 63623872FLZ2001 and Study 63623872FLZ2002. No serious ADRs have been identified to date. Diarrhea is considered a non-serious ADR because most cases were mild or moderate.

Adverse events in healthy subjects:

Based on the data available at the time of protocol writing, only headache and diarrhea were seen consistently in healthy subjects. In the pooled analysis of the Phase 1 and Phase 2a studies, the occurrences of headache were equally distributed among pimodivir and placebo, while diarrhea occurred more often after treatment with pimodivir compared to placebo. The investigator-reported term for the diarrhea cases were “loose stools”, “diarrhea” and “acute diarrhea”. The severity was recorded as mild, with 1 exception of a case reported as “diarrhea” of moderate severity in a subject receiving pimodivir 600 mg bid.

Adverse events in subjects naturally infected with influenza A:

In subjects naturally infected with influenza A, pimodivir was generally safe and well tolerated and a favorable safety profile was established. In the community study (Study 63623872FLZ2001), the overall incidence of diarrhea was comparable in subjects treated with pimodivir or pimodivir + OST, but higher than in those treated with placebo. Increased incidence of diarrhea was reported and was more common with pimodivir 600 mg (as mono- or combination therapy) than with pimodivir 300 mg. In hospitalized subjects (Study63623872FLZ2002), the overall incidences of headache and diarrhea were higher in subjects treated with pimodivir + OST than in those treated with placebo + OST.

1.4.4. Potential Risks of Pimodivir

Reproductive Risk and Pregnancy

Based on preclinical studies, no reproductive (embryo-fetal, fertility and early embryonic development) liabilities have been identified for pimodivir.

In the current study, subjects who are heterosexually active must follow the contraception requirements detailed in Section 4.1. Subjects' study treatment will be discontinued if they become pregnant (see Section 10.2).

Increased Transaminases

In the Phase 2a Proof-of-concept study (VX12-787-101), conducted in healthy volunteers inoculated with influenza A and treated for 5 days with placebo (N=32) or pimodivir (N=72; from 100 mg qd to 1,200 mg (loading dose)/600 mg qd doses), liver function test (ALT and AST) elevations were observed in both placebo and pimodivir groups (ALT: placebo, 15.6%; pimodivir, 13.9%; AST: placebo, 3.1%; pimodivir 5.6%). The pimodivir group had a higher incidence of subjects with ALT increases of >2x upper limit of normal (ULN; among the 6 subjects with increases of >2x ULN, all had complete resolution on follow-up: 1 subject in the placebo group, 1 subject in the pimodivir 400-mg qd group, and 4 subjects in the pimodivir 1,200/600-mg qd group). The majority of adverse events (AEs) due to liver function test elevations were observed in subjects who had evidence of a successful influenza A inoculation; similarly, for the majority of subjects with ALT elevation AEs, the event occurred on or after the date that the first dose of OST (≥ Day 7) was administered. ALT elevation has been previously described in influenza and upper respiratory infections and following administration of OST. Conclusions could not be drawn about the relationship between viral inoculation, pimodivir administration, and OST administration with ALT AEs.

In the Phase 2b study 63623872FLZ2001 conducted in acute uncomplicated seasonal influenza A-infected adults, among the 147 patients treated with pimodivir 600 mg bid (with or without OST) for 5 days, 3 had TEAEs corresponding to transaminase elevations ≥ grade 3. These 3 events were considered of moderate severity by the investigators. Among them, there was one SAE (moderate severity) of increased ALT in the pimodivir 600 mg bid treatment group (doubtfully related to study drugs according to the investigator), which started on Day 14 and was reported resolved 21 weeks later. In 2 of these cases, potential confounding factors were

observed (use of OST, likely presence of NASH). No transaminase TEAE was reported in the placebo group (N=71).

In the Phase 2b study 63623872FLZ2002 conducted in acute seasonal influenza A-infected hospitalized adults, among the 64 patients treated with pimodivir 600 mg bid + OST 75 mg bid for 7 days, one had a TEAE corresponding to a grade 3 ALT elevation. The event was considered of mild severity by the investigator, and possibly related to pimodivir and OST. The following confounding factors were noted: OST, paracetamol and clarithromycin use. One patient in the placebo + OST treatment group had a moderate TEAE (grade 2 ALT and grade 3 AST elevation), considered possibly related to placebo by the investigator.

No Hy's law case (>3x ULN ALT + >2x ULN total bilirubin) was reported in the Phase 1 or 2 pimodivir clinical studies.

To date, transaminases elevations remain a potential risk, hence, due to the limited amount of data available, this study will exclude subjects with chronic hepatitis C undergoing hepatitis C treatment and subjects with known severe hepatic impairment (Child Pugh C cirrhosis) (see Section 4.2), and include study treatment hepatic-related discontinuation criteria (see Section 10.2).

Potential Toxicity

No genotoxicity (mutagenicity, in vitro chromosomal aberration, or mammalian erythrocyte), phototoxicity (in vitro), or safety pharmacology (battery of in vitro studies designed to evaluate effects of pimodivir against multiple cellular targets and a battery of in vivo cardiovascular, central nervous system, and respiratory systems) liabilities have been identified for pimodivir. There were no toxicological effects in acute studies in mice and rats at doses up to 1,000 mg/kg. The no observed adverse effect level (NOAEL) in 14-day, repeat-dose toxicology studies was 100 mg/kg/day in rats and 150 mg/kg/day in monkeys. These doses correspond to animal to human exposure multiples (AUC from time 0 to 24 hours after dosing [AUC_{24h}] basis) of 41-fold and 24-fold in male and female rats, respectively, and 2-fold and 4-fold in male and female monkeys, respectively, based on a clinical dose of 600 mg bid for 5 days. When using the exposures measured in the 63623872FLZ2002 study (600 mg pimodivir bid in subjects at steady-state), these doses correspond to animal to human exposure multiples (AUC_{24h} basis) of 17-fold and 10-fold in male and female rats, respectively, and 0.7-fold and 1.6-fold in male and female monkeys, respectively. Although exposure ratios vs the NOAEL in monkeys are small, all adverse effects seen at the medium dose of 250 mg/kg/day show recovery after dosing and are monitorable in the clinic. At oral doses of 250 mg/kg/day and above, specific organ toxicity (liver, kidney, bone marrow, spleen, and lymph nodes) and other toxicological findings were noted in rats and monkeys. When rats were dosed at 50, 100, or 250 mg/kg/day for 3 months, the NOAEL was set at 100 mg/kg/day, which corresponds to animal to human exposure multiples of 12-fold in males and 15-fold in females (multiple vs Study 63623872FLZ2002). At 250 mg/kg/day, body weight gain was decreased in both sexes. Additionally, minor alterations were seen in red blood cell (RBC) parameters. Full recovery of the adverse effects was noted at the end of the 1-month recovery period. The NOAEL in 14-day continuous IV infusion studies

was 180 mg/kg/day in rats and 40 mg/kg/day in monkeys. Pimodivir exposure at the NOAEL in the IV studies was in the same range (AUC) or lower (C_{max}) than at the NOAEL in the oral toxicity studies.

Based on human experience to date at high doses (up to 3,000 mg) no toxicology findings were observed, however this study will include study treatment discontinuation and study withdrawal criteria for individual subjects as a precaution (see Section 10.2 and Section 10.3).

1.4.5. Overall Benefit/Risk Assessment

Based on the available data and proposed safety measures, the overall benefit/risk assessment for this study is acceptable for the following reasons:

- Pimodivir has been studied in healthy subjects receiving single oral doses of pimodivir up to 3,000 mg (Studies VX11-787-001, VX12-787-002, 63623872FLZ1001, 63623872FLZ1005, 63623872FLZ1006, 63623872FLZ1007 [administration of a single dose of ^{14}C-pimodivir], and 63623872FLZ1008), multiple oral doses of pimodivir as monotherapy up to 800 mg once daily for 10 days (Studies VX11-787-001, 63623872FLZ1001, and 63623872FLZ1009), multiple oral doses of pimodivir of 600 mg bid for 5 days coadministered with OST (Study 63623872FLZ1001), and single IV doses up to 300 mg pimodivir (Study VX12-787-002). In addition, pimodivir has been studied in multiple oral doses in subjects infected with a challenge dose of influenza A (up to 1,200 mg loading dose on the first day followed by 600 mg once daily for an additional 4 days; Study VX11-787-101). Pimodivir has also been studied in multiple oral doses in subjects naturally infected with influenza either as monotherapy up to 600 mg bid for 5 days or coadministered with OST 600 mg bid for 7 days (Studies 63623872FLZ2001 and 63623872FLZ2002). Pimodivir was generally safe and well tolerated.
- Only subjects who meet all of the inclusion criteria and none of the exclusion criteria (as specified in the protocol) will be allowed to participate in this study. The selection criteria include adequate provisions to minimize the risk and protect the well-being of subjects in the study.
- Safety will be closely monitored by the investigator throughout the study. Safety and tolerability assessments (including vital signs, electrocardiograms [ECGs], physical examination, clinical laboratory tests, and assessment of AEs or SAEs) will be performed at scheduled visits throughout the study.
- Several safety measures have been proposed to minimize potential risks to subjects, including:
  - The safety margins for the projected exposures calculated from non-clinical toxicology studies in monkeys warrant close laboratory monitoring during the study, thus samples for clinical laboratory tests will be collected throughout the study.
  - Utilization of treatment discontinuation and withdrawal criteria (see Section 10.2 and Section 10.3).
  - Pregnancy and breastfeeding are exclusion criteria for all clinical studies conducted to date. All subjects are required to use contraceptive methods as detailed in the protocol.

– An independent data monitoring committee (IDMC) will be established to monitor safety and efficacy data on a regular basis.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

2.1.1. Objectives

Primary Objective

The primary objective is to evaluate superiority of pimodivir in combination with SOC treatment compared to placebo in combination with SOC treatment, with respect to the time to resolution of influenza-related symptoms.

Secondary Objectives

The secondary objectives are:

- To investigate the safety and tolerability of pimodivir in combination with SOC treatment compared to placebo in combination with SOC treatment.
- To evaluate superiority with respect to the hospital admission rate 28 days after initiation of treatment in the pimodivir in combination with SOC treatment arm, compared to the placebo in combination with SOC treatment arm.
- To evaluate superiority with respect to the incidence of complications associated with influenza after the start of study treatment in the pimodivir in combination with SOC treatment arm, compared to the placebo in combination with SOC treatment arm.
- To investigate time to resolution of each of the 10 individual influenza-related symptoms as assessed by the PRO measure Flu-iiQ^{TM}.
- To investigate the time to return to daily activities as assessed by the subject in the pimodivir in combination with SOC treatment arm, compared to the placebo in combination with SOC treatment arm.
- To investigate the time to resolution of fever in the pimodivir in combination with SOC treatment arm, compared to the placebo in combination with SOC treatment arm.
- To investigate all-cause mortality in the pimodivir in combination with SOC treatment arm, compared to the placebo in combination with SOC treatment arm.
-
- To assess the PK of pimodivir and to explore the PK/pharmacodynamic (PD) relationships of pimodivir for efficacy and safety.
- To investigate the acceptability (taste and swallowability) of the pimodivir formulation in adolescents.
- To investigate the emergence of viral resistance against pimodivir detected by genotyping and/or phenotyping.

- To evaluate superiority with respect to time to viral negativity in the pimodivir treatment arm compared to the control arm by qRT-PCR and viral culture.

2.1.2. Endpoints

Primary Endpoint

The primary endpoint is the time to resolution of influenza-related symptoms as assessed by the patient-reported outcome (PRO) measure Flu-iiQ^{TM}. The resolution of influenza-related symptoms is defined as the beginning of the 24-hour period that the 7 primary influenza symptom scores (cough, sore throat, headache, nasal congestion, feeling feverish, body aches and pains, fatigue) are at most mild or at least back to previous level of symptom severity in case the subject reported the symptom as pre-existing.

Secondary Endpoint

The secondary endpoints are:

- Safety and tolerability based on assessment of AEs, clinical laboratory assessments, 12-lead ECGs and vital signs.
- The hospital admission rate 28 days after treatment initiation.
- Incidence of complications associated with influenza after the start of study treatment:
  - Pulmonary complications:

    The pulmonary complications of influenza include respiratory failure, primary viral pneumonia, secondary bacterial pneumonia (including pneumonia attributable to unusual pathogens), exacerbations of chronic underlying pulmonary diseases such as COPD, asthma, and bronchitis.

    - Respiratory failure: defined as either hypoxemic respiratory failure characterized by an arterial oxygen tension (PaO_2) lower than 60 mmHg with a normal or low arterial carbon dioxide tension ($PaCO_2$), or hypercapnic respiratory failure characterized by a $PaCO_2$ higher than 50 mmHg.
    - Primary viral pneumonia: a progressive event involving the lower respiratory tract with bilateral and/or diffuse radiological findings. No bacterial agent is identified using sputum cultures.
    - Secondary bacterial pneumonia (including pneumonia attributable to unusual pathogens): a clinical event compatible with lower respiratory tract involvement, with lobar infiltrates on radiological studies and/or microbiological isolate of a bacterial pathogen, including unusual pathogens.
    - Exacerbations of chronic underlying pulmonary diseases such as COPD and asthma: subjects with documented medical history of COPD or asthma with a sudden worsening of symptoms and deteriorating respiratory function (the latter as evidenced by worsening hypoxia, tachypnea, etc.) The event must start before a full recovery from the influenza infection occurred.
    - Bronchitis

- Extrapulmonary complications:
  - Cardiovascular and cerebrovascular disease (eg, myocardial infarction, congestive heart failure, arrhythmia, stroke)
  - Muscular disorders (eg, myositis, rhabdomyolysis)
  - Central nervous system (CNS) involvement
  - Acute exacerbation of chronic kidney disease
  - Severe dehydration
  - Decompensation of previously controlled diabetes mellitus
  - Other infections (eg, sinusitis, otitis)

A blinded Adjudication Committee (AC) will be established to adjudicate AEs on predefined criteria for complications (pulmonary versus extrapulmonary, major versus minor, as well as infectious versus non-infectious complications). The AC will receive data on AEs, including medical assessments (eg, chest X-ray results, lab results) and concomitant therapy of cases selected from the AEs. Details will be provided in an AC charter.

- Time to resolution of each of the 10 individual influenza-related symptoms as assessed by the PRO measure Flu-iiQ^{TM}. The resolution of each influenza-related symptom is defined as the beginning of the 24-hour period when the influenza symptom score is at most mild or at least back to previous level of symptom severity in case the subject reported the symptom as pre-existing.
- Time to return to daily activities as assessed by the subject.
- Time to resolution of fever. Resolution of fever is defined as a body temperature <37.0°C during a period of 24 hours without the use of antipyretics.
- All-cause mortality.
- PK parameters of pimodivir (ie, plasma concentration just prior to the beginning or at the end of a dosing interval [C_{trough}], C_{max}, t_{max}, and AUC_{12h}), as determined by population PK analysis.
- The acceptability of the pimodivir formulation in adolescents, as measured by a taste and swallowability questionnaire.
- The emergence of viral resistance against pimodivir detected by genotyping and/or phenotyping.
- Time to viral negativity by qRT-PCR and viral culture.
- Viral load over time by qRT-PCR and viral culture.

Refer to Section 9, Study Evaluations, for evaluations related to endpoints.

Exploratory Endpoints

- Time to resolution of impact of influenza on daily activities, emotions and others, as defined by the Flu-iiQ^{TM} questionnaire (Modules 2, 3, and 4).

2.2. Hypothesis

The time to resolution of the 7 primary influenza-related symptoms, as assessed by a PRO measure (Flu-iiQ^{TM}), with pimodivir in combination with SOC treatment is statistically superior to treatment with placebo in combination with SOC treatment in subjects with influenza A infection who are at risk of developing complications.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of pimodivir in combination with SOC treatment versus placebo in combination with SOC treatment in adolescent (13 to 17 years), adult (18 to 65 years), and elderly (>65 to ≤85 years) non-hospitalized subjects with influenza A infection who are at risk of developing complications. A target of 720 subjects will be randomly assigned in this study with 360 subjects planned per treatment arm. The aim is to enroll a minimum of 72 adolescent subjects in this study in selected countries and study sites consistent with local regulations. The target population of the study are influenza-infected, non-hospitalized subjects who, due to their age (65 to 85 years) or underlying comorbidities (regardless of age), are at increased risk of developing influenza-related complications. The randomization will be stratified by type of baseline SOC (including or not including antiviral treatment) and time since onset of symptoms (first administration of study drug ≤48 hours or >48 hours since onset of influenza symptoms). The study population should consist of at least 60% of subjects with first administration of study drug ≤48 hours since onset of influenza symptoms .

Subjects who meet all eligibility criteria will be randomized in a 1:1 ratio to receive 1 of the following 2 treatments:

- Treatment Arm 1: pimodivir 600 mg bid for 5 days + SOC treatment*
- Treatment Arm 2: pimodivir placebo bid for 5 days + SOC treatment*

* SOC treatment will be determined by the investigator based on local practice, and may include influenza antivirals and/or supportive care only. The choice to use influenza antivirals as part of the SOC should be made before randomization. The influenza antiviral should be started no later than Day 2 morning (up to noon). An influenza antiviral as part of the SOC cannot be changed (eg, switching one influenza antiviral for another) during the treatment period, with the exception that an influenza antiviral may be discontinued in the case of a suspected AE.

Study drugs will be taken orally. Refer to the pharmacy manual/study site investigational product manual for additional guidance on study drug preparation, handling, and storage.

The study will consist of a screening/baseline visit, a double-blind treatment period of 5 days, and a follow-up period of 23 days after the last dosing day. The entire study duration for each subject will be 28 days. The study is considered complete with the completion of the last study assessment for the last subject participating in the study.

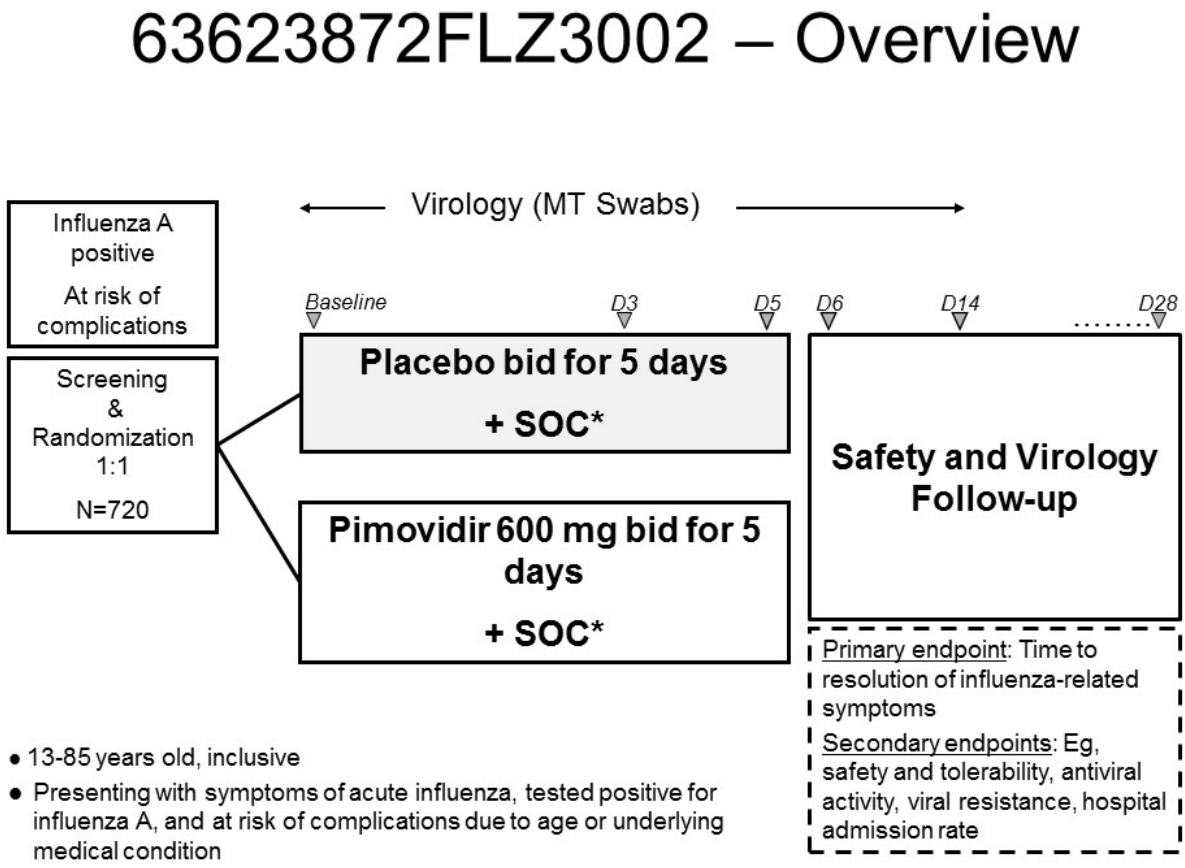
When subjects are hospitalized during the course of the study, the reason for hospitalization should be recorded and every effort should be made by the investigator to perform all the assessments as indicated in the TIME AND EVENTS SCHEDULE, if practically feasible.

The impact of influenza infection and its treatment (efficacy and safety) on patient-reported symptoms and functioning will be evaluated using the Flu-iiQ™ questionnaire throughout the study. Sparse blood samples for the measurement of plasma concentrations of pimodivir will be taken on Days 3 and 6. Safety and tolerability will be assessed throughout the study from signing of the Informed Consent Form (ICF)/assent form until the subject's last study-related activity. The acceptability of the pimodivir formulation in adolescents will be assessed using a taste and swallowability questionnaire. Safety evaluations will include the monitoring of AEs, clinical laboratory tests, 12-lead ECGs, and vital signs measurements, and (symptom-directed) physical examinations. Nasal mid-turbinate (MT) swabs for viral quantification and resistance testing will be collected.

An IDMC will be commissioned for this study to monitor efficacy and safety data on a regular basis. Refer to Section 11.12, Data Monitoring Committee, for details.

A diagram of the study design is provided in Figure 1.

Figure 1: Schematic Overview of the Study



Abbreviations: bid: twice daily; MT: mid-turbinate; SOC: standard-of-care.

*SOC treatment will be determined by the investigator based on local practice, and may include influenza antivirals and/or supportive care only. The choice to use influenza antivirals as part of the SOC should be made before randomization. The influenza antiviral should be started no later than Day 2 morning (up to noon). An influenza antiviral as part of the SOC cannot be changed (eg, switching one influenza antiviral for another) during the treatment period, with the exception that an influenza antiviral may be discontinued in the case of a suspected adverse event.

3.2. Study Design Rationale

Blinding, Control, Randomization, Treatment Arms

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active treatment and to minimize bias. Randomization will be used to minimize bias in the assignment of subjects to treatment arms, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment arms, and to enhance the validity of statistical comparisons across treatment arms. Blinding will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

Stratification Factors

Stratification will be used to ensure equal allocation of treatment to subjects over the (combination of) prognostic factors, thereby minimizing bias when comparing treatment effects. Subjects will be stratified at enrollment by type of SOC used (supportive care including antiviral therapy or supportive care excluding antiviral therapy) and time of symptom onset relative to treatment initiation (first administration of study drug ≤48 hours or >48 hours since onset of influenza symptoms).

- The use of an antiviral therapy is considered to be predictive of the time to recovery of the 7 primary symptoms of influenza, as this has been the basis for approval of influenza antiviral therapies in the community setting.[3]
- The time of symptom onset relative to treatment initiation has been shown to have an impact on the efficacy of antiviral therapy in the community setting and is also recommended by Food and Drug Administration (FDA) guidance on studying influenza drugs for use as a stratification factor.

Study Population

Given the limitations of the currently available anti-influenza therapies, such as a short window for treatment initiation and concerns about drug resistance, there is a clear high unmet medical need for better influenza therapies. Beyond these limitations, which are general to the treatment of influenza in all populations, to date there are no commercially available antivirals approved for the treatment of influenza in those subjects most vulnerable to complications related to this infection.

Accordingly, the study population for this study are subjects with influenza A, who are at risk of developing influenza-related complications due to their age or underlying medical conditions, but are not in immediate need of in-hospital medical care.

Dose Regimen Selection

The dose of pimodivir (600 mg bid) was selected based on efficacy and PK/PD modeling data, as well as safety and viral resistance data from the completed Phase 2 studies (63623872FLZ2001 and 63623872FLZ2002).

The SOC treatment will be determined by the investigator based on local practice, and may include influenza antivirals and/or supportive care only. The choice to use influenza antivirals as part of the SOC should be made before randomization. The influenza antiviral should be started no later than Day 2 morning (up to noon). An influenza antiviral as part of the SOC cannot be changed (eg, switching one influenza antiviral for another) during the treatment period, with the exception that an influenza antiviral may be discontinued in the case of a suspected AE.

4. SUBJECT POPULATION

Screening for eligible subjects will be performed during the screening/baseline visit, before administration of the study drug.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

For a discussion of the statistical considerations of subject selection, refer to Section 11.3, Sample Size Determination.

4.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study:

1. Male or female, 13 to 85 years of age, inclusive. Note: Adolescent subjects (13 to 17 years) will be enrolled in selected countries and study sites consistent with local regulations.

2. Present to the clinic with symptoms suggestive of a diagnosis of acute influenza and have at least 1 respiratory symptom and at least 1 systemic symptom, both scored as at least “moderate” if the symptom did not pre-exist before influenza onset, or scored worse than usual if the symptom pre-existed as determined by subject’s ratings on Module 1 of the Flu-iiQ™ and the Pre-existing Symptom Questionnaire in the ePRO device. Symptoms must include the following by category:

    1. Respiratory symptoms: cough, sore throat, nasal congestion
    2. Systemic symptoms: headache, body aches or pain, feverishness, fatigue

3. Tested positive for influenza A infection after the onset of symptoms, using a rapid influenza diagnostic test (RIDT) or, if available, a PCR-based or other rapid molecular diagnostic assay.

4. Not be in need of hospitalized medical care at screening. Emergency room or hospital observation status for an anticipated duration of <24 hours is not considered hospitalization as long as a determination of the need for hospitalization has not been made.

5. Enrollment and initiation of study drug treatment ≤72 hours after onset of influenza symptoms.

6. Must sign an ICF/assent form (or their legally acceptable representative must sign) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study. Assent is also required of children capable of understanding the nature of the study, typically subjects 7 years of age and older. Subjects must sign a separate ICF/assent form if he or she agrees to provide an optional DNA sample for research (where local regulations permit). Refusal to give consent for the optional DNA research sample does not exclude a subject from participation in the study.

7. Before randomization, a woman must be either:

    a. Not of childbearing potential defined as:

        - Premenarchal
          A premenarchal state is one in which menarche has not yet occurred.
        - Postmenopausal
          A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy, however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
        - Permanently sterile
          Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

    b. Of childbearing potential and

        - Practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly)

          Examples of highly effective contraceptives include
          - User-independent methods:
            implantable progestogen-only hormone contraception associated with inhibition of ovulation; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); vasectomized partner; sexual abstinence (s*exual abstinence is considered a highly effective method* ***only*** *if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. 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 subject.)

- User-dependent methods:
  combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, transdermal; progestogen-only hormone contraception associated with inhibition of ovulation: oral and injectable

Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.

- Agrees to remain on a highly effective method throughout the study and for at least 30 days after the last dose of study drug.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active) a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria.

8. A woman of childbearing potential must have a negative urine or serum pregnancy test at screening.

9. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for a period of at least 30 days after the last dose of study drug.

10. During the study and for a minimum of 1 spermatogenesis cycle (defined as approximately 90 days) after receiving the last dose of study drug, in addition to the highly effective method of contraception being used by the female partner, a man regardless of having been vasectomized

- Who is sexually active with a woman of childbearing potential must agree to use a barrier method of contraception (eg, condom preferably with spermicidal foam/gel/film/cream/suppository).
- Who is sexually active with a woman who is pregnant must use a condom.
- Must agree not to donate sperm.

Note: If the female sexual partner is postmenopausal (defined as no menses for 12 months without an alternative medical cause), is permanently sterilized (eg, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), or otherwise incapable of becoming pregnant, the birth control methods mentioned are not applicable.

11. Willing and able to adhere to the prohibitions and restrictions specified in this protocol (see Section 4.3).

12. Subjects 13 to 65 years of age, inclusive must also have at least one of the following:

a. Cardiovascular or cerebrovascular disease (including congenital heart disease, chronic heart failure, coronary artery disease, or stroke; excluding isolated hypertension).

b. Chronic lung disease (eg, asthma, chronic obstructive lung disease [COPD] or cystic fibrosis).

c. Weakened immune system due to disease or medication (eg, subjects with human immunodeficiency virus [HIV], cancer, or chronic liver or kidney disease [presence of kidney damage for >3 months, defined by structural or functional abnormalities of the kidney, with or without decreased GFR manifested by: pathological abnormalities; OR markers of kidney damage, including abnormalities in the composition of the blood or urine or abnormalities in imaging tests], or subjects taking chronic systemic steroids).

4.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study:

1. Received more than 1 dose of influenza antiviral medication (eg, OST or zanamivir), or any dose of ribavirin within 2 weeks, prior to first study drug intake, or received IV peramivir more than 1 day prior to screening.

2. Unwilling to undergo regular nasal MT swabs or has any physical abnormality which limits the ability to collect regular nasal MT specimens.

3. Unstable angina pectoris or myocardial infarction within 30 days prior to screening (inclusive).

4. Presence of clinically significant heart arrhythmias, uncontrolled, unstable atrial arrhythmia, or sustained ventricular arrhythmia, or risk factors for Torsade de Pointes syndrome.

5. Known severe hepatic impairment (Child Pugh C cirrhosis) or chronic hepatitis C infection undergoing hepatitis C antiviral therapy.

6. Severely immunocompromised in the opinion of the investigator (eg, known cluster of differentiation 4^+ [$CD4^+$] count <200 cells/mm^3, absolute neutrophil count <750/mm^3, first course of chemotherapy completed within 2 weeks prior to screening, history of stem cell transplant within 1 year prior to screening, history of a lung transplant).

7. Known allergies, hypersensitivity, or intolerance to pimodivir or its excipients (refer to IB).[9]

8. Received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 30 days or has received an investigational biological product within 3 months or 5 half-lives (whichever is longer) before the planned first dose of study drug or is currently enrolled in an investigational study.

9. Taken any disallowed therapies as noted in Section 8, Pre-study and Concomitant Therapy before the planned first dose of study drug.

10. A woman who is pregnant, or breast-feeding, or planning to become pregnant while enrolled in this study or female subject of childbearing potential who is unwilling to use an acceptable method of contraception as outlined in the inclusion criteria.

11. A man who plans to father a child while enrolled in this study.

12. Subject has any condition that could prevent, limit, or confound the protocol-specified assessments (eg, subjects is unable to swallow tablets, unable to complete PROs, or is illiterate), or in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being).

13. Subject has presence of any pre-existing illness, clinically significant laboratory abnormalities, ECG findings, or physical examination findings that, in the opinion of the investigator, would place the subject at an unreasonably increased risk through participation in this study. The investigator should consider the laboratory parameter criteria for study drug discontinuation (see Section 10.2) when screening a subject for enrollment.

14. An employee of the investigator or study site, with direct involvement in the study or other studies under the direction of that investigator or study site, or a family member of an employee or the investigator, or an employee of the sponsor.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

1. Refer to Section 8, Prestudy And Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

2. Agree to follow the contraceptive requirements as noted in the inclusion criteria.

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation: Procedures for Randomization

Central randomization will be implemented in this study. Subjects will be randomly assigned to 1 of 2 treatment arms in a 1:1 ratio based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by type of baseline SOC (including or not including antiviral treatment) and time since onset of symptoms (first administration of study drug ≤48 hours or >48 hours since onset of influenza symptoms). The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant subject details to uniquely identify the subject.

Blinding

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual subject.

Data that may potentially unblind the treatment assignment (ie, study drug plasma concentrations) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding.

Under normal circumstances, the blind should not be broken until all subjects have completed the study and the database is finalized. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In such cases, the investigator may in an emergency determine the identity of the treatment by contacting the IWRS. It is recommended that the investigator contact the sponsor or its designee if possible to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented in the IWRS, in the appropriate section of the electronic case report form (eCRF) and in the source documents. The documentation received from the IWRS indicating the code break must be retained with the subject's source documents in a secure manner.

6. DOSAGE AND ADMINISTRATION

During the treatment period, all subjects will receive study drug in a 1:1 ratio in 1 of the 2 treatment arms. Depending on the time of screening/enrollment, subjects will receive 1 dose

(evening) or 2 doses (morning and evening) of study drug on Day 1. Subjects may delay or bring forward administration of the second dose (by no more than 4 hours) only if the nominal timing for this second dose falls in the middle of the night. For subjects who receive only 1 dose of pimodivir or placebo on Day 1 (evening), dosing should continue until the morning of Day 6 so that all subjects receive 10 doses in total.

	Treatment Arm 1	**Treatment Arm 2**
Test Article(s)	Pimodivir (Day 1 through Day 5) + SOC treatment[a,b]	Placebo (Day 1 through Day 5) + SOC treatment[a,b]
Description	300 mg tablet	Placebo tablet
Dose per Delivery	Day 1 to Day 5 600 mg pimodivir (2 tablets)	Day 1 to Day 5 Placebo (2 tablets)
Frequency	Bid	Bid
Total Dose	1,200 mg	NAP
Delivery Method[c]	Oral	Oral
Food/Fasting Requirement	No food requirements	No food requirements

Abbreviations: bid: twice daily; NAP: not applicable; SOC: standard-of-care.

[a] SOC treatment will be determined by the investigator based on local practice, and may include influenza antivirals and/or supportive care only. The choice to use influenza antivirals as part of the SOC should be made before randomization. The influenza antiviral should be started no later than Day 2 morning (up to noon). An influenza antiviral as part of the SOC cannot be changed (eg, switching one influenza antiviral for another) during the treatment period, with the exception that an influenza antiviral may be discontinued in the case of a suspected adverse event.

[b] Depending on the time of screening/enrollment, subjects will receive 1 dose (evening) or 2 doses (morning and evening) of study drug on Day 1. For subjects who receive only 1 dose of pimodivir or placebo on Day 1 (evening), dosing should continue until the morning of Day 6 so that all subjects receive 10 doses in total.

[c] Refer to the pharmacy manual/study site investigational product manual for additional guidance on study drug preparation, handling, and storage.

Study-site personnel will instruct subjects on how to store study drug for at-home use as indicated for this protocol.

No post-study medication is provided as part of this protocol.

7. TREATMENT COMPLIANCE

Missed doses of pimodivir or placebo will be recorded in the source documents and the eCRF, and re-dosed if the missed dose is discovered <6 hours past the scheduled dosing time. If the missed dose is discovered >6 hours past the scheduled dosing time, the missed dose should be skipped, and the next dose should be taken as scheduled. In case of vomiting within 6 hours after dosing and visual confirmation of tablet(s) in the vomit, the subject should be re-dosed (2x 300-mg tablets). In case of vomiting >6 hours after dosing or in case of no visual confirmation of tablet(s) in the vomit, the subject should not be re-dosed.

A dosing time memory aid will be available in the ePRO device for patients in order to document date and time of intakes. Subjects receive study drug for at-home use. Compliance will be assessed by phone follow-up on days when the intake is to occur at home and at each visit by

counting study drug dispensed and study drug returned. Discrepancies will be discussed with the subject and date and time of study drug intakes recorded in the source documents and the eCRF.

If a subject's study drug intake (pimodivir or placebo) is not according to the protocol, the investigator will take the necessary measures to ensure future adherence to the protocol.

8. PRESTUDY AND CONCOMITANT THERAPY

Prestudy therapies administered up to 30 days before first dose of study drug must be recorded at screening.

Concomitant therapies must be recorded throughout the study beginning with start of the first dose of study drug through the Final Study Visit/Safety Follow-up Visit. Medications that are part of the SOC should be recorded as concomitant medications throughout the study. Concomitant therapies should also be recorded beyond Final Study Visit/Safety Follow-up Visit if in conjunction with SAEs that meet the criteria outlined in Section 12.3.2. Serious Adverse Events.

To avoid the confounding effects of antipyretic medications, temperature measurements must be taken, whenever possible, at least 4 hours after administration of the antipyretic medication.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens) different from the study drug must be recorded in the eCRF. Recorded information will include a description of the type of the drug, treatment period, dosing regimen, route of administration, and its indication.

The following pre-study and concomitant therapies are disallowed:

1. More than 1 dose of influenza antiviral medication (eg, OST, zanamivir), or ribavirin within 2 weeks, prior to first study drug intake.
2. IV peramivir more than 1 day prior to screening.
3. An investigational drug (including investigational vaccines) or an invasive investigational medical device within 30 days, or an investigational biological product within 3 months or 5 half-lives (whichever is longer) prior to the first dose of study drug until the end of the study.
4. Use of a live attenuated intranasal spray influenza vaccine within 3 weeks before study entry.

Substrates of OATP1B1 and/or OATP1B3, including atrasentan, bosentan, ezetimibe, glyburide, irinotecan, repaglinide, rifampin, telmisartan, valsartan, and olmesartan may be continued. Statins (ie, 3-hydroxy-3-methylglutaryl-coenzyme A [HMG CoA] reductase inhibitors) may also be continued, but subjects should be cautioned and observed for potential statin-related toxicity.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The TIME AND EVENTS SCHEDULE summarizes the frequency and timing of efficacy, PK, PD, biomarker, and safety measurements applicable to this study.

If applicable, visit-specific PRO assessments should be conducted/completed before any tests, procedures, or other consultations for that visit to prevent influencing subject perceptions.

If multiple assessments are scheduled for the same time point, it is recommended that procedures be performed in the following sequence: ECG, vital signs, blood sampling. Blood collections for PK and PD assessments should be kept as close to the specified time as possible. Other measurements may be done earlier than specified time points if needed. Actual dates and times of assessments will be recorded in the source documentation and eCRF. At the time points where both nasal MT swabs and PK samples are obtained, these samples should be obtained as close together in time as possible.

Additional urine or serum 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 subject's participation in the study.

The total blood volume to be collected from each subject is considered to be within the acceptable range allowed for this subject population over this time frame.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1.2. Screening Phase

At the screening visit, after signing of the ICF/assent form (see Section 16.2.3 for more details), the overall eligibility of the subject to participate in the study will be assessed and documented in the eCRF. First study drug intake should take place immediately after all screening/baseline procedures have taken place and eligibility has been established. Screening/baseline assessments start at signing of the ICF/assent form. Note: It is recommended that the screening/baseline assessments are completed as quickly as possible, in order to start study drug treatment as soon as possible. However, if needed, screening/baseline assessments and establishment of eligibility can continue the next calendar day, in which case the first study drug intake will be on that day, immediately after establishing eligibility. For analysis purposes, the day of first study drug intake will be considered Day 1. Subjects who successfully meet all inclusion criteria and none of the exclusion criteria will be eligible for participation in the study.

The subject’s characteristics, demographic data, medical and surgical history, and prestudy and concomitant medication, including influenza vaccination status, will be recorded. A virology test capable of distinguishing between influenza types A and B, will be carried out locally as part of

the screening procedures. It is recommended to use MT swabs for local virology testing, although nasopharyngeal (NP) swabs are allowed if required by local procedures. Nasal swabs (either for local or central virology testing) should be obtained from the left and right nostrils (from both nostrils if feasible, but from only one nostril otherwise) and pooled into the same collection tube. The results of an earlier sample collected and tested positive for influenza A infection after the onset of symptoms can be used in lieu of the local virology testing at screening (this sample is used to determine eligibility). Leftovers from the local virology samples (with the exception of "earlier sample") will be shipped to and stored at the central lab for further testing, regardless of local influenza test result. Only those subjects testing positive for influenza A will be considered for enrollment. A physical examination (including height and [recent] body weight measurements, if not already available and if practically feasible) will be conducted. A urine or serum pregnancy test will be performed for all female subjects of childbearing potential. The result of a prior urine or serum pregnancy test that occurred within 1calendar day before signing of the ICF/assent form can be used in lieu of the baseline requirement.

In case a subject does not remember the exact hour of onset of symptoms, a granular imputation method for the missing onset time will be applied by the investigator at screening.

Subjects will be requested to complete PRO assessments at sites where appropriate translations are available and approved (see Section 9.2.1.1 for more details). Screening PRO assessments (Pre-existing Symptom Questionnaire and Flu-iiQ^{TM} Module 1) must be performed on the ePRO device, before randomization, in order to assess inclusion criterion n°2 (flu symptoms severity). The baseline PRO assessments (Flu-iiQ^{TM} Modules 2-4, PGIS, daily activities resumption, and EQ-5D) should be completed on the ePRO device prior to first study drug intake.

Blood samples (for hematology, chemistry, and biomarker analysis) and a urine sample (for urinalysis) will be taken. Vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse rate, respiratory rate, and body temperature) will be measured, and a 12-lead ECG will be performed. An ECG recorded within 1 calendar day before signing of the ICF/assent form can be used in lieu of the baseline ECG requirement.

Subjects will be observed/interviewed for any AEs, concomitant medication will be reviewed, and AEs and concomitant medication will be recorded.

9.1.3. Double-blind Treatment Phase

Subjects who meet all eligibility criteria will be randomized in a 1:1 ratio to receive 1 of the following 2 treatments:

- Pimodivir 600 mg bid on Days 1 through 5 + SOC treatment; OR
- Pimodivir placebo bid on Days 1 through 5 + SOC treatment.

For subjects who receive only 1 dose of pimodivir or placebo on Day 1 (evening), dosing should continue until the morning of Day 6 so that all subjects receive 10 doses in total.

The SOC treatment will be determined by the investigator based on local practice, and may include influenza antivirals and/or supportive care only. The choice to use influenza antivirals as part of the SOC should be made before randomization. The influenza antiviral should be started no later than Day 2 morning (up to noon). An influenza antiviral as part of the SOC cannot be changed (eg, switching one influenza antiviral for another) during the treatment period, with the exception that an influenza antiviral may be discontinued in the case of a suspected AE.

Subjects will undergo sparse PK sampling at the time points specified in the TIME AND EVENTS SCHEDULE.

Throughout the treatment period, and if applicable, PRO assessments will be completed before any other assessments for a specific visit. At the time points specified in the TIME AND EVENTS SCHEDULE, a symptom-directed physical examination, blood sampling (for hematology, chemistry, drug concentrations, and biomarker analysis), urine sampling (for urinalysis), and a pregnancy test (urine or serum for females of childbearing potential) will be performed; nasal MT swabs will be obtained for central virology testing; and vital signs will be measured. A taste and swallowability questionnaire will be completed by adolescent subjects for pimodivir or placebo. The questionnaire should be completed within approximately 15 minutes after the first and last intake of the pimodivir or placebo tablet.

Subjects will be observed/interviewed for any AEs, concomitant medication will be reviewed, and AEs and concomitant medication will be recorded.

End of Treatment

A subject will be considered to have completed treatment after 5-day therapy of pimodivir or placebo (ie, 10 doses).

Early Withdrawal

Subjects who prematurely discontinue study drug treatment for any reason (except withdrawal of consent) will be asked to continue with their remaining study visits and assessment schedule. Subjects who withdraw consent during the treatment phase will be offered an optional Safety Follow-up Visit. The optional Safety Follow-up Visit will occur the day of consent withdrawal or the day after and will consist of the same assessments as at the Final Study Visit (Day 28), with optional PRO completion. If the subject discontinues treatment due to an AE or other medical reason, efforts will be made by the investigator to continue following up with the subject at regular intervals until the AE normalizes or returns to the subject's baseline condition. The sponsor and the investigator will agree on an acceptable individual follow-up schedule for these subjects.

9.1.4. Post-treatment Phase (Follow-up)

The procedures to be completed during the follow-up phase are listed in the TIME AND EVENTS SCHEDULE.

Subjects who withdraw consent during the follow-up phase will be offered an optional Safety Follow-up Visit. The optional Safety Follow-up Visit will occur the day of consent withdrawal or the day after and will consist of the same assessments as at the Final Study Visit (Day 28), with optional PRO completion. In case of ongoing AEs, efforts will be made by the investigator to continue following up with the subject at regular intervals until the AE normalizes or returns to the subject's baseline condition.

9.2. Efficacy

9.2.1. Evaluations

9.2.1.1. Patient-reported Outcomes

Flu-iiQ™

The Flu-iiQ is a PRO that measures influenza symptom intensity and symptom impacts. The Flu-iiQ™ consists of 4 domains: 1) influenza symptoms, including systemic and upper respiratory symptoms, 2) impact on daily activities, 3) impact on emotions, and 4) impact on others.[10] The response rating scales are 4-point Likert scales, where "0" represents the absence of symptom or impact and "3" represents the severe or significant limitations/difficulty. Table 1 summarizes the items and response options within each Flu-iiQ™ domain.

Table 1: Flu-iiQ™ Items and Response Options, by Domain

Domain	Number of items	Items	Response Options
Influenza symptoms	10	Symptom severity of the following: cough, sore throat, headache, nasal congestion, feeling feverish, body aches and pain, fatigue, neck pain, interrupted sleep, and loss of appetite	"None", "Mild", "Moderate", and "Severe"
Impact on daily activities	6	Perceived ability to get out of bed, prepare meals, perform usual activities, leave the home, concentrate on tasks, take care of oneself due to influenza	"No difficulty", "Some difficulty", "Moderate difficulty", and "Great difficulty"
Impact on emotions	4	Influenza's impacts on feelings of irritability, feeling of helplessness, worry, and frustration	"Not at all", "Somewhat", "Moderately", and "Extremely"
Impact on others	5	Concerns about others worry, being a burden, others being annoyed, needing to depend on other people, others doing extra things due to influenza	"Not at all concerned", "Somewhat concerned", "Moderately concerned", and "Extremely concerned".

The Flu-iiQ™ questionnaire will be completed twice daily throughout the study. At screening, the answers to the first module questions (influenza symptoms, see Attachment 3) will be used to assess inclusion criterion n°2.

Pre-existing Symptom Questionnaire

The Pre-existing Symptom Questionnaire (within Module 1 of the Flu-iiQ™) will inquire about the presence and severity of the 10 symptoms approximately a week prior to the onset of influenza in order to capture the prevalence of these symptoms in the subjects' usual health state (refer to Attachment 6). The response options will not deviate from those in the symptoms domains of the Flu-iiQ™ (None, Mild, Moderate, Severe). This questionnaire will be administered as a screening assessment after the subject completes the Flu-iiQ™ Module 1. Answers to this questionnaire will be used to assess eligibility criterion n°2.

Patient Global Impression of Severity (PGIS)

The PGIS is a single item PRO that captures daily influenza symptom severity from the subjects' perspective. Subjects rate their perception of overall influenza symptoms for the day using the following response scale: "Mild", "Moderate", "Severe", "Very severe", or "No flu symptoms today". Study participants will complete the PGIS once daily from screening/baseline throughout Final Study Visit/Safety Follow-up Visit. The screening/baseline assessment should be done as close as possible to the first study drug intake.

Patient Global Impression of Change (PGIC)

The PGIC is a single item PRO aimed to capture the subject's perceptions of improvement or deterioration in the severity of influenza symptoms compared to when the subject arrived to the investigational site for influenza treatment.[8] Response options include: "Much better", "Somewhat better", "A little better", "About the same", "A little worse", "Somewhat worse" and "Much worse". Study participants will complete the PGIC once daily on Days 6, 14, and 28.[6]

EQ-5D

The EQ-5D is a standardized measure of health status designed for self-completion and developed in order to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D includes 5 levels of severity (EQ-5D-5L) in each of the existing five EQ-5D dimensions (no problems, slight problems, moderate problems, severe problems, and extreme problems). The EQ-5D questionnaire consists of the EQ-5D descriptive system and the EQ-5D visual analogue scale. The descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The subject is asked to indicate his/her health state by ticking the box against the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number expressing the level selected for that dimension. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent's health state. It should be noted that the numerals 1-5 have no arithmetic properties and should not be used as a cardinal score. The EQ-5D visual analogue scale records the subject's self-rated health on a vertical, visual analogue scale with endpoints labelled 'the best health you can imagine' and 'the worst health you can imagine'. This information can be used as a quantitative measure of health as judged by the individual subjects.[4] Study participants will complete the EQ-5D once daily at screening/baseline (as close as possible to the first study drug intake) and on Days 6, 14, and 28.

Assessment of Daily Activities Resumption

Return to daily activities will be assessed once daily from screening/baseline (screening/baseline assessment to be performed as close as possible to the first study drug intake) through the Final Study Visit/Safety Follow-up Visit by means of the subject's response to the question 'Over the past 24 hours, how much has influenza (flu) interfered with your ability to carry out your daily activities?'.

Subjects will respond to the above by means of the following response scale:

1. Not at all
2. A little bit
3. Somewhat
4. Quite a bit
5. Very much

9.2.1.2. Administration of Patient-reported Outcomes

The PRO assessments will be completed by all subjects at sites where appropriate PROs and translations are available and approved. Subjects should complete the PRO assessments in a language in which the subject is fluent and literate. Study personnel will instruct subjects how to self-complete the PRO assessment. Assessment of inclusion criterion n°2 (flu symptoms severity) must be performed through the evaluation of the subject's answers to Pre-existing Symptom Questionnaire and Flu-iiQ^{TM} Module 1 questions programmed on the ePRO device (before randomization). Subjects who develop a decreased level of consciousnessor are intubated will not complete PROs.

Subjects will complete the PRO assessments electronically on a touch screen computer (ePRO device) provided for this study. The subject should be in a quiet place to complete the PRO assessments. When deciding which answer to report, subjects should not be influenced by anyone accompanying them (such as family members and friends) or study personnel; the responses should reflect the subject's interpretation and response.

Subjects' responses to the PRO questionnaires will not be reported as AEs or SAEs.

PRO completion compliance should be assessed daily by the site staff via the ePRO web platform. Reasons for missing assessment should be documented on the web platform by the site after discussion with the subject.

9.2.1.3. Viral Kinetics (Nasal MT Swabs)

Influenza viral load will be quantified in nasal MT swab samples taken at scheduled times throughout the study as indicated in the TIME AND EVENTS SCHEDULE. Nasal MT swabs will be analyzed centrally using qRT-PCR and viral culture. Influenza A subtype will be

determined from the baseline sample. The presence of viral (other than influenza) and/or bacterial pathogens can be analyzed in selected samples using the same MT swabs.

Details about the nasal MT swab sample collection, processing, and shipping will be provided in the laboratory manual or other instruction documents.

Nasal swab sampling should be done at approximately the same time (±4 hours) on each sampling day. The investigator should designate a limited number of trained study site personnel to collect the nasal MT swabs for the sake of consistency.

9.2.2. Efficacy Endpoints

Refer to Section 2.1.2, for an overview of efficacy endpoints.

9.3. Resistance Evaluations

9.3.1. Viral Sequencing

Nasal MT swab will be collected as described in Section 9.2.1.3 at the time points specified in the TIME AND EVENTS SCHEDULE and will be used for sequence analysis of the PB2 region of the influenza polymerase gene, and of neuraminidase (and HA, if applicable) genes for subjects using an NAI as part of their SOC. For subjects who meet criteria for reduced virologic response or viral rebound, the PA and PB1 regions of the influenza polymerase will be sequenced as well. Gene sequencing will be performed on all baseline samples and on the last evaluable post-baseline sample (on-treatment), including time points of viral rebound. Additional samples might be selected for analysis if required. Exploratory sequencing of other regions of the influenza virus genome may also be performed.

9.3.2. Phenotyping

Nasal MT swabs will be used for the analysis of phenotypic resistance against pimodivir (and other antivirals if applicable) at the time points specified in the TIME AND EVENTS SCHEDULE. Phenotypic analysis will be performed on all baseline and the last evaluable post-baseline sample (on-treatment), including time points of viral rebound. Additional samples might be selected for analysis if required.

Details about sample collection, processing, and shipping will be provided in the laboratory manual.

9.4. Pharmacokinetics

Sparse PK sampling will be performed if feasible at the time points specified in the TIME AND EVENTS SCHEDULE.

9.4.1. Evaluations

Venous blood samples of approximately 1-2 mL per sample will be collected for measurement of plasma concentrations of pimodivir. Samples are processed, handled and identified according to the laboratory manual, which will be provided before the start of the study. The exact dates and

times of blood sampling and the preceding study drug intake must be recorded in the eCRF and/or laboratory requisition form.

9.4.2. Analytical Procedures

Plasma samples will be analyzed to determine concentrations of pimodivir using a validated, specific, and sensitive liquid chromatography-mass spectrometry/mass spectrometry method by or under the supervision of the sponsor.

If required, some plasma samples may be analyzed to document the presence of circulating metabolites using a qualified research method. In addition, plasma PK samples may be stored for future analysis of protein binding.

9.4.3. Pharmacokinetic Endpoints

Refer to Section 2.1.2, for an overview of study endpoints.

9.4.4. Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Evaluations

The plasma concentration-time data of pimodivir will be analyzed using population PK modeling. Typical population values of basic PK parameters (eg, clearance and distribution volume) will be estimated together with the interindividual variability. Effects of subject demographics, laboratory parameter values, and other covariates on the PK of pimodivir will be evaluated. The relationship between the PK and PD (clinical outcomes, safety parameters, and antiviral activity) after repeated oral administration of pimodivir will be explored. If there is any visual trend in graphical analysis, suitable models will be applied to describe the PK/PD relationships. The results of the population PK/PD analysis will be reported in a separate report.

9.5. Taste and Swallowability

A taste and swallowability questionnaire will be completed by adolescent subjects within approximately 15 minutes after the first and last intake of the pimodivir or placebo tablet to evaluate the taste and swallowability (see Attachment 4). The results of the taste and swallowability questionnaire will be filled out on paper and will be transcribed into the eCRF by a member of the study site personnel.

9.6. Safety Evaluations

Details regarding the IDMC are provided in Section 11.12.

Safety and tolerability will be evaluated throughout the study from signing of the ICF/assent form onwards until the last study-related activity.

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the eCRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

The study will include the following evaluations of safety and tolerability according to the time points provided in the TIME AND EVENTS SCHEDULE.

9.6.1. Adverse Events

Adverse events (including influenza complications) will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting. Any events persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

Special attention will be paid to those subjects who discontinue the study or study drug for an AE, or who experience an AE of at least grade 3, or an SAE.

9.6.2. Clinical Laboratory Tests

Blood samples for serum chemistry and hematology and a urine sample for urinalysis will be collected. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the Adverse Event section of the eCRF. The laboratory reports must be filed with the source documents.

If feasible, safety blood samples will be collected after fasting for at least 10 hours.

In case a **grade 3** or **grade 4** laboratory abnormality occurs (defined in Attachment 1), a confirmatory test may be performed, preferably within 48 hours but no later than 72 hours after the results have become available.

The following tests will be performed by the central laboratory:

- Hematology Panel

-hemoglobin
-hematocrit
-RBC count
-RBC parameters
  *mean corpuscular hemoglobin (MCH)
  *MCH concentration
  *mean corpuscular volume
-white blood cell (WBC) count
-WBC differential
  *neutrophils
  *lymphocytes
  *monocytes
  *eosinophils
  *basophils
-platelet count

A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. A RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the laboratory.

- Serum Chemistry Panel

-sodium
-potassium
-chloride
-uric acid
-estimated glomerular filtration rate
-calcium

-bicarbonate
-blood urea nitrogen (BUN)
-creatinine
-glucose
-aspartate aminotransferase (AST)
-ALT
-gamma-glutamyltransferase
-total, direct, and indirect bilirubin
-alkaline phosphatase (ALP)
-creatine phosphokinase (CPK)
-lactate dehydrogenase
-calcium (corrected for albumin)
-phosphate
-serum albumin
-total protein
-total cholesterol
-high-density lipoprotein cholesterol
-low-density lipoprotein cholesterol
-triglycerides
-magnesium
-lipase
-pancreatic amylase

- Urinalysis

Dipstick
-specific gravity
-pH
-glucose
-protein
-blood
-ketones
-bilirubin
-urobilinogen
-nitrite
-leukocyte esterase

Sediment (if dipstick result is abnormal)
-RBCs
-WBCs
-epithelial cells
-crystals
-casts
-bacteria

In case the dipstick shows 4+ (or >1.0%) proteinuria, a confirmatory test must be performed preferably within 48 hours but no later than 72 hours after the results have become available. If dipstick result is abnormal, microscopy will be used to measure sediment. Dipstick and microscopic testing will be performed by the central lab.

- At screening/baseline, Day 3, and at the Final Study Visit/Safety Follow-up Visit (Day 28), a urine or serum pregnancy test will be performed for female subjects of childbearing potential only. The result of a prior urine or serum pregnancy test that occurred within 1 calendar day before signing of the ICF/assent form can be used in lieu of the baseline requirement.
- At screening/baseline, FSH will be tested for female subjects who are amenorrheic for 12 months or less.

9.6.3. Electrocardiogram (ECG)

12-lead ECGs will be performed at the time points provided in the TIME AND EVENTS SCHEDULE.

During the collection of ECGs, subjects should be in a quiet setting without distractions (eg, television, cell phones). Subjects should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital signs measurement is scheduled for the same time point as ECG recording, the procedures

should be performed in the following order: ECG(s), vital signs, blood draw. An ECG recorded within 1 calendar day before signing of the ICF/assent form can be used in lieu of the baseline ECG requirement.

Twelve-lead ECGs will be recorded so that the different ECG intervals (PR, QRS, and QT) and heart rate will be measured. The QT intervals will be corrected for heart rate according to Bazett's (QTcB) and Fridericia's (QTcF) QT correction.[1,5,12]

Clinically relevant abnormalities (as defined in Attachment 5) occurring during the study should be recorded in the Adverse Event section of the eCRF.

9.6.4. Vital Signs

Vital signs including temperature, pulse rate, respiratory rate, and blood pressure will be assessed at the time points provided in the TIME AND EVENTS SCHEDULE. In case, per standard practice, vital signs are measured more frequently than required per protocol, these additional measurements will also be recorded in the eCRF.

Temperature will be measured during study visits using the local, standardized method by a healthcare professional. Oral temperature will also be measured and recorded in the ePRO device by the subject twice daily until Day 14 by all subjects at sites where appropriate forms and translations are available and approved. Dedicated thermometers will be sourced for oral temperature measurement and can be used optionally. To avoid the confounding effects of antipyretic medications, temperature measurements must be taken, whenever possible, at least 4 hours after administration of the antipyretic medication.

Blood pressure, pulse rate, and respiratory rate measurements should be preceded by at least 5 minutes of rest in the supine position in a quiet setting without distractions (eg, television, cell phones). These measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Clinically relevant abnormalities (as defined in Attachment 5) occurring during the study should be recorded in the Adverse Event section of the eCRF.

9.6.5. Physical Examination

To evaluate the subject's eligibility, a physical examination (including height and [recent] body weight measurement if not already available and if practically feasible) will be performed at screening. In addition, a symptom-directed physical examination will be performed at the time points provided in the TIME AND EVENTS SCHEDULE.

A physical examination includes a review of the following systems: head/neck/thyroid; eyes; ears/nose/throat; respiratory; cardiovascular; lymph nodes; abdomen; skin; musculoskeletal; and neurological. Breast, anorectal, and genital examinations will be performed when medically indicated.

To obtain the actual body weight, subjects must be weighed lightly clothed. The height should be measured barefoot.

Any clinically relevant changes occurring during the study must be recorded in the Adverse Event section of the eCRF.

9.6.6. Specific Toxicities

Diarrhea

Loperamide can be administered.

AST and ALT Elevation

Subjects should be followed until resolution (return to baseline). A subject's study treatment must be discontinued if the subject experiences specific hepatic-related laboratory abnormalities (refer to Section 10.2).

Clinical Hepatitis

Subjects taking the study drugs should be monitored for the development of signs and symptoms of hepatitis which include fatigue, malaise, anorexia, nausea, dark urine and clay-colored stools, bilirubinuria, jaundice, liver tenderness, or hepatomegaly, with or without initially abnormal serum transaminase levels.

Subjects with these signs and symptoms must seek medical attention immediately and have hepatic parameters assessed. Relevant markers of viral hepatitis should also be assessed.

Subjects reporting AST/ALT elevations or clinical hepatitis should be followed until resolution of the AE or toxicity and necessary standard management should be undertaken.

9.7. Biomarker Evaluations

At the time points specified in the TIME AND EVENTS SCHEDULE, a blood sample will be collected for exploratory analyses of biomarkers (host RNA). In addition, leftovers from MT nasal swabs or blood samples may be used for other biomarker analyses (eg, proteins including cytokines).

Samples can only be used for research related to safety, PK and efficacy of the influenza treatment, or influenza disease. They may also be used to develop tests/assays related to influenza treatment, or influenza disease.

Analyses of biomarkers may be conducted at the sponsor’s discretion and may be reported separately from this study.

9.8. Pharmacogenomics Evaluations

A pharmacogenomic blood sample may be collected for future exploratory pharmacogenomic analyses (where local regulations permit). This pharmacogenomic sample collection is optional.

The sample will be collected only from subjects who consent separately to this component of the study.

Pharmacogenomic samples will be analyzed if it is hypothesized that this may help understand the clinical outcomes.

Pharmacogenomic samples may be used for research related to pimodivir or influenza A. They may also be used to develop tests/assays related to pimodivir or influenza A. Pharmacogenomic research may consist of the analysis of one or more candidate genes or of the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate) in relation to pimodivir clinical endpoints.

9.9. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form. If blood samples are collected via an indwelling cannula, an appropriate amount (1 mL) of serosanguineous fluid slightly greater than the dead space volume of the lock will be removed from the cannula and discarded before each blood sample is taken. After blood sample collection, the cannula will be flushed with 0.9% sodium chloride, United States Pharmacopeia (USP) (or equivalent) sodium heparin of 10 U/mL and charged with a volume equal to the dead space volume of the lock.

Refer to the TIME AND EVENTS SCHEDULE for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

10. SUBJECT COMPLETION/DISCONTINUATION OF STUDY TREATMENT/ WITHDRAWAL FROM THE STUDY

10.1. Completion

A subject will be considered to have completed the study if he or she has completed treatment and has completed assessments at the Safety Follow-up Visit/Final Study Visit (Day 28).

10.2. Discontinuation of Study Treatment

If a subject's study treatment must be discontinued before the end of the treatment regimen, this will not result in automatic withdrawal of the subject from the study.

A subject's study treatment must be discontinued if:

- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the subject to discontinue study treatment.
- The subject becomes pregnant.

- The subject experiences any of the following laboratory abnormalities:
  - If baseline AST or ALT within normal range: enzyme activity increases >10x ULN
  - If baseline AST or ALT not within normal range: enzyme activity increases >10x baseline or >500 U/L (whichever occurs first)
  - Total bilirubin increases >5x ULN
  - ALT or AST >3x ULN and total bilirubin >2x ULN

If a subject prematurely discontinues study drug treatment, the subject will be asked to continue with their remaining study visits and assessment schedule. Subjects who withdraw consent during the treatment phase, will be offered an optional Safety Follow-up Visit. The optional Safety Follow-up Visit will occur the day of consent withdrawal or the day after and will consist of the same assessments as at the Final Study Visit (Day 28), with optional PRO completion.

10.3. Withdrawal From the Study

A subject will be automatically withdrawn from the study for any of the following reasons:

- Lost to follow-up.
- Withdrawal of consent/assent.
- Death.

If a subject is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. No additional subjects will be enrolled for subjects who withdraw early. If a subject withdraws from the study before the end of the treatment or the follow-up phase, he or she will be offered an optional Safety Follow-up Visit. The optional Safety Follow-up Visit will occur on the day of withdrawal or the day after and will consist of the same assessments as at the Final Study Visit (Day 28), with optional PRO completion.

10.4. Withdrawal From the Use of Research Samples

A subject who withdraws from the study will have the following options regarding the optional pharmacogenomics sample:

- The collected sample will be retained and used in accordance with the subject's original separate ICF/assent form for optional research samples.
- The subject may withdraw consent/assent for optional pharmacogenomics sample, in which case the sample will be destroyed and no further testing will take place. To initiate the sample destruction process, the investigator must notify the sponsor study site contact of withdrawal of consent/assent for the optional pharmacogenomics samples and to request

sample destruction. The sponsor study site contact will, in turn, contact the biomarker representative to execute sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the samples have been destroyed.

Withdrawal From the Use of Samples in Future Research

The subject may withdraw consent/assent for use of samples for research (refer to Section 16.2.5, Long-Term Retention of Samples for Additional Future Research). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF/assent form.

11. STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy, PK and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

The primary analysis will be performed when all randomized subjects have completed the final study visit or discontinued earlier.

11.1. Analysis Sets

The efficacy endpoints will be analyzed on the Intent-to-Treat-infected (ITT‑i) set, consisting of all subjects who were randomized, treated and had a confirmed influenza A infection, and will be analyzed by treatment arm as randomized.

The primary endpoint will also be analyzed on the Per Protocol set, consisting of all subjects in the ITT-i set without major protocol deviations that have an effect on efficacy and who were not prematurely unblinded during the study.

All safety endpoints will be evaluated on the Safety population, consisting of all subjects who received at least one dose of study drug and will be analyzed by treatment arm as treated.

Pharmacokinetic data will be evaluated on subjects in the ITT-i set who received pimodivir. Subjects will be excluded from the population PK analysis if their data do not allow for accurate assessment of the PK parameters (eg, incomplete administration of the study drug; missing information of dosing and sampling times).

11.2. Subject Information

For all subjects who receive at least 1 dose of study drug descriptive statistics will be provided. All demographic characteristics (eg, age, race, ethnicity [if allowed per local regulations], height, body weight, body mass index) and other initial subject characteristics (eg, physical examination, medical and surgical history, concomitant diseases) will be tabulated and analyzed descriptively or listed.

11.3. Sample Size Determination

The study will aim to enroll 720 subjects, with 360 subjects per treatment arm.

The sample size is based on the primary endpoint of time to resolution of influenza-related symptoms. Time to resolution of influenza-related symptoms, ie, the proposed primary endpoint, will be based on the subjects' ratings on 7 items from the symptoms domain of the Flu-iiQ™ (cough, sore throat, headache, nasal congestion, feeling feverish, body aches and pains, and fatigue).

For the sample size, it is assumed that the recovery time is distributed similar to the time of symptom recovery in uncomplicated influenza, albeit with a somewhat longer average time to recovery due to the increased risk for complications and the increased time to recover for this population.

An underlying log-logistic distribution of the recovery time is assumed with a scale parameter of 0.55 and an intercept of 5.0 (in hours). Using the Gehan-Wilcoxon test to analyze the data and based on the assumption that the time to recovery is improved with 25%, a sample size of 600 subjects (randomized 1:1) will have an estimated power of 90% as based on 10,000 simulations. It is expected that approximately 15% of the total enrolled subjects may not be centrally-confirmed influenza A positive, resulting in a total of 720 subjects to be enrolled.

The effect of different distributional assumptions has been assessed, using estimates of the intercept and scale parameter from the accelerated failure time (AFT) model of time to resolution of influenza symptoms for both the log-logistic and log-normal distributions, based on data from the pimodivir Phase 2 Study 63623872FLZ2001. These estimates are provided in Table 2. The scale parameter is a measure for variability of the recovery times. The intercept is a constant that cancels out in effect size estimation/simulations.

Table 2: Estimates of Intercept and Scale Parameter From Study 63623872FLZ2001

Model	Parameter	Estimate	95% CI
Log-logistic	Intercept	3.8546	(3.2000, 4.5092)
	Scale	0.5213	(0.4633, 0.5867)
Log-normal	Intercept	3.6277	(2.8897 4.3656)
	Scale	0.9880	(0.8919 1.0945)

For a trial with a sample size of 600 patients, recovery times were simulated based on the log-logistic model and separately also based on the log-normal distribution, assuming that the time to recovery is reduced by 25% in the pimodivir with SOC treatment arm compared to the placebo with SOC treatment arm, and that the subjects are randomized in a 1:1 ratio between the 2 treatment groups. To consider the variability in the intercept and scale parameters, the simulated recovery times were derived using the estimate of each parameter and using the upper limit of the 95% CI for each parameter. A trial was simulated 10,000 times.

The Gehan-Wilcoxon test, log-logistic AFT model, and log-normal AFT model were used to analyze each of the 10,000 simulated datasets, for each recovery time distribution (log-logistic, log-normal) and for each parameter estimate (estimate, upper limit of the 95% CI). The power, for each statistical test, was estimated as the number of datasets where the 1-sided p-value from the test was <0.025 out of the 10,000 simulated datasets.

Table 3 provides the estimates of power for each statistical test and simulated time to resolution of influenza symptoms distributions.

Table 3: Estimated Power From 3 Statistical Tests

	Estimated Power (%)		
Simulated Distribution of Recovery Time	Gehan-Wilcoxon	AFT Log-logistic Model	AFT Log-normal Model
Log-logistic (estimate)	97.3	97.3	96.2
Log-logistic (upper CL)	93.3	93.4	91.3
Log-normal (estimate)	93.7	94.2	94.8
Log-normal (upper CL)	88.3	89.1	89.6

For the simulated recovery times based on the log-logistic model, the estimated power was greater than 90% when using both the estimate and the upper limit of the 95% CI for the intercept and scale parameter from the Phase 2 study.

For the simulated recovery times based on the log-normal model, the estimated power was greater than 90% and greater than 85% when using the estimate and the upper limit of the 95% CI, respectively, for the intercept and scale parameters from the Phase 2 study.

The sample size considerations are not based on accrual time and estimates of median survival times because all patients will have the same follow-up time by study design (28 days) and censoring is independent from time point of enrollment in the study, making accrual time not a concern. Also, the treatment effect is expressed as a 25% improvement (reduction) in time to resolution of influenza symptoms, and therefore does not require median times for sample size and power calculations.

11.4. Efficacy Analyses

Descriptive statistics will be used for all efficacy endpoints and will be tabulated by treatment arm and stratification factors (baseline SOC and time since onset of symptoms).

Subgroup analyses will be performed by, but might not be limited to, region and age group.

As a confirmatory strategy, to account for multiplicity in the statistical evaluation of the most important efficacy endpoints, hierarchical testing will be applied to control for overall Type I error. The following endpoints are included in the confirmatory strategy:

1. Time to resolution of the 7 primary influenza-related symptoms (cough, sore throat, headache, nasal congestion, feeling feverish, body aches and pains, fatigue), ie, primary endpoint
2. Incidence of complications associated with influenza after the start of study treatment
3. Hospital admission rates 28 days after treatment initiation

First, the primary endpoint will be tested for superiority of pimodivir in combination with SOC over placebo in combination with SOC at the 2-sided 5% significance level. If superiority is shown on the primary endpoint, the first secondary endpoint in the sequence as indicated above

will be tested for superiority at the same significance level. If superiority is shown for this secondary endpoint, the second (and last) secondary endpoint in sequence will be tested. In case superiority is not shown for an endpoint, no further endpoints in the sequence will be tested for superiority.

For the primary endpoint, the results from the Gehan-Wilcoxon test will be used in the hypothesis testing. For the secondary endpoints, incidence of complications associated with influenza after the start of study treatment and hospital admission rates 28 days after treatment initiation, the results of the logistic regression will be used.

Primary Endpoint

Time to resolution of the 7 primary influenza-related symptoms is defined as the time from initiation of study treatment to when all symptoms are considered resolved for at least 24 hours. A symptom is considered resolved, depending on pre-existence of the symptom:

- The symptom is pre-existing:
  - The symptom is considered resolved if post-baseline severity is equal or lower than the pre-existing severity
- The symptom is not pre-existing:
  - The symptom is considered resolved if its severity is scored at most mild post-baseline

The primary efficacy analysis of the time to resolution of the 7 primary influenza-related symptoms (cough, sore throat, headache, nasal congestion, feeling feverish, body aches and pains, fatigue) will consist of a stratified Gehan-Wilcoxon test (using the randomization stratification factors, ie, type of baseline SOC and time since onset of symptoms as strata). Kaplan‑Meier curves, overall and by stratum, and a stratified log-rank test for time to symptom resolution will also be provided. Additionally, the data will be analyzed using an accelerated failure time model. Also, a Cox proportional hazards model will be applied. Both models will be adjusted for stratification factors and baseline symptom domain score.

Secondary Endpoints

The incidence of hospital admissions 28 days after treatment initiation will be analyzed using a logistic regression. Stratification factors will be added as covariates to the model.

Return to daily activities will be assessed once daily by means of the question 'Over the past 24 hours, how much has influenza (flu) interfered with your ability to carry out your daily activities?' The responses will be dichotomized: 'Not at all' and 'A little bit' will be considered as returned to daily activities and 'Somewhat', 'Quite a Bit' and 'Very much' will be considered as not having returned to daily activities. "Time to return to daily activities" is defined as the time from initiation of study treatment to when return to daily activities is reached for at least 24 hours. This endpoint will be analyzed analogously to the primary endpoint.

Time to resolution of fever will be analyzed analogously to the primary endpoint.

The incidence of treatment-emergent adjudicated complications will be analyzed using a logistic regression. Stratification factors will be added as covariates to the model.

The time to viral negativity, by qRT-PCR and viral culture, will be analyzed analogously to the primary endpoint. The viral load over time will be analyzed using mixed effects modeling. Stratification factors will be added as covariates to the model. Additional predictive baseline covariates may be added.

Exploratory Endpoints

Time to resolution of impact of influenza on daily activities, emotions, and others, as defined by the Flu-iiQ^{TM} questionnaire, is the time at which all scores within each module are reported as "no difficulty" (Module 2), "not at all" (Module 3), and "not at all concerned" (Module 4), respectively, and will be analyzed analogously to the primary endpoint. Each module will be evaluated separately.

Other Analyses

Descriptive statistics by day of assessment will be provided for PGIS and PGIC questionnaires. The EQ 5D total scores and EQ-5D visual analog scale (VAS) 'thermometer' scores will be evaluated at each time point.

The PGIS and PGIC questionnaire responses will be used as anchors to perform responder analyses for selected PROs. The anchor-based analysis, if performed, will be defined and described in a separate report.

For the EQ-5D questionnaire a post-hoc analysis plan will be developed when the economic model structure is finalized, and results of this analysis will be reported separately.

11.5. Resistance Analyses

Development of resistance against pimodivir (and other antivirals in the SOC if applicable) will be determined by viral sequencing and phenotypic testing. All baseline samples as well as the last evaluable post-baseline samples will be analyzed. Additional genotypic and phenotypic testing might be requested by the Sponsor virologist.

The presence of baseline polymorphisms potentially affecting virologic response will be analyzed. The incidence of emerging mutations as well as changes in drug susceptibility (fold change in EC_{50} value) will be described and compared between treatment arms. Results of the resistance analysis may be reported in a separate report.

11.6. Pharmacogenomic Analyses

Pharmacogenomic samples may be used for research related to pimodivir or influenza A. They may also be used to develop tests/assays related to pimodivir or influenza A. Pharmacogenomic research may consist of the analysis of one or more candidate genes or of the analysis of genetic

markers throughout the genome or analysis of the entire genome (as appropriate) in relation to pimodivir clinical endpoints. Results of pharmacogenomic analysis will be reported in a separate report.

11.7. Pharmacokinetic Analyses

Population PK analysis of plasma concentration-time data of pimodivir will be performed using nonlinear mixed-effects modeling. Data may be combined with those of other selected studies (ie, Phase 1 and 2 studies) to support a relevant structural model. Available baseline subject characteristics (eg, demographics, body weight, laboratory variables, race) will be tested as potential covariates affecting PK parameters. The results of the population PK analysis will be reported in a separate report.

Data will be listed for all subjects with available plasma concentrations per treatment arm. Subjects will be excluded from the PK analysis if their data do not allow for accurate assessment of the PK (eg, incomplete administration of the study drug; missing information of dosing and sampling times; concentration data not sufficient for PK parameter calculation).

All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. All subjects and samples excluded from the analysis will be clearly documented in a separate PK report.

Descriptive statistics, including arithmetic mean, standard deviation (SD), coefficient of variation, median, minimum, and maximum will be calculated for all individual derived PK parameters (ie, C_{trough}, C_{max}, t_{max}, and AUC_{12h}) including exposure information of pimodivir.

11.8. Pharmacokinetic/Pharmacodynamic Analyses

The PK/PD relationship of pimodivir exposure (AUC_{12h}, C_{max}, or C_{trough}) with selected efficacy (eg, time to resolution of influenza symptoms, change in viral load from baseline and in other virologic response parameters) and safety (including AEs and laboratory abnormalities) parameters will be explored. If there is any visual trend in graphical analysis, suitable models will be applied to describe the exposure-effect relationships. Results will be described in a separate report.

11.9. Taste and Swallowability

Taste and swallowability questionnaire results (collected for adolescents who take pimodivir or placebo tablets) will be summarized per tablet intake (first and last intake of study drug) by means of frequency tabulations. For overall taste, a dichotomization will be made for the overall question, categorizing ‘bad’ and ‘almost acceptable’ versus ‘acceptable’ and ‘good’. For the swallowability, a dichotomization will be made of ‘slightly difficult’ or worse versus ‘neither difficult nor easy’ or better. The number of subjects (%) will be presented by category.

11.10. Safety Analyses

Safety will be evaluated by means of AEs (including influenza complications), clinical laboratory tests, ECGs, vital signs, and (symptom-directed) physical examinations. The safety

analysis will be performed using descriptive statistics for the safety population and for each study phase separately (treatment, follow-up, and the combination of both).

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs are AEs with onset after start of study medication or that are a consequence of a pre-existing condition that has worsened since baseline. All reported AEs will be included in the analysis. For each AE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment arm.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an AE, or who experience a severe AE or an SAE.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the Statistical Analysis Plan) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Changes from baseline results will be presented in pre- versus post-treatment cross-tabulations (with classes for below, within, and above normal ranges). Frequency tabulations of the abnormalities will be made. A listing of subjects with any laboratory results outside the reference ranges will be provided. A listing of subjects with any markedly abnormal laboratory results will also be provided.

The laboratory abnormalities will be determined according to the criteria specified in the WHO grading table (see Attachment 1) and in accordance with the normal ranges of the clinical laboratory if no gradings are available. Laboratory abnormalities will be tabulated by scheduled time point.

Electrocardiogram

The effects on cardiovascular variables will be evaluated by means of descriptive statistics and frequency tabulations. These tables will include observed values and changes from baseline values (the predose ECG will be used as baseline).

Electrocardiogram data will be summarized by ECG parameter. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

The ECG variables that will be analyzed are heart rate, PR interval, QRS interval, QT interval, and QTc interval using the following correction methods: QTcB and QTcF.[1,5,7,12]

Descriptive statistics of QTc intervals and changes from baseline will be summarized at each scheduled time point. The percentage of subjects with QTc interval >450 milliseconds,

>480 milliseconds, or >500 milliseconds will be summarized, as will the percentage of subjects with QTc interval increases from baseline >30 milliseconds or >60 milliseconds.

All clinically relevant abnormalities in ECG waveform that are changes from the baseline readings will be reported (eg, changes in T-wave morphology or the occurrence of U-waves).

The percentage of subjects with abnormalities will be tabulated by treatment arm.

Vital Signs

Descriptive statistics of temperature, pulse rate, respiratory rate, and blood pressure (systolic and diastolic) (supine) values, and changes from baseline will be summarized at each scheduled time point. The percentage of subjects with values beyond clinically important limits (Attachment 5) will be summarized.

Physical Examination

Descriptive statistics of changes from baseline will be summarized at each scheduled time point.

Physical examination findings will be listed.

11.11. Interim Analysis

An interim analysis will be implemented to re-estimate the study sample size and to perform an assessment of futility. The maximum total number of subjects that may be enrolled in the study will be approximately 1,080. This interim analysis will be implemented through an IDMC (see Section 11.12), providing recommendations to a Sponsor Committee. Only the IDMC and the independent Statistical Support Group will be unblinded to the data. Details will be specified in the IDMC charter.

Details on the statistical decision rules will be provided in a separate Modeling and Simulation Report. The interim analysis will be conducted at the end of the first influenza season when between 360 and 540 subjects have been enrolled or during the season when 540 subjects have been enrolled. Further details will be specified in the IDMC charter.

11.12. Independent Data Monitoring Committee

An IDMC will be established to monitor data on a regular basis. The committee will meet periodically to review interim data. After the review, the IDMC will make recommendations regarding the continuation of the study. The details will be provided in a separate IDMC charter.

The IDMC will consist of at least 3 members, including one medical expert in the relevant therapeutic area and at least one statistician knowledgeable about statistical methods for clinical studies and sequential analysis of study data. One of these individuals will chair the Committee. The IDMC responsibilities, authorities, and procedures will be documented in its charter.

11.13. Adjudication Committee

A blinded Adjudication Committee (AC) will be established to adjudicate AEs on predefined criteria for complications (pulmonary versus extrapulmonary, major versus minor, as well as infectious versus non-infectious complications). The AC will receive data on AEs, including medical assessments (eg chest X-ray results, lab results) and concomitant therapy of cases selected from the AEs. Details will be provided in an AC charter.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product (Definition per ICH).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects AEs starting with the signing of the ICF/assent form (refer to Section 12.3.1, All Adverse Events, for time of last AE recording).

Serious Adverse Event

An SAE event based on ICH and European Union Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.

- Is a congenital anomaly/birth defect.
- Is a suspected transmission of any infectious agent via a medicinal product.
- Is Medically Important*.

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also 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 subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study drug and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For pimodivir, since no serious ADRs are currently identified in the IB, all related SAEs are considered unexpected for reporting purposes. For medications part of the SOC treatment, the expectedness of an AE will be determined by whether or not it is listed in the manufacturer's prescribing information.

Adverse Event Associated With the Use of the Drug

An AE is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2, Attribution Definitions.

12.1.2. Attribution Definitions

Not Related

An AE that is not related to the use of the drug.

Doubtful

An AE for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An AE that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An AE that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely

An AE that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

12.1.3. Severity Criteria

An assessment of severity grade will be made using the general categorical descriptors outlined in the WHO Toxicity Grading Scale in Attachment 1.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

12.2. Special Reporting Situations

Safety events of interest on a sponsor study drug that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug.
- Suspected abuse/misuse of a sponsor study drug.
- Accidental or occupational exposure to a sponsor study drug.
- Medication error involving a sponsor product (with or without subject exposure to the sponsor study drug, eg, name confusion).

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the Serious Adverse Event section of the eCRF.

12.3. Procedures

12.3.1. All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF/assent form is obtained until completion of the subject's last study-related procedure, which may include contact for follow-up of safety. Serious AEs, including those spontaneously reported to the investigator within 30 days after the last dose of study drug, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All events, including influenza complications,that meet the definition of an SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments. Anticipated events will be recorded and reported as described in Attachment 2.

All AEs, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions. Whenever diarrhea is reported, the site will be asked to capture detailed information on the diarrhea (eg, frequency, consistency) in the AE verbatim term.

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

The subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number.
- Statement, in the local language(s), that the subject is participating in a clinical study.
- Investigator's name and 24-hour contact telephone number.
- Local sponsor's name and 24-hour contact telephone number (for medical staff only).
- Site number.
- Subject number.
- Any other information that is required to do an emergency breaking of the blind.

12.3.2. Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding SAEs will be transmitted to the sponsor (or designee) through the eCRF, which must be completed and confirmed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be made in the eCRF. In case eDC is inaccessible, SAE reports (paper form) should be submitted by fax or email.

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves.
- The event stabilizes.
- The event returns to baseline, if a baseline value/status is available.
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct.
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

Suspected transmission of an infectious agent by a medicinal product will be reported as an SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility).
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). Note: Hospitalizations that were planned before the signing of the ICF/assent form, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.
- For convenience, the investigator may choose to hospitalize the subject for the duration of the treatment period.

Disease progression should not be recorded as an AE or SAE term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the SAE definition (refer to Section 12.1.1, Adverse Event Definitions and Classifications).

12.3.3. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must discontinue further study treatment.

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported as noted above.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with an SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 12.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug(s)

The pimodivir supplied for this study is formulated as: 300-mg tablets for oral administration, containing pimodivir, hypromellose, polysorbate 20, crospovidone, silica colloidal anhydrous, silicified microcrystalline cellulose, microcrystalline cellulose, pregelatinized starch, sodium stearyl fumarate, Opadry II yellow. It will be manufactured and provided under the responsibility of the sponsor.

Matching pimodivir placebo tablets will be provided for subjects randomized to the placebo arm. Placebo tablets will be manufactured and provided under the responsibility of the sponsor.

SOC treatment will be determined by the investigator based on local practice, and may include influenza antivirals and/or supportive care only. The choice to use influenza antivirals as part of the SOC should be made before randomization. The influenza antiviral should be started no later than Day 2 morning (up to noon). An influenza antiviral as part of the SOC cannot be changed (eg, switching one influenza antiviral for another) during the treatment period, with the exception that an influenza antiviral may be discontinued in the case of a suspected AE.

14.2. Packaging

The investigational supplies will be uniquely packaged in child-resistant blisters to assure that they are appropriately managed throughout the supply chain process.

No study drugs can be repacked without prior approval from the sponsor.

14.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements.

No study drugs can be relabeled without prior approval of the sponsor.

14.4. Preparation, Handling, and Storage

All study drug must be stored as specified on the label.

Refer to the pharmacy manual/study site investigational product manual for additional guidance on study drug preparation, handling, and storage.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the subject, and the return of study drug from the subject (if applicable), must be documented on the drug accountability form. Subjects, or their legally acceptable representatives where applicable, must be instructed to return all original containers, whether empty or containing study drug. All study drug will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study drug containers.

Study drug must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug (and study drug returned by the subject, where applicable) must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study drug (or used returned study drug for destruction) will be documented on the Drug Return Form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Whenever a subject brings his or her study drug to the study site for pill count, this is not seen as a return of supplies. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator's Brochure of pimodivir.
- Pharmacy manual/study site investigational product and procedures manual.
- Laboratory manual (including procedures for nasal swabs).
- Contact information pages.
- ePRO device and user manual.
- IWRS Manual.
- Electronic data capture (eDC) Manual.
- Sample ICF/assent form.

16. ETHICAL ASPECTS

16.1. Study-specific Design Considerations

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent/assent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent/assent voluntarily will be enrolled.

When referring to the signing of the ICF/assent form, the terms legal guardian and legally acceptable representative refer to the legally appointed guardian of the child with authority to authorize participation in research. For each subject, his or her parent(s) (preferably both parents, if available) or legally acceptable representative(s), as required by local regulations, must give written consent/assent (permission) according to local requirements after the nature of the study has been fully explained and before the performance of any study-related assessments. Assent must be obtained from children (minors) capable of understanding the nature of the study, typically

subjects 7 years of age and older, depending on the institutional policies. For the purposes of this study, all references to subjects who have provided consent/assent (and assent as applicable) refers to the subjects and his or her parent(s) or the subject's legal guardian(s) or legally acceptable representative(s) who have provided consent/assent according to this process. Minors who assent to a study and later withdraw that assent should not be maintained in the study against their will, even if their parents still want them to participate.

The total blood volume to be collected is considered to be within the normal range allowed for this subject population over this time frame.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments.
- Sponsor-approved ICF/assent form (and any other written materials to be provided to the subjects).
- Investigator's Brochure (or equivalent information) and amendments/addenda.
- Sponsor-approved subject recruiting materials.
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable.
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB).
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects.
- Any other documents that the IEC/IRB requests to fulfill its obligation.

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no

consequences for subjects, data or study conduct, unless required locally), the ICF/assent form, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

Approval for the collection of optional samples for research and for the corresponding ICF/assent form must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of this optional research component.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct).
- Revision(s) to ICF/assent form and any other written materials to be provided to subjects.
- If applicable, new or revised subject recruiting materials approved by the sponsor.
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable.
- New edition(s) of the IB and amendments/addenda.
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually).
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study drug.
- New information that may adversely affect the safety of the subjects or the conduct of the study.
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects.
- Report of deaths of subjects under the investigator's care.
- Notification if a new investigator is responsible for the study at the site.
- Development Safety Update Report and Line Listings, where applicable.
- Any other requirements of the IEC/IRB.

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF/assent form revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

16.2.3. Informed Consent and Assent Form

Each subject (or a legally acceptable representative) must give written consent/assent according to local requirements after the nature of the study has been fully explained. The ICF(s)/assent form must be signed before performance of any study-related activity. The ICF(s) and assent form(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent/assent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects or their legally acceptable representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent/assent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF/assent form the subject or legally acceptable representative is authorizing such access, which includes permission to obtain information about his or her survival status and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent/assent for additional safety evaluations, and subsequent disease-related treatments, if needed. The physician may also recontact the subject for the purpose of obtaining consent/assent to collect information about his or her survival status.

The subject or legally acceptable representative will be given sufficient time to read the ICF/assent form and the opportunity to ask questions. After this explanation and before entry into the study, consent/assent should be appropriately recorded by means of either the subject's or his or her legally acceptable representative's personally dated signature. After having obtained the consent/assent, a copy of the ICF/assent form must be given to the subject.

Subjects will be asked for consent/assent to provide optional samples for research. After informed consent/assent for the study is appropriately obtained, the subject or his or her legally acceptable representative will be asked to sign and personally date a separate ICF/assent form indicating agreement to participate in the optional research component. Refusal to participate in the optional research will not result in ineligibility for the study. A copy of this signed ICF/assent form will be given to the subject.

Children (minors) or subjects who are unable to comprehend the information provided can be enrolled only after obtaining consent/assent of a legally acceptable representative. Assent must

be obtained from children (minors) capable of understanding the nature of the study, typically subjects 7 years of age and older, depending on the institutional policies. Written assent should be obtained from subjects who are able to write. A separate assent form written in language the subject can understand should be developed for adolescents. After having obtained the assent, a copy of the assent form must be given to the subject, and to the subject's parent or if applicable legally acceptable representative.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent/assent obtained from the subject (or his or her legally acceptable representative) includes explicit consent/assent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent/assent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory biomarker and pharmacogenomics research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

16.2.5. Long-term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand pimodivir, to understand influenza A infection, to understand differential drug responders, and to develop tests/assays related to pimodivir and influenza A infection. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent/assent for their samples to

be stored for research (refer to Section 10.4, Withdrawal From the Use of Samples in Future Research.

16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drug to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator.

- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF/assent form, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable.
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable.
- Documentation of investigator qualifications (eg, curriculum vitae).
- Completed investigator financial disclosure form from the principal investigator, where required.
- Signed and dated Clinical Trial Agreement, which includes the financial agreement.
- Any other documentation required by local regulations.

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all subinvestigators.
- Documentation of subinvestigator qualifications (eg, curriculum vitae).
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable.
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable.

17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth. In cases where the subject is not randomized into the study, the date seen and date of birth will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: subject identification, eligibility, and study identification; study discussion and date of signed informed consent/assent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The following data will be recorded directly into the eCRF and will be considered source data:

- Race.
- History of smoking.
- Blood pressure and pulse/heart rate.
- Height and weight.
- Details of physical examination.

The minimum source documentation requirements for Section 4.1, Inclusion Criteria and Section 4.2, Exclusion Criteria (that specify a need for a fully documented medical history) are as follows:

- Complete history of medical notes at the site.
- Discharge summaries.

In case the documented medical history at site is incomplete, medical history must be verified at a minimum by subject interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

17.5. Case Report Form Completion

Case report forms are provided for each subject in electronic format.

Electronic Data Capture will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto an eCRF, if applicable. Study-specific data will be transmitted in a secure manner within the timeframe agreed upon between the sponsor and the study site. The electronic file will be considered to be the eCRF.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subject's source documents. All data relating to the study must be recorded in the eCRFs prepared by the sponsor. Data must be entered into the eCRF in English. The eCRF must be completed as soon as possible after a subject visit and the forms should be available for review at the next scheduled monitoring visit.

All subjective measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible. The investigator must verify that all data entries in the eCRF are accurate and correct.

All eCRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool. The eCRF must be adjusted (if applicable) and a response provided to the query (complete, sign, and date the data clarification form).

If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in 3 different ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Study site manager can generate a query for resolution by the study-site personnel.
- Clinical data manager can generate a query for resolution by the study-site personnel.

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, periodic monitoring visits by the sponsor, direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base, and direct transmission of PRO data to the ePRO vendor database and then into the sponsor’s database. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Site investigators will receive training on the importance of subjects completing the PROs during the study. Subjects will receive a training guide outlining the importance of completing the PROs on the electronic device. Site investigators will train subjects on how to complete the PROs using the subject guide. The ePRO devices will include programmed alarms to remind the subjects to complete the PROs within the allowable windows of completion.

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study. The sponsor will review eCRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

17.8. Monitoring

The sponsor will use a combination of monitoring techniques to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel at the study initiation visit.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related

documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

The study is considered completed with the last visit for the last subject participating in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject visit at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of subjects by the investigator.
- Discontinuation of further study drug development.

17.10. On-site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a

regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding pimodivir or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomic and exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent/assent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of pimodivir, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of pharmacogenomics and exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication

data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law.

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ATTACHMENTS

Attachment 1: WHO Toxicity Grading Scale for Determining the Severity of Adverse Events (Feb 2003)

ABBREVIATIONS (used in the table)

ULN = Upper Limit of Normal

LLN = Lower Limit of Normal

R_x = Therapy

IV = Intravenous

FEV_1 = forced expiratory volume in 1 second

ESTIMATING SEVERITY GRADE

For abnormalities NOT found elsewhere in the Toxicity Tables use the scale below to estimate grade of severity:

GRADE 1	Mild	Transient or mild discomfort (<48 hours); no medical intervention/therapy required.
GRADE 2	Moderate	Mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention/ therapy required.
GRADE 3	Severe	Marked limitation in activity; some assistance usually required; medical intervention/therapy required; hospitalizations possible.
GRADE 4	Potentially life-threatening[a]	Extreme limitation in activity; significant assistance required; significant medical intervention/therapy required; hospitalization or hospice care probable.

[a] Revised by the sponsor

COMMENTS REGARDING THE USE OF THESE TABLES

- For parameters not included in the following Toxicity Tables, sites should refer to the "Guide For Estimating Severity Grade" located above.
- Criteria are generally grouped by body system. Some protocols may have additional protocol-specific grading criteria, which will supersede the use of these tables for specified criteria.

Item	Grade 1	Grade 2	Grade 3	Grade 4
Hematology				
Hemoglobin	9.5-10.5 gm/dL	8.0-9.4 gm/dL	6.5-7.9 gm/dL	<6.5 gm/dL
Absolute Neutrophil Count	1,000-1,500/mm³	750-999/mm³	500-749/mm³	<500/mm³
Platelets	75,000-99,000/mm³	50,000-74,999/mm³	20,000-49,999/mm³	<20,000/mm³
Prothrombin Time (PT)	≥1.01 to ≤1.25 x ULN	>1.25 to ≤1.50 x ULN	>1.50 to ≤3.00 x ULN	>3.00 x ULN
Activated Partial Thromboplastin Time (aPTT)	≥1.01 to ≤1.66 x ULN	>1.66 to ≤2.33 x ULN	>2.33 to ≤3.00 x ULN	>3.00 x ULN
Fibrinogen	≥0.75 to ≤0.99 x LLN	≥0.50 to <0.75 x LLN	≥0.25 to <0.50 x LLN	<0.25 x LLN
Fibrin Split Product	20-40 mcg/mL	41-50 mcg/mL	51-60 mcg/mL	>60 mcg/mL
Methemoglobin	5.0-9.9%	10.0-14.9%	15.0-19.9%	>20.0%
Liver Enzymes				
AST (SGOT)	≥1.25 to ≤2.50 x ULN	>2.50 to ≤5.00 x ULN	>5.00 to ≤10.00 x ULN	>10.00 x ULN
ALT (SGPT)	≥1.25 to ≤2.50 x ULN	>2.50 to ≤5.00 x ULN	>5.00 to ≤10.00 x ULN	>10.00 x ULN
Gamma-glutamyltransferase	≥1.25 to ≤2.50 x ULN	>2.50 to ≤5.00 x ULN	>5.00 to ≤10.00 x ULN	>10.00 x ULN
Alkaline Phosphatase	≥1.25 to ≤2.50 x ULN	>2.50 to ≤5.00 x ULN	>5.00 to ≤10.00 x ULN	>10.00 x ULN
Amylase	≥1.1 to ≤1.5 x ULN	>1.5 to ≤2.0 x ULN	>2.0 to ≤5.0 x ULN	>5.0 x ULN
Chemistries				
Hyponatremia	130-135 mEq/L	123-129 mEq/L	116-122 mEq/L	<116 mEq/L or mental status changes or seizures
Hypernatremia	146-150 mEq/L	151-157 mEq/L	158-165 mEq/L	>165 mEq/L or mental status changes or seizures
Hypokalemia	3.0-3.4 mEq/L	2.5-2.9 mEq/L	2.0-2.4 mEq/L or intensive replacement Rx required or hospitalization required	<2.0 mEq/L or paresis or ileus or life-threatening arrhythmia
Hyperkalemia	5.6-6.0 mEq/L	6.1-6.5 mEq/L	6.6-7.0 mEq/L	>7.0 mEq/L or life-threatening arrhythmia
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or mental status changes or coma
Hyperglycemia (note if fasting)	116-160 mg/dL	161-250 mg/dL	251-500 mg/dL	>500 mg/dL or ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4-7.8 mg/dL	7.7-7.0 mg/dL	6.9-6.1 mg/dL	<6.1 mg/dL or life-threatening arrhythmia or tetany

Item	Grade 1	Grade 2	Grade 3	Grade 4
Hypercalcemia (corrected for albumin)	10.6-11.5 mg/dL	11.6-12.5 mg/dL	12.6-13.5 mg/dL	>13.5 mg/dL or life-threatening arrhythmia
Hypomagnesemia	1.4-1.2 mEq/L	1.1-0.9 mEq/L	0.8-0.6 mEq/L	<0.6 mEq/L or life-threatening arrhythmia
Hypophosphatemia	2.0-2.4 mg/dL	1.5-1.9 mg/dL or replacement Rx required	1.0-1.4 mg/dL intensive Rx or hospitalization required	<1.0 mg/dL or life-threatening arrhythmia
Hyperbilirubinemia	≥1.1 to ≤1.5 x ULN	>1.5 to ≤2.5 x ULN	>2.5 to ≤5.0 x ULN	>5.0 x ULN
BUN	≥1.25 to ≤2.50 x ULN	>2.50 to ≤5.00 x ULN	>5.00 to ≤10.00 x ULN	>10.00 x ULN
CPK*	3 to <6 x ULN	6 to <10 x ULN	10 to <20 x ULN	≥20 x ULN
Creatinine	≥1.1 to ≤1.5 x ULN	>1.5 to ≤3.0 x ULN	>3.0 to ≤6.0 x ULN	>6.0 x ULN or required dialysis
Lipase*	1.1 to <1.5 x ULN	1.5 to <3.0 x ULN	3.0 to <5.0 x ULN	≥5.0 x ULN
Urinalysis				
Proteinuria	1+ or <0.3% or <3g/L or 200 mg – 1 gm loss/day	2-3+ or 0.3-1.0% or 3-10 g/L or 1-2 gm loss/day	4+ or >1.0% or >10 g/L or 2-3.5 gm loss/day	nephrotic syndrome or >3.5 gm loss/day
Hematuria	microscopic only	gross, no clots	gross + clots	obstructive or required transfusion
Cardiac Dysfunction				
Cardiac Rhythm	-	asymptomatic, transient signs, no Rx required	recurrent/persistent; no Rx required	requires Rx
Hypertension	transient inc. >20 mm; no Rx	recurrent, chronic, >20 mm, Rx required	requires acute Rx; no hospitalization	requires hospitalization
Hypotension	transient orthostatic hypotension, no Rx	symptoms correctable with oral fluids Rx	requires IV fluids; no hospitalization required	requires hospitalization
Pericarditis	minimal effusion	mild/moderate asymptomatic effusion, no Rx	symptomatic effusion; pain; ECG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	microscopic/occult	mild, no transfusion	gross blood loss; 1-2 units transfused	massive blood loss; >3 units transfused

* Grading based on Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.0, November 2014.

Item	Grade 1	Grade 2	Grade 3	Grade 4
Respiratory				
Cough	transient; no Rx	treatment associated cough; local Rx	uncontrolled	-
Bronchospasm, Acute	transient; no Rx <80-70% FEV_1 (or peak flow)	requires Rx normalizes with bronchodilator; FEV_1 50-70% (or peak flow)	no normalization with bronchodilator; FEV_1 25-50% (or peak flow retractions)	cyanosis: FEV_1 <25% (or peak flow) or intubated
Gastrointestinal				
Stomatitis	mild discomfort; no limits on activity	some limits on eating/drinking	eating/talking very limited	requires IV fluids
Nausea	mild discomfort; maintains reasonable intake	moderate discomfort; intake decreased significantly; some activity limited	severe discomfort; no significant intake; activities limited	minimal fluid intake
Vomiting	transient emesis	occasional/moderate vomiting	orthostatic hypotension or IV fluids required	hypotensive shock or hospitalization required for IV fluid therapy
Constipation	mild	moderate	severe	distensions w/vomiting
Diarrhea	transient 3-4 loose stools/day	5-7 loose stools/day	orthostatic hypotension or >7 loose stools/day or required IV fluids	hypotensive shock or hospitalization for IV fluid therapy required
Neuro & Neuromuscular				
Neuro-Cerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
Mood	mild anxiety or depression	moderate anxiety or depression and Rx required	severe anxiety or depression or mania; needs assistance	acute psychosis; incapacitated, requires hospitalization
Neuro Control (ADL = activities of daily living)	mild difficulty concentrating; no Rx; mild confusion/agitation; ADL unaffected	moderate confusion/agitation some limitation of ADL; minimal Rx	severe confusion/agitation needs assistance for ADL; Rx required	toxic psychosis; hospitalization
Muscle Strength	subjective weakness no objective symptoms/ signs	mild objective signs/symptoms no decrease in function	objective weakness function limited	paralysis

Item	Grade 1	Grade 2	Grade 3	Grade 4
Other Parameters				
Fever: oral, >12 hours	37.7-38.5 °C or 100.0-101.5 °F	38.6-39.5 °C or 101.6-102.9 °F	39.6-40.5 °C or 103-105 °F	>40 °C or >105 °F
Headache	mild, no Rx	transient, moderate; Rx required	severe; responds to initial narcotic therapy	intractable; required repeated narcotic therapy
Fatigue	no decrease in ADL	normal activity decreased 25-50%	normal activity decreased >50% can't work	unable to care for self
Allergic Reaction	pruritus without rash	localized urticaria	generalized urticaria; angioedema	anaphylaxis
Local Reaction	tenderness or erythema	induration <10 cm or phlebitis or inflammation	induration >10 cm or ulceration	necrosis
Mucocutaneous	Erythema; pruritus	diffuse, maculopapular rash, dry desquamation	vesiculation, moist desquamation, or ulceration	exfoliative dermatitis, mucous membrane involvement, or erythema multiforme or suspected Stevens-Johnson or necrosis requiring surgery

Attachment 2: Anticipated Events

Anticipated Event

An anticipated event is an AE (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease related) or background regimen.

For the purposes of this study the following events will be considered anticipated events:

- Pneumonia
- Bronchitis
- Sinus infection
- Ear infection
- Worsening of asthma, asthma attack
- COPD exacerbation
- Complications of sickle cell disease, sickle cell crisis
- Complications of diabetes mellitus, diabetic ketoacidosis
- Acute respiratory distress syndrome

Reporting of Anticipated Events

These events will be captured on the eCRF and in the database, and will be reported to the sponsor as described in Section 12.3.1, All Adverse Events. Any event that meets SAE criteria will be reported to the sponsor within the appropriate timeline as described in Section 12.3.2, Serious Adverse Events. These anticipated events are exempt from expedited reporting as individual single cases to Health Authorities. However if based on an aggregate review, it is determined that an anticipated event is possibly related to study drug, the sponsor will report these events in an expedited manner.

Anticipated Event Review Committee (ARC)

In this study, the IDMC will perform the role of an Anticipated Event Review Committee (ARC) and will conduct reviews of pre-specified anticipated events at an aggregate level. The IDMC will provide the recommendation to the Sponsor Committee as to whether there is a reasonable possibility that an anticipated event is related to the study drug.

Statistical Analysis

Details of statistical analysis of anticipated events, including the frequency of review and threshold to trigger an aggregate analysis of anticipated events will be provided in a separate Anticipated Events Safety Monitoring Plan.

Attachment 3: Influenza Intensity and Impact Questionnaire (Flu-iiQ™)

This attachment provides a representative example of the Flu-iiQ™ questionnaire that will be used in this study.

Measured Solutions for Health P/L [MESH]
PO Box 5127 Alphington 3078
Victoria Australia
Telephone +61 (0)4000 355 29

measuredsolutions@bigpond.com
ABN 16105 383 640

Influenza intensity and impact questionnaire (Flu-iiQ™)

Please read each question below and check one box that best describes your symptoms.

Complete the questionnaire when you rise from bed in the morning and right before you go to bed at night.

1. Because of influenza do you have any of the following symptoms now?

	None	Mild	Moderate	Severe
a. Cough	☐	☐	☐	☐
b. Sore throat	☐	☐	☐	☐
c. Headache	☐	☐	☐	☐
d. Nasal congestion	☐	☐	☐	☐
e. Feeling feverish	☐	☐	☐	☐
f. Body aches and pains	☐	☐	☐	☐
g. Fatigue (tiredness)	☐	☐	☐	☐
h. Neck pain	☐	☐	☐	☐
i. Interrupted sleep	☐	☐	☐	☐
j. Loss of appetite	☐	☐	☐	☐

IMPACT OF INFLUENZA

2. Does influenza affect your ability to do any of the following activities now?

	No Difficulty	Some Difficulty	Moderate Difficulty	Great Difficulty
a. Get out of bed	☐	☐	☐	☐
b. Prepare meals / get your own food	☐	☐	☐	☐
c. Perform usual activities	☐	☐	☐	☐
d. Leave the home	☐	☐	☐	☐
e. Concentrate on tasks	☐	☐	☐	☐
f. Take care of yourself	☐	☐	☐	☐

3. Does influenza currently make you:

	Not at all	Somewhat	Moderately	Extremely
a. Irritable	☐	☐	☐	☐
b. Feel helpless	☐	☐	☐	☐
c. Worried	☐	☐	☐	☐
d. Frustrated	☐	☐	☐	☐

4. Because of influenza are you currently concerned about:

	Not at all concerned	Somewhat concerned	Moderately concerned	Extremely concerned
a. People worrying about you	☐	☐	☐	☐
b. Being a burden	☐	☐	☐	☐
c. People being annoyed with you	☐	☐	☐	☐
d. Needing to depend on people	☐	☐	☐	☐
e. People having to do extra things for you	☐	☐	☐	☐

Attachment 4: Taste/Swallowability Questionnaire

The taste and swallowability questionnaire should be completed within approximately 15 minutes after the first and last intake of the study drug (consequently, the questionnaire should be completed 2 times in total by the subject).

Date (DD/MM/YYYY): _____

Subject Clinical Trial ID number: _____

Questionnaire completion time: (24-hours format→ insert a time between 00:00 and 23:59):
_____:_____

Questions:

1. Taste (Put a cross in the box beneath your appreciation):

Sweetness

None	Weak	Moderate	Strong

Bitterness

None	Weak	Moderate	Strong

Flavour

None	Weak	Moderate	Strong

Overall

None	Weak	Moderate	Strong

2. Swallowability:
On a scale of 1-7, how difficult/easy was it to swallow the tablet? (Circle the number corresponding to your appreciation)

1. Very difficult

2. Moderately difficult
3. Slightly difficult
4. Neither difficult or easy
5. Slightly easy
6. Moderately easy
7. Very easy

Attachment 5: Cardiovascular Safety - Abnormalities

ECG

All important abnormalities from the ECG readings will be listed.

Abnormality Code	ECG parameter			
	HR	**PR**	**QRS**	**$QT_{corrected}$**
Abnormalities on actual values				
Abnormally low	<45 bpm	<110 ms	-	-
Abnormally high	≥120 bpm	>220 ms	≥ 120 ms	-
Borderline prolonged QT (males)	-	-	-	450 ms<QTc ≤480 ms
Borderline prolonged QT (females)	-	-	-	470 ms<QTc ≤480 ms
Prolonged QT	-	-	-	480 ms<QTc ≤500 ms
Pathologically prolonged QT	-	-	-	QTc >500 ms
Abnormalities on changes from baseline (ΔQTc)				
Normal QTc change	-	-	-	ΔQTc <30 ms
Borderline QTc change	-	-	-	30 ms≤ΔQTc ≤60 ms
Abnormally high QTc change	-	-	-	ΔQTc >60 ms

For absolute QTc parameters the categories are defined based on the ICH E14 Guidance[a]

Vital Signs[b]

The following abnormalities will be defined for vital signs:

Abnormality Code	Vital Signs parameter		
	Pulse	**DBP**	**SBP**
Abnormalities on actual values			
Abnormally low	<45 bpm	≤50 mmHg	≤90 mmHg
Grade 1 or mild	-	>90 mmHg - <100 mmHg	>140 mmHg - <160 mmHg
Grade 2 or moderate	-	≥100 mmHg - <110 mmHg	≥160 mmHg - <180 mmHg
Grade 3 or severe	-	≥110 mmHg	≥180 mmHg
Abnormally high	≥120 bpm	-	-

[a] The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs CHMP/ICH/2/04, May 2005.

[b] The classification of AEs related to hypotension and hypertension will be done according to the WHO grading scale (see also Attachment 1).

Attachment 6: Pre-existing Symptom Questionnaire

This questionnaire is about your usual health.

Thinking back to before you had this illness, about a week ago, read each symptom and check the box that best describes how you felt back then.

	None	Mild	Moderate	Severe
a. Cough	☐	☐	☐	☐
b. Sore throat	☐	☐	☐	☐
c. Headache	☐	☐	☐	☐
d. Nasal congestion	☐	☐	☐	☐
e. Feeling feverish	☐	☐	☐	☐
f. Body aches and pains	☐	☐	☐	☐
g. Fatigue (tiredness)	☐	☐	☐	☐
h. Neck pain	☐	☐	☐	☐
i. Interrupted sleep	☐	☐	☐	☐
j. Loss of appetite	☐	☐	☐	☐

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Lorant Leopold, MD

Institution: Janssen Research & Development

Signature: [electronic signature appended at the end of the protocol] Date: _____

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

SIGNATURES

Signed by	Date	Justification
Lorant Leopold	09Feb2018, 14:19:07 PM, UTC	Document Approval