SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development*
Name of Investigational Product	JNJ-63623872-ZCD (pimodivir)

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Status: Approved

Date: 8 February 2021

Prepared by: Janssen Research & Development

Protocol No.: 63623872FLZ3001

Title of Study: A Phase 3 randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of pimodivir in combination with the standard-of-care treatment in adolescent, adult, and elderly hospitalized patients with influenza A infection

EudraCT Number: 2017-002156-84

NCT No.: NCT03376321

Clinical Registry No.: CR108399

Study Center(s): 276 sites opened, of which 123 sites screened at least 1 participant. Of those 123 sites, 95 sites randomized at least one participant in this study and were located in Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Chile, France, Germany, India, Israel, Italy, Latvia, Lithuania, Malaysia, Mexico, Netherlands, New Zealand, Poland, Russian Federation, Singapore, Slovakia, South Africa, Spain, Sweden, Taiwan, Thailand, Turkey, Ukraine, the United Kingdom, United States of America, and Vietnam.

Publication (Reference): none

Study Period: 16 January 2018 (date first participant signed informed consent) to 26 May 2020 (date of last observation for last participant recorded as part of the database)

Phase of Development: 3

Rationale for Early Study Termination: On 31 July 2020, a pre-planned interim analysis was performed for Study 63623872FLZ3001 by the pimodivir Independent Data Monitoring Committee (IDMC) as specified in the study protocol (ie, when at least 50%, but no more than 75% of participants had been randomized). The interim analysis evaluated the treatment effect in the subgroup of participants who started study treatment between 72 and 96 hours after onset of influenza symptoms, followed by a sample size re-estimation based on the primary endpoint and the evaluation of futility for the primary endpoint and 2 important secondary endpoints, based on the new sample size. The IDMC informed the Sponsor Committee that futility was noted on the 3 efficacy endpoints assessed in the interim analysis, comparing pimodivir plus standard of care (SOC) treatment to placebo plus SOC in hospitalized participants with influenza A, and recommended that Study 63623872FLZ3001 be terminated. Therefore, the Sponsor decided to terminate the study on 28 August 2020.

Since the study was terminated early, the Sponsor performed a limited statistical analysis on the available data. As a result, not all planned objectives and endpoints were evaluated. Therefore, the results section of

this abbreviated Clinical Study Report describes the analysis of the safety parameters (AE, laboratory parameters, electrocardiogram [ECG], vital signs, and National Early Warning Score [NEWS2]), selected efficacy parameters (the primary parameter Hospital Recovery Scale on Day 6 and 4 secondary endpoints: time to hospital discharge, treatment-emergent adjudicated influenza complications, viral load over time, and viral titer over time), genotypic resistance, and descriptive pharmacokinetic (PK) data.

The description of study objectives and assessments below provides an overview of the study as it was planned per protocol.

Objectives

Primary Objective

The primary objective was to evaluate superiority of pimodivir in combination with SOC treatment compared to placebo in combination with SOC treatment on Day 6, with respect to the clinical outcome on the Hospital Recovery Scale.

Secondary Objectives

The secondary objectives were:

- 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 time from start of study drug to hospital discharge in participants treated with pimodivir in combination with SOC treatment compared to placebo in combination with SOC treatment.
- To evaluate superiority with respect to the time from intensive care unit (ICU) admission to ICU discharge in participants treated with pimodivir in combination with SOC treatment compared to placebo in combination with SOC treatment.
- To evaluate superiority with respect to the time from start to end of mechanical ventilation in participants treated with pimodivir in combination with SOC treatment compared to placebo in combination with SOC treatment.
- To evaluate superiority of pimodivir in combination with SOC treatment compared to placebo in combination with SOC treatment each separated day from Days 2 to 14 (excluding the primary time point), with respect to the clinical outcome on the Hospital Recovery Scale.
- To evaluate superiority with respect to the time to return to daily activities in participants treated with pimodivir in combination with SOC treatment compared to placebo in combination with SOC treatment.
- To evaluate superiority with respect to the incidence of complications associated with influenza after the start of study treatment in participants treated with pimodivir in combination with SOC treatment compared to placebo in combination with SOC treatment.
- 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 investigate the incidence and duration of antibiotic treatment in the pimodivir in combination with SOC treatment arm, compared to the placebo in combination with SOC treatment arm.
- To investigate the number (proportion) of participants needing extended treatment in the pimodivir in combination with SOC treatment arm, compared to the placebo in combination with SOC treatment arm.

- To investigate the number (proportion) of participants requiring re-hospitalization in the pimodivir in combination with SOC treatment arm, compared to the placebo in combination with SOC treatment arm.
- To investigate the number (proportion) of participants not hospitalized at Day 6 in the pimodivir in combination with SOC treatment arm, compared to the placebo in combination with SOC treatment arm.
- To investigate the time to clinical response in the pimodivir in combination with SOC treatment arm, compared to the placebo in combination with SOC treatment arm.
- To investigate the time to improvement of respiratory status 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 evaluate superiority with respect to the following influenza A viral parameters in the pimodivir treatment arm compared to the control arm by quantitative real time polymerase chain reaction (qRT-PCR) and viral culture:
  - Time to viral negativity.
  - Viral load over time.
- To investigate the emergence of viral resistance against pimodivir detected by genotyping and/or phenotyping.

Exploratory Objective

- To evaluate the measurement performance of the Influenza Symptom Diary for hospitalized influenza participants.

Hypothesis

The outcome on the Hospital Recovery Scale with pimodivir in combination with SOC treatment was statistically superior to treatment with placebo in combination with SOC treatment on Day 6 in hospitalized participants with influenza A infection.

Methodology

This was a Phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of pimodivir in combination with SOC treatment vs placebo in combination with SOC treatment in adolescent (13 to 17 years), adult (18 to 65 years), and elderly (>65 to ≤85 years) hospitalized participants with influenza A infection.

Participants who met all eligibility criteria were randomized in a 1:1 ratio to receive either pimodivir 600 mg twice daily (bid) for 5 days + SOC treatment (Treatment Arm 1) or pimodivir placebo bid for 5 days + SOC treatment (Treatment Arm 2). Initiation of study drug treatment had to occur ≤96 hours after onset of influenza symptoms. There was a possibility to extend the treatment phase with 5 days, but only for participants who met predefined criteria (see below). Treatment in the extended treatment phase was the same blinded treatment and SOC as received in the first 5-day treatment phase.

The SOC treatment was determined by the investigator based on local practice, and could include influenza antivirals and/or supportive care only. The choice to use influenza antivirals as part of the SOC had to be made before randomization. The influenza antiviral had to be started no later than the day of first study drug intake. An influenza antiviral as part of the SOC could not be changed (eg, switching one influenza

antiviral for another) during either the 5-day treatment period or during the optional 5-day extended treatment period, with the exception that an influenza antiviral could be discontinued in the case of a suspected adverse event (AE). The randomization was stratified for baseline NEWS2 (4-5 or >5), type of baseline SOC (including or not including influenza antiviral treatment), and time since onset of influenza symptoms (first administration of study drug within 72 hours or between 72 and 96 hours since onset of influenza symptoms). The study population had to consist of at least 75% of participants with first administration of study drug ≤72 hours since onset of influenza symptoms.

Participants (1) who completed the 5-day treatment, (2) who were still hospitalized upon treatment completion, (3) who were on invasive mechanical ventilation or who had an ongoing respiratory deficiency as evidenced by having an peripheral capillary oxygen saturation (SpO_2) <94% on room air, or in case of known pre-influenza SpO_2 <94% (eg, due to chronic obstructive pulmonary disease [COPD]), the blood oxygen saturation on room air was lower than pre-influenza infection levels by at least 3%, (4) who, in the opinion of the investigator, were expected to derive clinical benefit from extending the treatment period, and (5) for whom the investigator agreed to extend treatment with the same SOC were given the option for treatment extension. In the second blinded course of treatment, participants continued treatment with pimodivir or placebo for another 5 days in combination with continued SOC treatment. If the SOC contained no influenza antiviral during the first treatment period, no influenza antiviral could be started in the treatment extension as part of the SOC.

The study consisted of a screening/baseline visit, a double-blind treatment period of 5 days (with the possibility to extend the treatment period with 5 days), and a follow-up period of 23 days after the last dosing day.

Assessments to be performed during the study at specified time points included the impact of influenza infection and its treatment on clinical outcomes and patient-reported symptoms (using a variety of tools), sparse blood samples for the measurement of plasma concentrations of pimodivir, acceptability of the pimodivir formulation (only in adolescents), safety and tolerability (AEs, clinical laboratory tests, 12-lead electrocardiograms [ECGs], vital signs, SpO_2 measurements, and physical examinations), and nasal mid-turbinate (MT) swabs for viral quantification and resistance testing.

An IDMC was commissioned for this study to monitor safety and efficacy data on a regular basis. The IDMC met periodically to review interim data and make recommendations to the Sponsor Committee regarding the safety and the continuation of the study. A blinded Adjudication Committee (AC) was established to adjudicate AEs on predefined criteria for complications (pulmonary versus extrapulmonary, major versus minor, as well as infectious versus non-infectious complications). Following the decision to terminate the study, further adjudication of AEs for the final analysis was not completed.

An interim analysis was performed to assess lack of efficacy in the subgroup with time since onset of influenza symptoms to first study intake between 72 and 96 hours, to re-assess the sample size, and to assess futility. This interim analysis was implemented through the IDMC supported by an Independent Statistical Support Group, providing recommendations to a Sponsor Committee. Only the IDMC and the Independent Statistical Support Group were unblinded to the data. Details on the statistical decision rules were pre-specified in a separate Modeling and Simulation Report. The interim analysis was conducted at the end of the first influenza season when between 300 and 450 participants had been enrolled.

It should be noted that the study began in January 2018 and was terminated in August 2020, which included the period during which the COVID-19 pandemic was occurring globally. The study was continued during the pandemic, however, recruitment was severely impacted. As of February 2020, enrollment rates decreased due to the COVID-19 pandemic, and enrollment completely stopped in March 2020, likely due to the combined effect of the ongoing pandemic and the end of the seasonal influenza circulation in the Northern Hemisphere. The impact on assessments for participants recruited during the pandemic was minimal. It mostly impacted follow-up visits for participants discharged from the hospital that may have

been missed, however, participants could complete their assessments on the patient-reported outcome (PRO) tool at home.

Number of Participants (Planned and Analyzed)

A target of 600 hospitalized influenza A-infected participants was planned to be randomly enrolled in this study with 300 participants planned per treatment arm. Additionally, it was planned that 10% of the overall target of 600 participants in this study were to be adolescent participants (ie, a minimum of 60 adolescent participants). They were enrolled in selected countries and study sites consistent with local regulations.

At the time of study termination, 334 participants were randomized, of which 326 participants were treated (and included in the Safety Set). Of the 334 randomized participants, 318 had a laboratory-confirmed influenza A infection and were included in the Intent-To-Treat infected (ITT-i) Set. Four (1.2%) participants in the Safety Set were adolescents (ie, ≥13 to <18 years).

Diagnosis and Main Criteria for Inclusion

Each potential participant had to satisfy the following key criteria to be enrolled in the study:

1. Male or female, 13 to 85 years of age, inclusive. Note: Adolescent participants (13-17 years) were enrolled in selected countries and study sites consistent with local regulations.
2. Tested positive for influenza A infection after the onset of symptoms using a polymerase chain reaction (PCR)-based or other rapid molecular diagnostic assay.
3. Required hospitalization to treat influenza infection and/or to treat complications of influenza infection (eg, radiological signs of lower respiratory tract disease, septic shock, central nervous system [CNS] involvement, myositis, rhabdomyolysis, acute exacerbation of chronic kidney disease, severe dehydration, myocarditis, pericarditis, ischemic heart disease, exacerbation of underlying chronic pulmonary disease, including asthma, COPD, decompensation of previously controlled diabetes mellitus), including participants admitted to the ICU. Note: For the purpose of the protocol, participants admitted under "observation" status with an anticipated length of stay beyond 24 hours were eligible for enrollment.
4. Enrollment and initiation of study drug treatment ≤96 hours after onset of influenza symptoms.
5. Were on invasive mechanical ventilation or had an SpO_2 <94% on room air during screening. Participants with known pre-influenza SpO_2 <94% had to have an SpO_2 decline ≥3% from pre-influenza SpO_2 during screening.
6. Had a screening/baseline NEWS2 of ≥4.

Test Product, Dose and Mode of Administration, Batch No.

Pimodivir was formulated as 300-mg tablets for oral administration, containing JNJ-63623872, microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, povidone K30, sodium stearyl fumarate, Opadry II, white. The lot numbers for pimodivir were 17G13/G027, 17G17/G027, 18B06/G027, 18B19/G027, 18C19/G027, 18F27/G027, 18H31/G027, IGL59, IIL1G, IIL1H, and IKL3F.

The planned dose of pimodivir was 600 mg (ie, two 300-mg tablets).

Reference Therapy, Dose and Mode of Administration, Batch No.

JNJ-63623872 placebo was supplied as tablets matching pimodivir 300-mg tablets for oral administration. The lot numbers for placebo were 17G04/G019, 17G05/G019, 18C09/G019, 18E24/G019, 18E29/G019, 18H27/G019, 18H29/G019, 19D02/G019, 19D03/G019, and 19D04/G019. The lot numbers for oseltamivir (OST) were 633178, 633179, F0163B07, and F0222B56.

Duration of Treatment: The planned treatment duration for each participant was 5 days (and could be extended with 5 days). The planned entire study duration for each participant was 28 days, except for participants receiving extended treatment, for whom the study lasted 33 days.

Criteria for Evaluation

The description of assessments below provides an overview of all parameters and data collected during the study.

Efficacy Evaluations

Hospital Recovery Scale Assessment

The Hospital Recovery Scale assessed the participant's clinical status and was based on the participant's condition on Day 6 as the primary endpoint. The Hospital Recovery Scale was assessed on Days 2 to 14 (excluding the primary time point) as secondary endpoints. The Hospital Recovery Scale provided 6 mutually exclusive conditions ordered from best to worst, and the score reflected the participant's worst situation on the day of assessment:

1. Not Hospitalized
2. Non-ICU Hospitalization, Not Requiring Supplemental Oxygen
3. Non-ICU Hospitalization, Requiring Supplemental Oxygen
4. Admitted to the ICU, Not Requiring Invasive Mechanical Ventilation
5. Requiring Invasive Mechanical Ventilation
6. Death

Complications of Influenza

From the moment participants signed the informed consent/assent form (ICF), any untoward event occurring with the participant was reported by investigators as an AE. For each reported event, investigators were asked if they considered the event to be a complication of influenza. When answered yes, additional data related to that event was collected when available. A blinded AC was established to adjudicate all reported AEs as complications of influenza based on predefined criteria.

Based on the collected data, events identified as complications by investigators were categorized into pulmonary versus extrapulmonary, major versus minor, as well as infectious versus noninfectious complications of influenza:

- Pulmonary complications: respiratory failure, primary viral pneumonia, secondary bacterial pneumonia (including pneumonia attributable to unusual pathogens), exacerbations of chronic underlying pulmonary diseases such as COPD and asthma, and bronchitis.
- Extrapulmonary complications: cardiovascular and cerebrovascular disease, muscular disorders, CNS involvement, acute exacerbation of chronic kidney disease, decompensation of previously controlled diabetes mellitus, and other infections (eg, sinusitis, otitis).

Patient-reported Outcomes

The following PRO assessments were included in the study: Influenza Symptom Diary, Patient Global Impression of Severity (PGIS), Patient Global Impression of Change (PGIC), EQ-5D, and Assessment of Daily Activities Resumption.

Viral Kinetics (Nasal MT Swabs)

Influenza viral load was quantified in nasal MT swab samples (and endotracheal aspirates in participants who were intubated) taken throughout the study at approximately the same time (±4 hours) on each sampling day. Nasal MT swabs were analyzed centrally using qRT-PCR and viral culture.

Resistance Evaluations

Nasal MT swabs and endotracheal samples were used for sequence analysis of the polymerase basic protein (PB)2 region of the influenza polymerase gene, and of neuraminidase (NA) (and hemagglutinin [HA], if applicable) genes for participants using an NA inhibitor (NAI) as part of their SOC. For some participants, the polymerase acidic protein (PA) and PB1 regions of the influenza polymerase were sequenced as well. In addition, nasal MT swabs and endotracheal samples were used for the analysis of phenotypic resistance against pimodivir and other antivirals, if applicable.

Pharmacokinetics

Sparse PK plasma samples were analyzed to determine concentrations of pimodivir using a validated, specific, and sensitive liquid chromatography-mass spectrometry/mass spectrometry method.

Taste and Swallowability

A taste and swallowability questionnaire was completed by adolescent participants within approximately 15 minutes after the first and last intake of the pimodivir or placebo tablet.

Safety Evaluations

Safety and tolerability were evaluated throughout the study from signing the ICF/assent form onwards until the last study-related activity. Safety evaluations included monitoring of AEs (including description, classification, and severity), clinical laboratory tests (hematology, serum chemistry, and urinalysis), ECG, vital signs, and physical examinations.

Sample Size Determination

The study planned to enroll 600 participants between the ages of 13 and 85 years, inclusive. The sample size was based on the primary endpoint of the Hospital Recovery Scale at Day 6. Based on the proportional odds model and assuming a benefit of approximately 38% reduction of the common odds ratio, a total sample size of 600 participants (randomized 1:1) was required to obtain a power of 90%. Inclusion of stratification factors could provide some improvement on the derived power.

In the sample size calculation, it was assumed that the distribution of participants treated with placebo in combination with SOC treatment would be as follows on Day 6: 30% not hospitalized, 30% non-ICU hospitalization, not requiring supplemental oxygen, 25% non-ICU hospitalization, requiring supplemental oxygen, 5% admitted to the ICU, not requiring invasive mechanical ventilation, 5% requiring invasive mechanical ventilation, and 5% death. This sample size was robust to mild to moderate changes in this distribution.

Statistical Methods

This report describes the final analysis of the results of Study 63623872FLZ3001. Due to the early termination of the study, only a limited analysis was performed on the available data. An overview of the analyses that were actually performed is provided in the below sections.

Data were analyzed based on the following populations:

- The ITT-i Set included all randomized participants who received at least 1 dose of study drug and who had a confirmed infection with influenza A and were analyzed by planned treatment.

- The OST ITT-i Set included the subset of participants from the ITT-i Set whose SOC treatment contains OST (first dose of OST could be given before the participant was randomized but no later than the day of first study drug intake).
- The Safety Set (or all participants treated) included all participants who received at least one dose of study drug and were analyzed by treatment arm as treated.

Efficacy Analyses

Primary Efficacy Analysis

The analysis on the primary endpoint was done for all participants and per subgroup for time since onset of influenza symptoms (≤72 hours, >72 hours, based on actual time since onset, not as randomized). This analysis was also performed on the subset of participants for whom OST was part of their SOC. A frequency tabulation of the Hospital Recovery Scale categories on Day 6 per treatment arm was shown. A proportional odds model was used to analyze the Hospital Recovery Scale on Day 6, estimating the common odds ratio of active treatment versus placebo. The model included treatment, Hospital Recovery Scale category at baseline and the stratification factors (screening NEWS2, type of baseline SOC, and time since onset of influenza symptoms). In a first step equal slopes (ie, proportional odds) for the treatment effect only and unequal slopes for the other covariates were modeled. If this model would not fit, a full proportional odds model was applied, ie, implying proportional odds for all covariates in the model. The common odds ratio from the final model was considered as the estimate of the treatment effect. The actual values of the stratification factors were used for all models, if they were incorrectly derived at the time of randomization. The proportional odds model was defined in such a way that a common odds ratio smaller than 1 indicated treatment benefit of pimodivir + SOC over placebo + SOC.

The proportional odds assumption was assessed by testing for parallel slopes in the final model for the treatment effect only. The Hospital Recovery Scale was also analyzed using the Van Elteren test with strata defined by the stratification factors. In case the proportional odds assumption on the treatment effect was violated, the p-value of the Van Elteren test was used for the formal testing.

Secondary Efficacy Analysis

The time to hospital discharge was analyzed using a stratified Gehan-Wilcoxon test with the strata screening NEWS2, type of baseline SOC, and time since onset of influenza symptoms. The analysis was summarized by providing the number of participants included in the analysis, number of participants censored, 25th and 75th percentiles, and median time-to-event with 95% CIs based on log-log transformation method. The data was presented graphically by means of Kaplan-Meier plots. This analysis was repeated for the subgroup time since onset of influenza symptoms.

For proportion of participants with any treatment-emergent adjudicated influenza complications, a logistic regression model (applying Firth's penalized likelihood approach), with treatment arm and stratification factors as fixed effects, was used to analyze the binary outcome and to obtain the odds ratios (95% CI) for the comparison of active treatment versus placebo. Frequency tabulations of adjudicated influenza complications were created by treatment arm and repeated by time of onset of symptoms.

Viral load and viral titer over time were analyzed descriptively.

Genotypic Resistance Analysis

The available genotypic resistance data were analyzed descriptively.

Pharmacokinetics

Pimodivir plasma concentrations were analyzed descriptively and listed.

Safety Analyses

Safety parameters were analyzed, as appropriate, by means of descriptive statistics, frequency, and worst-case cross-tabulations.

RESULTS

STUDY POPULATION

Overall, 334 participants were randomized, of which 326 (97.6%) participants were treated (and included in the Safety Set). Of the 334 randomized participants, 318 were treated and had a laboratory-confirmed influenza A infection and were included in the ITT-i Set. Eight participants were randomized but not treated and in 8 (2.4%) of the 334 randomized participants, influenza A infection was not confirmed by the central lab qRT-PCR test. These 16 participants were not included in the ITT-i Set. The OST ITT-i Set (ie, subset from ITT-i Set whose SOC treatment contained OST) included 296 participants.

All 326 randomized and treated participants were analyzed in the Safety Set, ie, 163 participants in the pimodivir + SOC arm and 163 participants in the placebo + SOC arm. Of the 326 participants, 26 (8.0%) participants discontinued the treatment (10 [6.1%] and 16 [9.8%] participants, respectively). The main reason for discontinuation of the treatment was withdrawal by participant (9 [2.8%] participants in total, with 3 [1.8%] and 6 [3.7%] participants, respectively).

The majority of participants in the Safety Set received 10 doses of pimodivir or matched placebo. Three participants in the pimodivir + SOC and 7 participants in the placebo + SOC arm received extended treatment.

Major protocol deviations were observed in 58 (35.6%) participants in the pimodivir + SOC arm and 59 (36.2%) participants in the placebo + SOC arm. The majority of major protocol deviations (ie, in 32 [19.6%] and 37 [22.7%] participants, respectively) were classified based on predefined criteria to belong to the group of violations related to the timing and order of assessments and assessment of eligibility criteria (NEWS2 and oxygen saturation) during screening. These violations occurred mostly at the start of the study. After a quality plan was implemented, the number of major protocol deviations decreased. It should also be noted that some sites only enrolled one or a few participants and, additionally, the seasonality of the influenza season did not allow sites to develop routine in the study conduct. Re-training on the protocol and conduct of the study was foreseen at the start of each influenza season. These major protocol deviations did not impact the outcome of the study as the majority occurred during screening and the deviations did not affect the primary efficacy analysis performed on the ITT-i Set.

Minor protocol deviations related to COVID-19 were observed in 5 (3.1%) participants in the pimodivir + SOC arm and 9 (5.5%) participants in the placebo + SOC arm. These minor protocol deviations did not affect the outcome of these participants in the study. None of the participants had a major protocol deviation related to COVID-19.

Demographic and baseline disease characteristics of the Safety Set are presented in the table below. The demographics and baseline characteristics were balanced between the treatment arms, with a higher percentage of females (56.4% vs 46.0%) and lower percentage of antiviral treatment use as part of SOC (90.8% vs 95.1%) in the pimodivir + SOC arm compared to the placebo + SOC arm.

Demographic and Baseline Disease Characteristics; Safety Set (Study 63623872FLZ3001)

	Pimodivir + SOC	Placebo + SOC	All Subjects
Analysis set: Safety Set	163	163	326
Sex			
N	163	163	326
Female	92 (56.4%)	75 (46.0%)	167 (51.2%)
Male	71 (43.6%)	88 (54.0%)	159 (48.8%)
Race			
N	160	158	318
American Indian or Alaska Native	4 (2.5%)	2 (1.3%)	6 (1.9%)
Asian	34 (21.3%)	30 (19.0%)	64 (20.1%)
Black or African American	5 (3.1%)	11 (7.0%)	16 (5.0%)
Multiple	3 (1.9%)	0	3 (0.9%)
Native Hawaiian or Other Pacific Islander	1 (0.6%)	1 (0.6%)	2 (0.6%)
White	113 (70.6%)	114 (72.2%)	227 (71.4%)
Missing	3	5	8
Age (years)			
N	163	163	326
Mean (S.D.)	59.7 (15.46)	57.7 (16.88)	58.7 (16.20)
Median	62.0	60.0	61.5
Min; Max	(17; 85)	(13; 84)	(13; 85)
Age (categories)			
N	163	163	326
≥13 - <18 Years	1 (0.6%)	3 (1.8%)	4 (1.2%)
≥18 - ≤65 Years	95 (58.3%)	97 (59.5%)	192 (58.9%)
>65 - ≤85 Years	67 (41.1%)	63 (38.7%)	130 (39.9%)
Body mass index (kg/m²)			
N	162	161	323
Mean (S.D.)	29.46 (7.818)	29.00 (6.797)	29.23 (7.319)
Median	27.90	27.80	27.90
Min; Max	(18.5; 70.3)	(15.2; 48.7)	(15.2; 70.3)
NEWS2 Score at screening, actual			
N	163	163	326
4-5	61 (37.4%)	62 (38.0%)	123 (37.7%)
>5	102 (62.6%)	101 (62.0%)	203 (62.3%)
Type of baseline SOC, actual			
N	163	163	326
Including influenza antiviral treatment	148 (90.8%)	155 (95.1%)	303 (92.9%)
Oseltamivir	148 (90.8%)	155 (95.1%)	303 (92.9%)
Peramivir	1 (0.6%)	0	1 (0.3%)
Not including influenza antiviral treatment	15 (9.2%)	8 (4.9%)	23 (7.1%)
OST as part of SOC treatment			
N	163	163	326
No	15 (9.2%)	8 (4.9%)	23 (7.1%)
Yes	148 (90.8%)	155 (95.1%)	303 (92.9%)
Time since onset of Influenza, actual			
N	163	163	326
≤72 hours	130 (79.8%)	130 (79.8%)	260 (79.8%)
>72 - ≤96 hours	33 (20.2%)	33 (20.2%)	66 (20.2%)
Temperature (C)			
N	163	163	326
Mean (S.D.)	37.34 (0.963)	37.37 (0.904)	37.35 (0.932)
Median	37.10	37.10	37.10
Min; Max	(35.0; 39.8)	(34.3; 39.5)	(34.3; 39.8)
Supplemental oxygen at baseline			
N	163	163	326
No	73 (44.8%)	79 (48.5%)	152 (46.6%)
Yes	90 (55.2%)	84 (51.5%)	174 (53.4%)
In ICU at baseline			
N	163	163	326
No	144 (88.3%)	140 (85.9%)	284 (87.1%)
Yes	19 (11.7%)	23 (14.1%)	42 (12.9%)

Demographic and Baseline Disease Characteristics; Safety Set (Study 63623872FLZ3001)

	Pimodivir + SOC	Placebo + SOC	All Subjects
Primary reason for hospitalization			
N	163	163	326
Influenza infection	153 (93.9%)	155 (95.1%)	308 (94.5%)
Medical history	10 (6.1%)	6 (3.7%)	16 (4.9%)
Other	0	2 (1.2%)	2 (0.6%)

EFFICACY RESULTS

Primary Efficacy Analysis

ITT-i Set

Overall, treatment of pimodivir + SOC showed no benefit over placebo + SOC on the Hospital Recovery Scale on Day 6, as expressed by an estimated common odds ratio (95% CI) adjusted for Hospital Recovery Scale category at baseline and the stratification factors screening NEWS2, type of baseline SOC, and time since onset of influenza symptoms of 0.943 (0.609; 1.462) (p-value = 0.397). The proportional odds assumption was not violated.

For the subgroup of participants with onset of symptoms ≤72 hours, the common odds ratio adjusted for Hospital Recovery Scale category at baseline and the stratification factors was 0.934 (0.571; 1.529), indicating a similar treatment result as for the full ITT-i Set (n=128 and 126 for the pimodivir + SOC arm and placebo + SOC arm, respectively).

For the subgroup of participants with onset of symptoms >72 hours, the common odds ratio adjusted for Hospital Recovery Scale category at baseline and the stratification factors was 1.009 (0.376; 2.708), indicating no difference in treatment with pimodivir + SOC (n=31) or treatment with placebo + SOC (n=33).

Primary Endpoint: Hospital Recovery Scale on Day 6; Intent-To-Treat Infected (Study 63623872FLZ3001)		
	Pimodivir + SOC	Placebo + SOC
Any time since onset influenza		
Analysis set: intent-to-treat infected	159	159
Not hospitalized	73 (48.0%)	69 (47.6%)
Non-ICU hospitalization, not requiring supplemental oxygen	50 (32.9%)	42 (29.0%)
Non-ICU hospitalization, requiring supplemental oxygen	18 (11.8%)	25 (17.2%)
Admitted to the ICU, not requiring invasive mechanical ventilation	6 (3.9%)	6 (4.1%)
Requiring invasive mechanical ventilation	2 (1.3%)	3 (2.1%)
Death	3 (2.0%)	0
Common odds ratio		
Estimate	0.943	
95% Confidence interval	[0.609,1.462]	
P-value[a]	0.397	
Test for parallel slopes for treatment p-value[b]	0.746	
Van Elteren test p-value[a]	0.366	

Note: - Model structure includes treatment, baseline hospital recovery scale and stratification factors: screening NEWS2, type of SOC and time since onset of influenza at baseline.
- The categories presented are number 1. Not hospitalized, 2. Non-ICU hospitalization, not requiring supplemental oxygen, 3. Non-ICU hospitalization, requiring supplemental oxygen, 4. Admitted to ICU, not requiring invasive mechanical ventilation, 5. Requiring invasive mechanical ventilation, 6. Death.
- The odds ratios presented are reflecting the comparison of better versus worse.

The fitted model is a full proportional odds model, assuming equal slopes for all covariates in the model.
[a]: One-sided p-value
[b]: Test for parallel slopes to assess the proportional odds assumption on treatment effect only.

OST ITT-i Set

Similar results were obtained when performing the analysis on the ITT-i Set only including participants having OST as part of their SOC (ie, referred to as the OST ITT-i Set): common odds ratio = 1.030 (0.655; 1.619) (p-value = 0.551).

Secondary Efficacy Analysis

Time to Hospital Discharge

Overall, a similar median (95% CI) time to hospital discharge was estimated in the pimodivir + SOC arm compared with the placebo + SOC arm (113.00 [94.20; 118.50] hours and 108.00 [92.70; 116.30] hours, respectively; Gehan-Wilcoxon test p-value = 0.4305).

For the subgroup with time since onset of influenza ≤72 hours, the estimated median (95% CI) time to hospital discharge was similar to the overall participant population: ie, 111.00 (87.90; 118.50) hours in the pimodivir + SOC arm (n=128) and 105.50 (90.00; 116.30) hours in the placebo + SOC arm (n=126).

For the subgroup with time since onset of influenza >72 hours, there was no relevant difference between the pimodivir + SOC arm and the placebo + SOC arm (estimated median [95% CI] time to hospital discharge of 117.30 [65.60; 137.70] hours and 111.20 [48.30; 119.80] hours, respectively; sample size n=31 and 33).

Kaplan-Meier Estimates of Time to Hospital Discharge; Intent-To-Treat Infected (Study 63623872FLZ3001)

	Pimodivir + SOC	Placebo + SOC
Analysis set: intent-to-treat infected	159	159
25th quantile	47.70	48.30
(95% CI)	(43.60; 68.30)	(41.10; 68.40)
50th quantile	113.00	108.00
(95% CI)	(94.20;118.50)	(92.70;116.30)
75th quantile	139.00	148.70
(95% CI)	(123.00;164.50)	(137.00;173.00)
Number assessed	159	159
Number censored	7	15
Number with event	152	144
P-value Gehan-Wilcoxon test[a]	0.4305	

[a]: One-sided p-value
The Gehan-Wilcoxon test is calculated with the actual value of the stratification factors: type of baseline SOC, time of onset of symptoms and screening NEWS2.

Treatment-emergent Adjudicated Influenza Complications

Overall, the incidence of adjudicated influenza complications was similar in the pimodivir + SOC arm compared to the placebo + SOC arm (17.6% [28/159] and 18.2% [29/159], respectively). The corresponding odds ratio (95% CI) adjusted for the stratification factors was 0.967 (0.545, 1.716) (p-value = 0.4549). For the subgroups with time since onset of influenza ≤72 hours and >72 hours, results for adjudicated influenza complications were similar to the overall participant population.

Incidence of Adjudicated Influenza Complications; Intent-To-Treat Infected (Study 63623872FLZ3001)

	Pimodivir + SOC	Placebo + SOC
Any time since onset influenza		
Analysis set: Intent-To-Treat Infected	159	159
Adjudicated influenza complications present	28 (17.6%)	29 (18.2%)
Adjudicated influenza complications absent	131 (82.4%)	130 (81.8%)
Odds-ratio between treatments	0.967	
[95% CI]	[0.545,1.716]	
P-value[a]	0.4549	

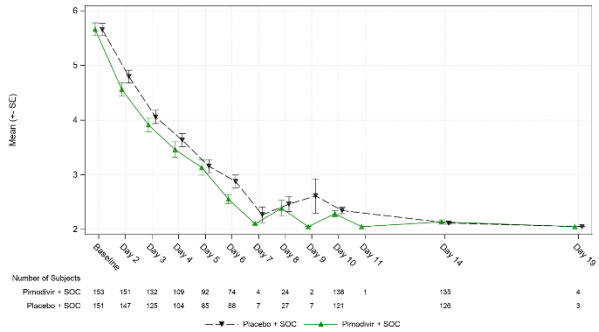
[a]: One-sided p-value
The model consists of a logistic regression model (applying Firth's penalized likelihood approach), with treatment group and stratification factors as fixed effects.
For some subjects not all of the adverse events were adjudicated. These subjects are included in the influenza complications absent category.

Viral Load and Viral Titer Over Time

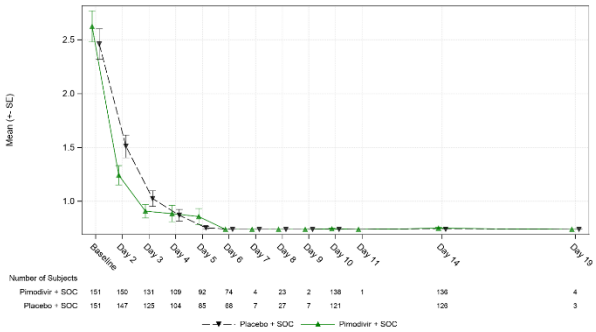
Mean $\log_{10}$ viral load (as measured by qRT-PCR) and mean $\log_{10}$ viral titer (as measured by viral culture) was reduced faster in the pimodivir + SOC arm compared to the placebo + SOC arm.

Mean-SE Plot of Actual Values of Log_{10} Viral Load by qRT-PCR and Log_{10} Viral Titer Over Time; Intent-To-Treat Infected; (Study 63623872FLZ3001)

Log_{10} Viral Load



Log_{10} Viral Titer



Resistance Results

Treatment-emergent mutations in PB2 were observed in 2 of 168 participants with available data (ie, 1.2%). One participant had emerging S324I on Day 14, the other participant had emerging K376R+N510K on Day 5.

PHARMACOKINETIC RESULTS

Plasma concentrations of pimodivir were measured and were in line with those observed in previous studies using the same dose regimen.

SAFETY RESULTS

The AEs discussed in this section are treatment-emergent events that were reported after study treatment start, unless specified otherwise.

Pimodivir + SOC was generally safe and well tolerated in this population of hospitalized influenza A-infected participants and the safety profile was similar to the profile of treatment with placebo + SOC.

Adverse Events

Treatment-Emergent Adverse Events Summary Table; Safety Set (Study 63623872FLZ3001)

	Pimodivir + SOC	Placebo + SOC
Analysis set: safety set	163	163
Treatment + Follow-up phase	163	163
Any TEAE	85 (52.1%)	84 (51.5%)
Any serious TEAE	13 (8.0%)	15 (9.2%)
Any TEAE with fatal outcome	4 (2.5%)	0
Any TEAE of worst grade 3 or 4	13 (8.0%)	16 (9.8%)
Any TEAE of worst grade 3	8 (4.9%)	13 (8.0%)
Any TEAE of worst grade 4	5 (3.1%)	3 (1.8%)
Any TEAE at least possibly related to Pimodivir/Placebo	24 (14.7%)	23 (14.1%)
Any TEAE leading to temporary withdrawal of Pimodivir/Placebo	0	1 (0.6%)
Any TEAE leading to permanent withdrawal of Pimodivir/Placebo	1 (0.6%)	5 (3.1%)
Any TEAE leading to study discontinuation	0	0
Any serious TEAE at least possibly related to Pimodivir/Placebo	0	1 (0.6%)

In this study, 85 (52.1%) participants in the pimodivir + SOC arm and 84 (51.5%) participants in the placebo + SOC arm experienced at least 1 treatment-emergent AE (TEAE). The most frequently reported

TEAEs during the study (reported in at least 5.0% of participants within any treatment arm) by preferred term were diarrhea (16 [9.8%] and 15 [9.2%] participants, respectively) and hypertension (11 [6.7%] and 3 [1.8%] participants, respectively).

During the study, 24 (14.7%) participants in the pimodivir + SOC arm and 23 (14.1%) participants in the placebo + SOC arm experienced TEAEs at least possibly related to the study treatment. The most frequently reported TEAEs (reported in at least 2.0% of participants within a treatment arm) at least possibly related to the study treatment by the investigator were diarrhea (11 [6.7%] and 8 [4.9%] participants, respectively) and nausea (2 [1.2%] and 4 [2.5%] participants, respectively).

Overall, 13 (8.0%) and 16 (9.8%) participants in the pimodivir + SOC arm and placebo + SOC arm, respectively, reported severe or life-threatening (ie, grade 3 or 4) TEAEs. Each of these AEs was reported in at most 1 participant per treatment arm, except for cardiac arrest (2 [1.2%] participants in the pimodivir + SOC arm), pneumonia bacterial (2 [1.2%] participants in the placebo + SOC arm), and hyperglycemia (3 [1.8%] participants in the placebo + SOC arm). No grade 3 or 4 TEAEs considered at least possibly related to study treatment were reported in the pimodivir + SOC arm. A grade 3 TEAE of hepatitis toxic at least possibly related to the study treatment was experienced by 1 participant in the placebo + SOC arm.

During the study, anticipated events were reported by 10 (6.1%) participants in the pimodivir + SOC arm and by 8 (4.9%) participants in the placebo + SOC arm. The most frequently reported anticipated events were infections and infestations in both treatment arms. Incidences did not differ significantly between the treatment arms. Influenza-related complications reported by investigators were observed in 31 (19.0%) participants in the pimodivir + SOC arm and 33 (20.2%) participants in the placebo + SOC arm. The most frequently reported influenza-related complications by investigators (reported in at least 3 participants within a treatment arm) were diarrhea (3 [1.8%] and 2 [1.2%] participants, respectively) and dyspnea (3 [1.8%] and 0 participants, respectively). During the study, adjudicated complications associated with influenza were reported by 29 (17.8%) participants in both the pimodivir + SOC arm and the placebo + SOC arm. The most frequently reported adjudicated complication associated with influenza (reported in at least 3 participants within a treatment arm) was pneumonia (3 [1.8%] and 2 [1.2%] participants, respectively).

No COVID-19-related TEAEs were reported.

For 4 participants, a fatal TEAE was reported in the pimodivir + SOC arm during this study; none were considered to be related to the study treatment. For 3 participants, the fatal TEAE was reported during the treatment phase (ie, grade 4 cardiac failure congestive, grade 4 cardiac arrest, and grade 3 septic shock in 1 participant each). For 1 participant, the fatal TEAE was reported during the follow-up phase (ie, grade 4 dyspnea). No AEs with fatal outcome were reported in the placebo + SOC arm during this study.

During the study, at least 1 SAE was reported by 13 (8.0%) participants in the pimodivir + SOC arm and 15 (9.2%) participants in the placebo + SOC arm. By preferred term, none of the SAEs were reported by more than 1 participant per treatment arm, except for cardiac arrest reported in 2 (1.2%) participants in the pimodivir + SOC arm. One SAE in the placebo + SOC arm was considered at least possibly related to the study treatment (ie, grade 2 drug hypersensitivity).

Treatment-emergent AEs resulting in permanent discontinuation of study treatment were reported by 1 (0.6%) participant in the pimodivir + SOC arm and 5 (3.1%) participants in the placebo + SOC arm. By preferred term, none of the TEAEs resulting in permanent discontinuation of study treatment were reported by more than 1 participant per treatment arm, except for nausea reported in 2 (1.2%) participants in the placebo + SOC arm. In the pimodivir + SOC arm, the TEAE resulting in permanent discontinuation of study treatment cardiac failure congestive was considered not related to the study treatment. In the placebo + SOC arm, all TEAEs leading to permanent discontinuation of study treatment were considered at least possibly related to the study treatment.

No clinically relevant differences in the overall incidence of AEs, SAEs, and AEs leading to permanent discontinuation of study treatment were noted between the treatment arms.

Clinical Laboratory Evaluation

The most frequent (ie, >10% of participants in any treatment arm) graded (any grade) treatment-emergent laboratory toxicitiesduring treatment and follow-up phase are presented in the table below. No clinically relevant differences were observed between the pimodivir + SOC and the placebo + SOC arm.

Tabulation of the Worst Treatment-emergent Toxicity Grades for Laboratory Parameters With at Least One Treatment-emergent Grade 2 Toxicity (>10% of Participants in Any Treatment Arm); Safety Set (Study 63623872FLZ3001)

	Pimodivir + SOC	Placebo + SOC
Treatment + Follow-up phase		
Alanine aminotransferase		
N	160	153
Grade 1	20 (12.5%)	29 (19.0%)
Grade 2	6 (3.8%)	8 (5.2%)
Grade 3	0	1 (0.7%)
Grade 4	0	0
Amylase		
N	160	153
Grade 1	15 (9.4%)	16 (10.5%)
Grade 2	7 (4.4%)	11 (7.2%)
Grade 3	5 (3.1%)	8 (5.2%)
Grade 4	0	0
Aspartate aminotransferase		
N	158	152
Grade 1	12 (7.6%)	21 (13.8%)
Grade 2	4 (2.5%)	7 (4.6%)
Grade 3	1 (0.6%)	1 (0.7%)
Grade 4	0	1 (0.7%)
Gamma glutamyl transferase		
N	161	153
Grade 1	5 (3.1%)	18 (11.8%)
Grade 2	3 (1.9%)	5 (3.3%)
Grade 3	3 (1.9%)	2 (1.3%)
Grade 4	2 (1.2%)	1 (0.7%)
Hyperglycemia		
N	160	153
Grade 1	28 (17.5%)	30 (19.6%)
Grade 2	12 (7.5%)	23 (15.0%)
Grade 3	8 (5.0%)	9 (5.9%)
Grade 4	0	1 (0.7%)
Hypernatremia		
N	160	153
Grade 1	20 (12.5%)	15 (9.8%)
Grade 2	2 (1.3%)	4 (2.6%)
Grade 3	0	0
Grade 4	0	0
Hypokalemia		
N	160	153
Grade 1	19 (11.9%)	11 (7.2%)
Grade 2	1 (0.6%)	1 (0.7%)
Grade 3	0	0
Grade 4	0	0
Hyponatremia		
N	160	153
Grade 1	9 (5.6%)	15 (9.8%)
Grade 2	2 (1.3%)	2 (1.3%)
Grade 3	0	0
Grade 4	0	0
Hypophosphatemia		

Tabulation of the Worst Treatment-emergent Toxicity Grades for Laboratory Parameters With at Least One Treatment-emergent Grade 2 Toxicity (>10% of Participants in Any Treatment Arm); Safety Set (Study 63623872FLZ3001)

	Pimodivir + SOC	Placebo + SOC
N	161	153
Grade 1	18 (11.2%)	14 (9.2%)
Grade 2	10 (6.2%)	8 (5.2%)
Grade 3	2 (1.2%)	4 (2.6%)
Grade 4	0	1 (0.7%)
Absolute neutrophil count		
N	159	152
Grade 1	10 (6.3%)	5 (3.3%)
Grade 2	4 (2.5%)	4 (2.6%)
Grade 3	3 (1.9%)	0
Grade 4	0	0
Proteinuria		
N	154	149
Grade 1	27 (17.5%)	15 (10.1%)
Grade 2	16 (10.4%)	13 (8.7%)
Grade 3	0	0
Grade 4	0	0

N = number of subjects with data; n = number of subjects with that worst toxicity.
Notes: Unscheduled time points, if any, are also considered in this display.
A toxicity is treatment-emergent if it is worse than the baseline.
An abnormality (toxicity grade or abnormality based on normal ranges) will be considered treatment-emergent if it is worse than the baseline value.
If the baseline is missing, the toxicity is always considered as treatment-emergent.
Only laboratory parameters with at least one worst treatment-emergent toxicity grade ≥2 were included.

During the study, the following treatment-emergent laboratory toxicities of grade 3 or 4 were reported in more than 2 participants per treatment arm: hyperglycemia in 8 (5.0%) participants in the pimodivir + SOC arm and 10 (6.5%) participants in the placebo + SOC arm, increased amylase in 5 (3.1%) and 8 (5.2%) participants, respectively, increased gamma glutamyltransferase in 5 (3.1%) and 3 (2.0%) participants, respectively, decreased absolute neutrophil count in 3 (1.9%) and 0 participants, respectively, hypophosphatemia in 2 (1.2%) and 5 (3.3%) participants, respectively, and increased creatinine in 2 (1.3%) and 3 (2.0%) participants, respectively.

During the study, the most frequent (ie, >20% of participants in any treatment arm with at least 20 participants for which the laboratory parameter was assessed) non-graded treatment-emergent laboratory abnormalities were low direct bilirubin (51 [32.7%] participants in the pimodivir + SOC arm and 47 [31.1%] participants in the placebo + SOC arm), high triglycerides (42 [26.3%] and 29 [19.0%] participants, respectively), high erythrocytes (/high power field [HPF]) (19 [25.3%] and 14 [20.3%] participants, respectively), high leukocytes (/HPF) (23 [24.0%] and 18 [20.7%] participants, respectively), low neutrophils (segmented) (33 [20.8%] and 17 [11.2%] participants, respectively), high leukocytes (31 [19.5%] and 38 [25.0%] participants, respectively), high neutrophils (segmented) (31 [19.5%] and 31 [20.4%] participants, respectively), low high-density lipoprotein cholesterol (24 [14.9%] and 31 [20.3%] participants, respectively), and high lactate dehydrogenase (20 [12.7%] and 37 [24.7%] participants, respectively).

No clinically relevant differences were observed for laboratory parameters between the pimodivir + SOC and the placebo + SOC arm.

Other Safety Observations

There were no clinically relevant changes over time in vital signs or ECG parameters. The incidence of ECG-related abnormalities was low in both treatment arms. No meaningful differences in the incidence of ECG-related abnormalities or vital signs-related abnormalities were observed between the treatment arms.

Overall, mean NEWS2 score was similar in both treatment arms throughout the study. In both treatment arms, there was a trend for decreasing NEWS2 scores over time.

STUDY LIMITATIONS

During the COVID-19 pandemic, which started at the end of the 2019-2020 influenza season in the Northern Hemisphere, recruitment for the study slowed down and eventually stopped, which caused significant delay in the enrollment of the study.

As the study was terminated early after a pre-planned interim analysis, the Sponsor performed a limited analysis on the available data to meet the requirement for reporting the study results. The presented results are based on a considerably lower sample size than planned per protocol (ie, approximately 50% lower).

CONCLUSIONS

- Overall, this study did not demonstrate a benefit, in terms of clinical efficacy, of treatment with pimodivir + SOC over treatment with placebo + SOC in hospitalized, influenza A-infected participants.
- Treatment of pimodivir + SOC showed no benefit over placebo + SOC on the Hospital Recovery Scale on Day 6 in the ITT-i Set, as expressed by an estimated common odds ratio (95% CI) adjusted for Hospital Recovery Scale category at baseline and the stratification factors screening NEWS2, type of baseline SOC, and time since onset of influenza symptoms of 0.943 (0.609; 1.462) (p-value = 0.397).
- In the ITT-i Set, the median (95% CI) time to hospital discharge was 113.00 (94.20; 118.50) hours in the pimodivir + SOC arm and 108.00 (92.70; 116.30) hours in the placebo + SOC arm. The incidence of adjudicated influenza complications in the ITT-i Set was similar in the pimodivir + SOC arm compared to the placebo + SOC arm (17.6% and 18.2%, respectively). Viral load, as measured by qRT-PCR and viral culture titer, was reduced faster in the pimodivir + SOC arm compared to the placebo + SOC arm.
- Treatment-emergent mutations in PB2 were observed in 2 of 168 participants with available data (ie, 1.2%).
- Pimodivir 600 mg bid in combination with SOC was generally safe and well tolerated in this population of hospitalized influenza A-infected patients. For 4 participants, a fatal TEAE was reported in the pimodivir + SOC arm during this study (for 3 participants during treatment period and for 1 participant during follow-up period); all were considered not related to study treatment. Treatment-emergent SAEs were reported by 13 participants in the pimodivir + SOC arm and 15 participants in the placebo + SOC arm. None were considered related, except 1 event of drug hypersensitivity that was considered possibly related in the placebo + SOC arm. Overall, 52.1% of participants in the pimodivir + SOC arm and 51.5% of participants in the placebo + SOC arm experienced at least 1 TEAE during the study.

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