SYNOPSIS

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

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Status: Approved

Date: 2 February 2021

Prepared by: Janssen Research & Development

Protocol No.: 63623872FLZ3002

Title of Study: 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

EudraCT Number: 2017-002217-59

NCT No.: NCT03381196

Clinical Registry No.: CR108400

Study Center(s): 434 sites opened, of which 227 sites screened at least 1 participant. Of the 227 sites, 138 sites randomized at least one participant in this study and were located in Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, Estonia, France, Germany, Hungary, India, Italy, Korea, Latvia, Lithuania, Malaysia, Mexico, Poland, Russian Federation, South Africa, Spain, Sweden, Taiwan, Thailand, Turkey, Ukraine, the United Kingdom, and the United States of America.

Publication (Reference): None

Study Period: 24 January 2018 (Date first participant signed informed consent) to 24 August 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 63623872FLZ3002 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 followed by a sample size re-estimation and evaluation of futility for the primary endpoint, based on the new sample size. The IDMC informed the Sponsor Committee that no futility was noted on the efficacy endpoint assessed in the interim analysis, comparing treatment with pimodivir plus standard of care (SOC) to placebo plus SOC in participants at risk of developing complication due to influenza and recommended that Study 63623872FLZ3002 could be continued with modifications. However, considering that futility was observed in Study 63623872FLZ3001 (the companion Phase 3 study with pimodivir in hospitalized participants), the Sponsor made the strategic decision to also terminate Study 63623872FLZ3002 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], and vital signs), selected efficacy parameters (the primary parameter time to resolution of the 7 primary influenza symptoms and 3 secondary endpoints: incidence of hospital admission rate, 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 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 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 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 patient-reported outcome (PRO) measure Flu-iiQ™.
- To investigate the time to return to daily activities as assessed by the participant 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 quantitative real time polymerase chain reaction (qRT-PCR) and viral culture.

Hypothesis

The time to resolution of the 7 primary influenza-related symptoms, as assessed by a PRO measure (Flu-iiQ™), with pimodivir in combination with SOC treatment is statistically superior to treatment with

placebo in combination with SOC treatment in participants with influenza A infection who are at risk of developing complications.

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 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 participants with influenza A infection who were at risk of developing complications. The target population of the study were influenza-infected, non-hospitalized participants who, due to their age (65 to 85 years) or underlying comorbidities (regardless of age), were at increased risk of developing influenza-related complications.

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 ≤72 hours after onset of influenza symptoms. 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 Day 2 morning (up to noon). An influenza antiviral as part of the SOC could not be changed (eg, switching one influenza antiviral for another) during the 5-day 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 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 to ≤72 hours since onset of influenza symptoms). The study population had to consist of at least 60% of participants with first administration of study drug ≤48 hours since onset of influenza symptoms.

The study consisted 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.

Assessments to be performed during the study at specified time points included: the impact of influenza infection and its treatment (efficacy and safety) on clinical outcomes and patient-reported symptoms and functioning (using the Flu-iiQ^{TM} questionnaire), sparse blood samples for the measurement of pimodivir plasma concentrations, safety and tolerability (AEs, laboratory tests, ECG, vital signs, and physical examination), acceptability of the pimodivir formulation (only in adolescents), 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 re-estimate the study sample size based on the observed treatment effect and to perform an assessment of 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 360 and 540 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 April 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 that may have been missed, however, participants could complete their assessments on the PRO tool at home.

Number of Participants (Planned and Analyzed)

A target of 720 participants was planned to be randomly assigned in this study with 360 participants planned per treatment arm. Additionally, it was planned that 10% of the overall target of 720 participants in this study were to be adolescent participants (ie, a minimum of 72 adolescent participants). They were enrolled in selected countries and study sites consistent with local regulations.

At the time of study termination, 553 participants were randomized, of which 544 (98.4%) participants were treated (and included in the Safety Set). Of the randomized and treated participants, 446 had a laboratory-confirmed influenza A infection and were included in the Intent-To-Treat infected (ITT-i) Set. Seventeen (3.1%) 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 to 17 years) were enrolled in selected countries and study sites consistent with local regulations.
2. Presented to the clinic with symptoms suggestive of a diagnosis of acute influenza and had 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 participant’s ratings on the Pre-existing Symptom Questionnaire in the electronic PRO (ePRO) device. Symptoms had to include the following by category: respiratory symptoms (cough, sore throat, nasal congestion); 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 polymerase chain reaction (PCR)-based or other rapid molecular diagnostic assay.
4. Not in need of hospitalized medical care at screening. Emergency room or hospital observation status for an anticipated duration of <24 hours was not considered hospitalization as long as a determination of the need for hospitalization had not been made.
5. Enrollment and initiation of study drug treatment ≤72 hours after onset of influenza symptoms.
6. Participants 13 to 65 years of age, inclusive, also had to 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 pulmonary disease [COPD] or cystic fibrosis).
    c. Weakened immune system due to disease or medication (eg, participants 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 glomerular filtration rate (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 participants taking chronic systemic steroids).

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 were 633178, 633179, F0163B07, and F0222B56.

Duration of Treatment: The planned treatment duration for each participant was 5 days. The planned entire study duration for each participant was 28 days.

Criteria for Evaluation

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

Efficacy Evaluations

Efficacy was evaluated through PRO and viral kinetics. The following PRO assessments were included in the study: Flu-iiQ^{TM,} Pre-existing Symptom Questionnaire, Patient Global Impression of Severity (PGIS), Patient Global Impression of Change (PGIC), EQ-5D, and Assessment of Daily Activities Resumption. Influenza viral load was quantified in nasal MT swab samples 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 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 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 informed consent form (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 aimed to enroll 720 participants, with 360 participants per treatment arm. The sample size was 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, was based on the participants' ratings on 7 items from the symptoms domain of the Flu-iiQ^{TM} (cough, sore throat, headache, nasal congestion, feeling feverish, body aches and pains, and fatigue).

For the sample size, it was assumed that the recovery time was 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 was 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 was improved with 25% compared to placebo + SOC, a sample size of 600 participants (randomized 1:1) would have an estimated power of 90% as based on 10,000 simulations. It was expected that approximately 15% of the total enrolled participants would not be centrally-confirmed influenza A positive, resulting in a total of 720 participants planned to be enrolled.

Statistical Methods

This report describes the final analysis of the results of Study 63623872FLZ3002. 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 oseltamivir (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 had to be started no later than Day 2 morning).
- 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 median time to resolution of the 7 primary influenza-related symptoms (cough, sore throat, headache, nasal congestion, feeling feverish, body aches and pains, fatigue) was estimated using the Kaplan-Meier method. The difference in time to resolution of the 7 primary influenza-related symptoms between treatment arms was tested using a Gehan-Wilcoxon test controlling for the stratification factors, ie, type of baseline SOC and time since onset of symptoms. The time to resolution of the 7 primary influenza-related symptoms was also analyzed using the accelerated failure time (AFT) model with the log-logistic distribution. From this model, the adjusted geometric means per treatment arm, the acceleration failure time ratio of adjusted geometric means, and the 95% confidence intervals (CIs) were derived. Survival curves of the AFT model were provided.

Secondary Efficacy Analysis

The secondary efficacy analysis included the number and percentage of participants that were hospitalized after treatment initiation. A listing with details of the hospitalization was also provided.

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, 553 participants were randomized, of which 544 (98.4%) participants were treated (and included in the Safety Set). Nine participants were randomized but not treated. Of the randomized and treated participants, 446 participants had a laboratory-confirmed influenza A infection and were included in the ITT-i Set. In 98 (17.7%) participants, influenza A infection was not confirmed by the central laboratory qRT-PCR test. These 98 participants as well as 9 randomized but not treated 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 381 participants.

All 544 randomized and treated participants were analyzed in the Safety Set: ie, 273 participants in the pimodivir + SOC arm and 271 participants in the placebo + SOC arm. Of the 544 participants, 20 (3.7%) participants discontinued the treatment (with 12 [4.4%] and 8 [3.0%] participants, respectively). The main reason for discontinuation of the treatment was withdrawal by participant (13 [2.4%] participants in total, with 7 [2.6%] and 6 [2.2%] participants, respectively).

The majority of participants in the Safety Set received 10 doses of pimodivir or matched placebo.

Major protocol deviations were observed in 74 (27.1%) participants in the pimodivir + SOC arm and 89 (32.8%) participants in the placebo + SOC arm. The majority of major protocol deviations (ie, in 53 [19.4%] and 63 [23.3%] participants, respectively) were classified based on predefined criteria to belong to the group of violations related to the timing and order of assessments 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 2 (0.7%) participants in the pimodivir + SOC arm and 3 (1.1%) 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.

The most frequently reported risk factors for developing complications were chronic lung disease (in 358 [65.8%] participants, respectively) and weakened immune system (in 215 [39.5%] participants).

Demographic and Baseline Disease Characteristics; Safety Set (Study 63623872FLZ3002)

	Pimodivir + SOC	Placebo + SOC	All Subjects
Analysis set: safety set	273	271	544
Sex			
N	273	271	544
Female	152 (55.7%)	141 (52.0%)	293 (53.9%)
Male	121 (44.3%)	130 (48.0%)	251 (46.1%)
Race			
N	271	267	538
American Indian or Alaska Native	2 (0.7%)	4 (1.5%)	6 (1.1%)
Asian	27 (10.0%)	34 (12.7%)	61 (11.3%)
Black or African American	33 (12.2%)	28 (10.5%)	61 (11.3%)
Native Hawaiian or Other Pacific Islander	1 (0.4%)	0	1 (0.2%)
White	206 (76.0%)	201 (75.3%)	407 (75.7%)
Multiple	2 (0.7%)	0	2 (0.4%)
Missing	2	4	6
Age (years)			
N	273	271	544
Mean (S.D.)	51.1 (16.60)	50.3 (17.35)	50.7 (16.97)
Median	54.0	51.0	52.0
Min; Max	(14; 84)	(13; 85)	(13; 85)
≥13 - <18 Years	9 (3.3%)	8 (3.0%)	17 (3.1%)
≥18 - ≤65 Years	200 (73.3%)	195 (72.0%)	395 (72.6%)
>65 - ≤85 Years	64 (23.4%)	68 (25.1%)	132 (24.3%)
Body mass index (kg/m²)			
N	273	271	544
Mean (S.D.)	29.52 (7.256)	29.58 (7.028)	29.55 (7.137)
Median	28.10	28.20	28.10
Min; Max	(15.8; 63.0)	(13.0; 66.0)	(13.0; 66.0)
Type of baseline SOC, actual			
N	273	271	544
Including influenza antiviral treatment	232 (85.0%)	225 (83.0%)	457 (84.0%)
Oseltamivir	231 (84.6%)	223 (82.3%)	454 (83.5%)
Peramivir	0	2 (0.7%)	2 (0.4%)
Zanamivir	1 (0.4%)	0	1 (0.2%)
Not including influenza antiviral treatment	41 (15.0%)	46 (17.0%)	87 (16.0%)
OST as part of SOC treatment			
N	273	271	544
No	42 (15.4%)	48 (17.7%)	90 (16.5%)
Yes	231 (84.6%)	223 (82.3%)	454 (83.5%)
Time since onset, actual hours			
N	273	271	544
Mean (S.D.)	34.90 (15.662)	35.81 (14.335)	35.35 (15.009)
Median	32.53	33.08	33.06
Min; Max	(0.2; 72.0)	(2.1; 70.5)	(0.2; 72.0)
Time since onset of Influenza, actual			
N	273	271	544
≤48 hours	216 (79.1%)	215 (79.3%)	431 (79.2%)
>48 hours	57 (20.9%)	56 (20.7%)	113 (20.8%)
Temperature (C)			
N	264	260	524
Mean (S.D.)	37.54 (0.794)	37.63 (0.880)	37.58 (0.838)
Median	37.50	37.70	37.60
Min; Max	(35.2; 40.0)	(35.0; 40.0)	(35.0; 40.0)
Any risk factor for developing complications	259 (94.9)	260 (95.9)	519 (95.4)
>65 years of age	64 (23.4)	68 (25.1)	132 (24.3)
Cardiovascular or cerebrovascular disease	48 (17.6)	58 (21.4)	106 (19.5)
Chronic lung disease	186 (68.1)	172 (63.5)	358 (65.8)
Weakened immune system	106 (38.8)	109 (40.2)	215 (39.5)

N = number of subjects with data

EFFICACY RESULTS

Primary Efficacy Analysis

ITT-i Set

Overall, for the pimodivir + SOC arm, a shorter median (95% CI) time to resolution of the 7 primary influenza symptoms was estimated compared with the placebo + SOC arm (92.62 [77.60; 104.20] hours and 105.13 [92.73; 128.63] hours, respectively; Gehan-Wilcoxon test p-value = 0.0216). The AFT analysis, adjusted for type of baseline SOC, time since onset of symptoms, and baseline composite score, resulted in an estimated acceleration failure time ratio (95% CI) of 0.86 (0.71; 1.04), indicating an on average 14% shorter time to resolution of the 7 primary influenza symptoms for the pimodivir + SOC arm compared with the placebo + SOC arm.

For the subgroup of participants using influenza antivirals as part of their SOC (sample size n=190 and 187) and the subgroup with time since onset of influenza ≤48 hours (sample size n=173 and 172), the results for the estimated median (95% CI) time to resolution of the 7 primary influenza symptoms were similar to the overall ITT-i population (ie, faster resolution of symptoms in the pimodivir + SOC arm). The estimated median (95% CI) time to resolution of the 7 primary influenza symptoms was 92.07 (74.25; 102.57) hours in the pimodivir + SOC arm and 106.13 (92.73; 135.42) hours in the placebo + SOC arm for the subgroup of participants using influenza antivirals as part of their SOC and 92.20 (77.25; 105.03) hours and 112.85 (96.63; 138.13) hours, respectively, for the subgroup with time since onset of influenza ≤48 hours.

The estimated median (95% CI) time to resolution of the 7 primary influenza symptoms was 117.17 (67.55; 233.02) hours in the pimodivir + SOC arm and 97.28 (69.95; 138.13) hours in the placebo + SOC arm for the subgroup of participants not using influenza antivirals as part of their SOC (sample size n=29 and 31, respectively) and 97.38 (60.52; 160.82) hours and 89.23 (68.00; 132.28) hours, respectively, for the subgroup with time since onset of influenza >48 hours (sample size n=46 and 46, respectively).

Kaplan-Meier Estimates of Time to Resolution of 7 Primary Influenza-related Symptoms; Intent-To-Treat Infected (Study 63623872FLZ3002)

	Pimodivir + SOC	Placebo + SOC
Analysis Set: Intent-To-Treat Infected	223	223
All subjects		
Time to resolution (hours)		
25th quantile	46.23	66.22
(95% CI)	(41.93; 54.97)	(52.02; 69.95)
50th quantile	92.62	105.13
(95% CI)	(77.60;104.20)	(92.73;128.63)
75th quantile	185.78	188.07
(95% CI)	(152.45;233.02)	(161.58;234.15)
Number assessed	219	218
Number censored	22	16
Number with event	197	202
p-value Gehan-Wilcoxon test*	0.0216	

*: one-sided p-value of the stratified Gehan-Wilcoxon test

Accelerated Failure Time model of the Time to Resolution of 7 Primary Influenza Symptoms; Intent-To-Treat Infected (Study 63623872FLZ3002)

	Estimate	95% Confidence Interval	
		Lower Bound	Upper Bound
Adjusted geometric means of time to resolution of 7 primary influenza symptoms (hours):			
Pimodivir + SOC	96.04	79.26	116.37
Placebo + SOC	111.53	92.82	134.00
Pimodivir + SOC vs. Placebo + SOC (ratio)	0.86	0.71	1.04

Time to resolution is modelled by an accelerated failure time (AFT) model with the log-logistic distribution. The covariates are treatment, actual type of baseline SOC, actual time since onset of symptoms and the baseline composite score.

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 (further referred to as OST ITT-i Set).

In the OST ITT-i Set, for the pimodivir + SOC arm, a shorter median (95% CI) time to resolution of the 7 primary influenza symptoms was estimated compared with the placebo + SOC arm (92.07 [71.72; 102.57] hours and 110.77 [93.45; 137.08] hours, respectively; Gehan-Wilcoxon test p-value = 0.0135). The AFT analysis, adjusted for type of baseline SOC, time since onset of symptoms, and baseline composite score, resulted in an estimated acceleration failure time ratio (95% CI) of 0.80 (0.66; 0.98), indicating an on average 20% shorter time to resolution of the 7 primary influenza symptoms for the pimodivir + SOC arm compared with the placebo + SOC arm.

For the subgroup with time since onset of influenza ≤48 hours in the OST ITT-i Set (sample size n=147 and 144), the estimated median (95% CI) time to resolution of the 7 primary influenza symptoms were similar to the overall participant population: ie, 86.87 (68.98; 102.57) hours in the pimodivir + SOC arm and 124.78 (99.23; 144.35) hours in the placebo + SOC arm. For the subgroup with time since onset of influenza >48 hours in the OST ITT-i Set (sample size n=42 and 41), the estimated median (95% CI) time to resolution of the 7 primary influenza symptoms was 97.38 (68.78; 137.65) hours in the pimodivir + SOC arm and 88.63 (68.00; 139.92) hours in the placebo + SOC arm.

Kaplan-Meier Estimates of Time to Resolution of 7 Primary Influenza-related Symptoms; OST Intent-To-Treat Infected (Study 63623872FLZ3002)

	Pimodivir + SOC	Placebo + SOC
Analysis Set: OST Intent-To-Treat Infected	192	189
All subjects		
Time to resolution (hours)		
25th quantile	46.20	65.68
(95% CI)	(40.95; 53.60)	(46.70; 73.28)
50th quantile	92.07	110.77
(95% CI)	(71.72;102.57)	(93.45;137.08)
75th quantile	172.65	203.27
(95% CI)	(137.72;215.92)	(162.37;237.88)
Number assessed	189	185
Number censored	17	12
Number with event	172	173
p-value Gehan-Wilcoxon test*	0.0135	

*: one-sided p-value of the stratified Gehan-Wilcoxon test

Secondary Efficacy Analysis

Hospitalization

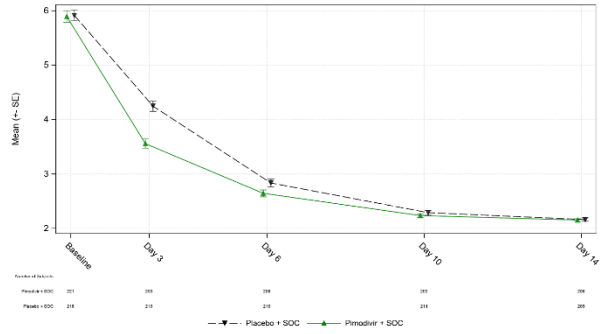
After treatment start, 4 (1.8%) participants in the pimodivir + SOC arm and 4 (1.8%) participants in the placebo + SOC arm were hospitalized for influenza complications.

Viral Load and Viral Titer Over Time

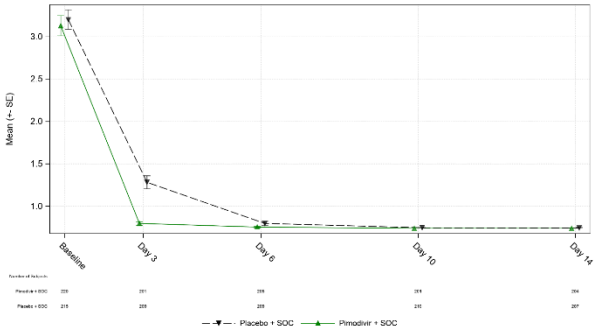
Mean log_{10} viral load (as measured by qRT-PCR) and mean log_{10} viral titer (as measured by viral culture) was reduced faster in the pimodivir + SOC arm compared to the placebo + SOC arm.

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 63623872FLZ3002)

Log_{10} Viral Load



Log_{10} Viral Titer



Resistance Results

Treatment-emergent mutations in PB2 were observed in 4 of 191 participants with available data (ie, 2.1%). One participant had emerging S324I on Day 6, one participant had emerging K376R on Day 6, one participant had emerging S324N on Day 6, and one participant had emerging S324G+K376R on Day 6.

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 participants at risk for influenza-related complications 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 63623872FLZ3002)

	Pimodivir + SOC	Placebo + SOC
Analysis set: safety set	273	271
Treatment + Follow-up phase	273	271
Any TEAE	123 (45.1%)	101 (37.3%)
Any serious TEAE	3 (1.1%)	4 (1.5%)
Any TEAE with fatal outcome	0	1 (0.4%)
Any TEAE of worst grade 3 or 4	4 (1.5%)	9 (3.3%)
Any TEAE of worst grade 3	4 (1.5%)	8 (3.0%)
Any TEAE of worst grade 4	0	1 (0.4%)
Any TEAE at least possibly related to Pimodivir/Placebo	63 (23.1%)	33 (12.2%)
Any TEAE of worst grade 3 or 4 at least possibly related to Pimodivir/Placebo	0	1 (0.4%)
Any TEAE leading to temporary withdrawal of Pimodivir/Placebo	0	1 (0.4%)
Any TEAE leading to permanent withdrawal of Pimodivir/Placebo	2 (0.7%)	1 (0.4%)
Any TEAE leading to study discontinuation	1 (0.4%)	0
Any serious TEAE at least possibly related to Pimodivir/Placebo	0	0

Note: Subjects are counted once for any given event, regardless of the number of times they actually experienced the event.

In this study, 123 (45.1%) participants in the pimodivir + SOC arm and 101 (37.3%) participants in the placebo + SOC arm experienced at least 1 treatment-emergent AE (TEAE). The most frequently reported TEAE during the study (reported in at least 5.0% of participants within a treatment arm) by preferred term was diarrhea (54 [19.8%] and 18 [6.6%] participants, respectively). Reported TEAEs of diarrhea were typically mild and transient. Diarrhea was identified as adverse drug reaction (ADR) based on the Phase 2 studies for pimodivir.

During the study, 63 (23.1%) participants in the pimodivir + SOC arm and 33 (12.2%) 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 (50 [18.3%] participants in the pimodivir + SOC arm and 12 [4.4%] participants in the placebo + SOC arm), nausea (4 [1.5%] and 6 [2.2%] participants, respectively), and vomiting (3 [1.1%] and 6 [2.2%] participants, respectively).

Overall, 4 (1.5%) and 9 (3.3%) 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 blood creatine phosphokinase increased, reported by 2 (0.7%) 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 neutropenia 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 23 (8.4%) participants in the pimodivir + SOC arm and by 26 (9.6%) 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 37 (13.6%) participants in the pimodivir + SOC arm and 34 (12.5%) participants in the placebo + SOC arm. The most frequently reported influenza-related complications by the investigator (reported in at least 2.0% of participants within a treatment arm) were bronchitis (7 [2.6%] and 9 [3.3%] participants, respectively) and sinusitis (6 [2.2%] and 3 [1.1%] participants, respectively).

No COVID-19-related TEAEs were reported.

No AEs with fatal outcome were reported in the pimodivir + SOC arm during this study. For one participant in the placebo + SOC arm, a TEAE with a fatal outcome was reported during this study. The participant

was reported with a grade 3 SAE pneumonia pneumococcal and a fatal grade 4 SAE streptococcal sepsis during follow-up. Both SAEs were considered not related to the study treatment according to the investigator.

During the study, at least 1 SAE was reported by 3 (1.1%) participants in the pimodivir + SOC arm and 4 (1.5%) participants in the placebo + SOC arm. By preferred term, none of the SAEs were reported by more than 1 participant per treatment arm. None of the SAEs were considered at least possibly related to the study treatment.

Treatment-emergent AEs resulting in permanent discontinuation of study treatment were reported by 2 (0.7%) participants in the pimodivir + SOC arm and 1 (0.4%) participant in the placebo + SOC arm. In the pimodivir + SOC arm, 1 participant experienced a grade 1 TEAE blood creatine phosphokinase increased that was considered possibly related to study treatment, and 1 participant experienced a grade 2 TEAE abdominal discomfort, considered doubtfully related to the study treatment. One participant in the placebo + SOC arm experienced a grade 2 TEAE nausea, considered probably related to the study treatment was reported.

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 toxicities during the study (ie, 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 63623872FLZ3002)

	Pimodivir + SOC	Placebo + SOC
Treatment + Follow-up phase		
Alanine aminotransferase		
N	265	263
Grade 1	21 (7.9%)	23 (8.7%)
Grade 2	5 (1.9%)	6 (2.3%)
Grade 3	1 (0.4%)	0
Grade 4	1 (0.4%)	0
Amylase		
N	265	263
Grade 1	20 (7.5%)	27 (10.3%)
Grade 2	11 (4.2%)	14 (5.3%)
Grade 3	4 (1.5%)	6 (2.3%)
Grade 4	2 (0.8%)	0
Aspartate aminotransferase		
N	265	263
Grade 1	20 (7.5%)	25 (9.5%)
Grade 2	2 (0.8%)	5 (1.9%)
Grade 3	2 (0.8%)	0
Grade 4	0	0
Hyperglycemia		
N	265	263
Grade 1	48 (18.1%)	58 (22.1%)
Grade 2	20 (7.5%)	22 (8.4%)
Grade 3	12 (4.5%)	8 (3.0%)
Grade 4	1 (0.4%)	0

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 63623872FLZ3002)

	Pimodivir + SOC	Placebo + SOC
Hypophosphatemia		
N	265	263
Grade 1	29 (10.9%)	28 (10.6%)
Grade 2	2 (0.8%)	2 (0.8%)
Grade 3	0	0
Grade 4	0	0
Absolute neutrophil count		
N	265	262
Grade 1	15 (5.7%)	29 (11.1%)
Grade 2	7 (2.6%)	3 (1.1%)
Grade 3	0	1 (0.4%)
Grade 4	1 (0.4%)	1 (0.4%)
Proteinuria		
N	264	262
Grade 1	54 (20.5%)	34 (13.0%)
Grade 2	14 (5.3%)	11 (4.2%)
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.
If the baseline is missing, the toxicity is always considered as treatment-emergent.

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 13 (4.9%) participants in the pimodivir + SOC arm and 8 (3.0%) participants in the placebo + SOC arm, increased amylase in 6 (2.3%) and 6 (2.3%) participants, respectively, and increased gamma-glutamyltransferase in 4 (1.5%) and 3 (1.1%) 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 (78 [29.5%] participants in the pimodivir + SOC arm and 98 [37.3%] participants in the placebo + SOC arm), low segmented neutrophils (63 [23.8%] and 64 [24.4%] participants, respectively), high triglycerides (61 [23.0%] and 57 [21.7%] participants, respectively), high leukocytes (/high power field) (33 [20.4%] and 16 [12.6%] participants, respectively), and low low-density lipoprotein cholesterol (51 [19.2%] and 57 [21.8%] 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.

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).

CONCLUSION(S):

- Overall, this study demonstrated a benefit, in terms of clinical efficacy, of the combination of pimodivir with OST over treatment with OST alone in non-hospitalized, influenza A-infected participants who are at risk of developing influenza-related complications
- The time to resolution of the 7 primary influenza symptoms in the ITT-I Set was shorter in the pimodivir + SOC arm compared to the placebo + SOC arm with a median (95% CI) Kaplan-Meier estimate of 92.62 (77.60; 104.20) hours compared to 105.13 (92.73; 128.63) hours (p-value=0.0216). The AFT model analysis estimated a 14% reduction in time to resolution of 7 primary influenza symptoms in the pimodivir + SOC arm versus the placebo + SOC arm. Results were similar for the OST ITT-i Set; the AFT model analysis shows that for the OST ITT-i Set in the pimodivir + SOC arm, there was a reduction in time to resolution of 7 primary influenza symptoms versus the placebo + SOC arm of 20%. For the subgroup with time since onset of influenza >48 hours, the estimated median (95% CI) time to resolution of the 7 primary influenza symptoms was 97.38 (60.52; 160.82) hours in the pimodivir + SOC arm and 89.23 (68.00; 132.28) hours in the placebo + SOC arm and it was 117.17 (67.55; 233.02) hours and 97.28 (69.95; 138.13) hours, respectively, in the subgroup of participants not using influenza antivirals as part of their SOC, however, both subgroups were limited in sample size.
- After treatment start, only few participants were hospitalized for influenza complications (ie, 1.8% of participants each in the pimodivir + SOC and placebo + SOC arm). 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 4 of 191 participants with available data (ie, 2.1%).
- Pimodivir 600 mg bid in combination with SOC was generally safe and well tolerated in this population of patients at risk for influenza-related complications. No AEs with fatal outcome were reported in the pimodivir + SOC arm during this study. Treatment-emergent SAEs were reported by 3 participants in the pimodivir + SOC arm and 4 participants in the placebo + SOC arm; none were considered related to the study treatment. Overall, 45.1% of participants in the pimodivir + SOC arm and 37.3% of participants in the placebo + SOC arm experienced at least 1 TEAE during the study. Diarrhea, previously identified as a non-serious ADR for pimodivir, was reported in 19.8% of participants in the pimodivir + SOC arm and 6.6% of participants in the placebo + SOC arm. Reported TEAEs of diarrhea were typically mild and transient.

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