The Journal of Infectious Diseases

MAJOR ARTICLE

A Phase 2 Study of Pimodivir (JNJ-63623872) in Combination With Oseltamivir in Elderly and Nonelderly Adults Hospitalized With Influenza A Infection: OPAL Study

Brian O'Neil,[1] Michael G. Ison,[2] Marie-Charlotte Hallouin-Bernard,[3] Anna C. Nilsson,[4] Antoni Torres,[5] John M. Wilburn,[1] Wilbert van Duijnhoven,[6] Ilse Van Dromme,[6] David Anderson,[7] Sofie Deleu,[6] Teddy Kosoglou,[7] Johan Vingerhoets,[6] Stefaan Rossenu,[6] and Lorant Leopold[7]

[1]Wayne State University School of Medicine, Detroit Medical Center, Detroit, Michigan, USA, [2]Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA, [3]University Hospital of Tours, Tours, France, [4]Infectious Disease Research Unit, Department of Translational Medicine, Skåne University Hospital, Malmö, Sweden, [5]Servei de Pneumologia Hospital Clinic, August Pi i Sunyer Biomedical Research Institute, Biomedical Research Networking Center on Respiratory Diseases, University of Barcelona, Barcelona, Spain, [6]Janssen Pharmaceutica NV, Beerse, Belgium, and [7]Janssen Research and Development, LLC, Titusville, New Jersey, USA

Background. Both the elderly and individuals with comorbidities are at increased risk of developing influenza-related complications. Novel influenza antivirals are required, given limitations of current drugs (eg, resistance emergence and poor efficacy). Pimodivir is a first-in-class antiviral for influenza A under development for these patients.

Methods. Hospitalized patients with influenza A infection were randomized 2:1 to receive pimodivir 600 mg plus oseltamivir 75 mg or placebo plus oseltamivir 75 mg twice daily for 7 days in this phase 2b study. The primary objective was to compare pimodivir pharmacokinetics in elderly (aged 65–85 years) versus nonelderly adults (aged 18–64 years). Secondary end points included time to patient-reported symptom resolution.

Results. Pimodivir pharmacokinetic parameters in nonelderly and elderly patients were similar. Time to influenza symptom resolution was numerically shorter with pimodivir (72.45 hours) than placebo (94.15 hours). There was a lower incidence of influenza-related complications in the pimodivir group (7.9%) versus placebo group (15.6%). Treatment was generally well tolerated.

Conclusions. No apparent relationship was observed between pimodivir pharmacokinetics and age. Our data demonstrate the need for a larger study of pimodivir in addition to oseltamivir to test whether it results in a clinically significant decrease in time-to-influenza-symptom alleviation and/or the frequency of influenza complications.

Clinical trials registration. NCT02532283.

Keywords. pimodivir; oseltamivir; influenza A virus; hospitalized; elderly; clinical trial; pharmacokinetics; viral clearance; influenza complications; duration of symptoms.

Influenza is a worldwide public health challenge, with considerable morbidity and mortality [1]. Elderly people and those with high-risk medical conditions (eg, chronic lung disease, heart disease, diabetes, or being immunocompromised) are vulnerable to complications [2, 3]. These populations are most likely to require hospital and/or intensive care unit (ICU) admission [2, 3]. In the United States, individuals aged >65 years have the highest hospitalization rate (59% of reported influenza-associated admissions), and death rate (approximately 90% of influenza-related deaths) due to influenza [4, 5].

Currently 3 antiviral drug classes are approved for influenza treatment: adamantanes, neuraminidase inhibitors (NAIs), and endonuclease inhibitors, all of which have limitations [6–8]. Widespread resistance to adamantanes precludes their routine clinical use and has led to a reliance on NAIs (including oseltamivir, the most widely prescribed NAI) [6]. The cap-dependent endonuclease inhibitor baloxavir marboxil has been approved in the United States and Japan for the treatment of acute uncomplicated influenza in adolescents, adults, and in populations at high-risk of developing flu-related complications [7, 8]. However, resistance has been reported in 2.2%–20% of cases in clinical trials, depending on age and other factors [7]. No direct-acting antivirals are approved for influenza-infected hospitalized patients. In patients hospitalized with influenza, intravenous NAIs, peramivir and zanamivir, showed no benefit over standard of care [9, 10].

Received 9 January 2020; editorial decision 18 June 2020; accepted 25 June 2020; published online July 1, 2020.

Correspondence: Lorant Leopold, MD, Janssen Research and Development, LLC, 1125 Trenton-Harbourton Road, Titusville, New Jersey 08560, United States (LLeopold@its.jnj.com).

The Journal of Infectious Diseases® 2022;226:109–18

DOI: 10.1093/infdis/jiaa376

Currently there are no antivirals approved to treat patients >48 hours after symptom onset, which is another challenge with available therapies [11]. NAIs are frequently utilized as influenza treatment in hospitalized adults; however, because NAI effectiveness is inversely correlated with time from symptom onset to treatment initiation, the benefit of NAIs is greatest when started ≤48 hours of symptom onset. This time window is often not met in the hospital setting, which likely affects the utility of antiviral therapy.

Pimodivir (previously JNJ-63623872 or VX-787) is under development for influenza A treatment in hospitalized and high-risk patients. Pimodivir is a nonnucleoside inhibitor of the polymerase basic protein 2 (PB2) subunit of the influenza A virus polymerase complex, resulting in reduced RNA replication [12]. In a phase 2b study (TOPAZ), pimodivir resulted in significant virologic improvements [13]. The primary objective of this study evaluated the effect on the pharmacokinetics of pimodivir in patients hospitalized with influenza A infection aged 65–85 years compared with patients aged 18–64 years; secondary objectives assessed the safety and the antiviral effect of pimodivir in combination with oseltamivir and the Hospital Recovery Scale was used to characterize potential clinical benefits of pimodivir.

METHODS

Study Design

Patients were randomized 2:1 (stratified by age) to receive a twice-daily combination of oral pimodivir 600 mg plus oseltamivir 75 mg, both for 7 days (pimodivir plus oseltamivir group) or placebo plus oseltamivir 75 mg twice daily (placebo plus oseltamivir group) (Figure 1). In patients with an estimated glomerular filtration rate (eGFR) $^{>}$ 30 to ≤ 60 mL/min/1.73 m^2, oseltamivir dose was reduced to 30 mg twice daily according to the modification of diet in renal disease equation; dose was subsequently adjusted from 30 mg to 75 mg and vice versa during treatment, based on eGFR [14].

An Independent Ethics Committee and Institutional Review Board reviewed the study protocol and amendments. The study was conducted in concordance with the Declaration of Helsinki. Patients or their legally acceptable representatives provided written informed consent before study enrollment. An Independent Data Monitoring Committee reviewed all safety data throughout the study. The study was registered with European Union Drug Regulating Authorities Clinical Trials (EudraCT; 2015-003002-17) and ClinicalTrials.gov (NCT02532283) databases.

Patient Population

Patients aged 18–85 years were included if they required hospitalization for influenza and/or complications of influenza, tested positive for influenza A (using a polymerase chain reaction [PCR]-based rapid molecular diagnostic assay) and were capable of swallowing the study drugs. Patients had to complete patient-reported outcome (PRO) assessments. There was no restriction at screening relative to time from influenza symptom onset. For detailed exclusion criteria see Supplementary Material.

Study Outcomes

The primary end point was pimodivir pharmacokinetics, aiming to compare results in patients aged 65–85 years (elderly) with patients aged 18–64 years (nonelderly), as assessed through venous blood sampling at different time points. A minimum of 24 patients were enrolled per arm. Secondary end points included: safety and tolerability; time to influenza viral negativity; area under the plasma concentration-time curve (AUC) of viral load using quantitative reverse transcription PCR (qRT-PCR) and/or viral culture; disease status/progression; incidence of investigator-determined influenza-related complications after the start of study treatment (including bacterial pneumonia, other bacterial superinfections, respiratory failure, pulmonary disease, cardiovascular and cerebrovascular disease, post baseline ICU admission, all-cause mortality); duration and severity of clinical symptoms as measured by PRO assessments (influenza intensity and impact questionnaire [FLU-iiQ], FLU-PRO, and additional

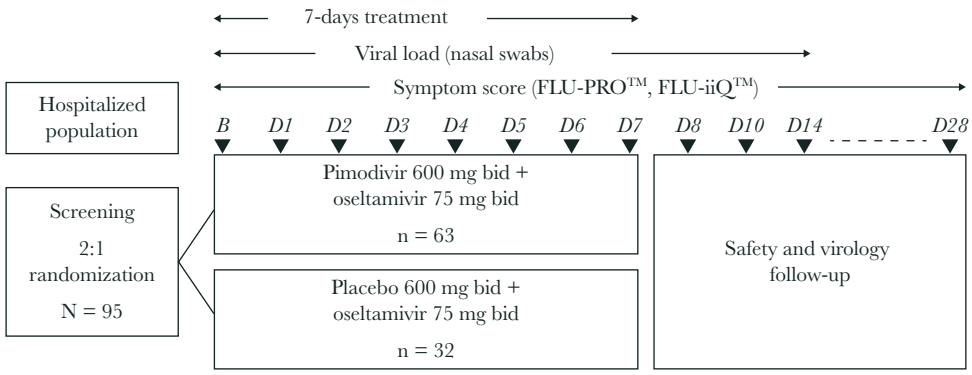

Figure 1. Study design schematic. Abbreviations: B, baseline; D, day.

daily diary items) using an electronic device for entering and transferring data on an ongoing basis [15]; and the Hospital Recovery Scale to capture clinical status.

Study Evaluations

Pharmacokinetics

Patients underwent intensive pharmacokinetic sampling on day 3: prior to the morning dose, and at 1, 2, 4, 6, 8, 10, and 12 hours post morning dose (prior to the evening dose). For patients discharged before day 3, no intensive sampling was performed. Plasma pimodivir concentrations were measured by PRA Health Sciences Bioanalytical Laboratories (Assen, the Netherlands) using a validated, specific, sensitive liquid chromatography with tandem mass spectrometry assay (lower limit of quantification of 2.00 ng/mL).

Safety

Adverse events (AEs), including investigator-determined influenza-related complications, were reported by patients voluntarily or through study visit interviews (Supplementary Material). AEs were coded using the *Medical Dictionary for Regulatory Activities,* version 19.1 [16]. Treatment-emergent AEs (TEAEs) were defined as AEs reported or worsened on or after the start of study drug(s) dosing through the 28-day safety follow-up.

Viral Kinetics and Resistance Testing

Nasal midturbinate swab samples from both nostrils were pooled and analyzed by qRT-PCR and/or by determining median tissue culture infective dose ($TCID_{50}$) and/or by PCR-based rapid molecular testing (if applicable). $TCID_{50}$ measurements were analyzed using nucleoprotein enzyme-linked immunosorbent assay (NP-ELISA) and hemagglutination inhibition assay. Virology testing was performed by Viroclinics Biosciences (Rotterdam, the Netherlands). Resistance testing was performed using genotypic analysis by Sanger sequencing of *PB2* and *NA* genes of baseline and last virus-positive post baseline sample; changes in *PB2* and *NA* sequences were evaluated against the seasonal reference strains; and phenotypic susceptibility analyses in a cell-culture based assay with Madin-Darby canine kidney cells (Influenza ViroSpot assay) and the influenza NA Inhibitor Reagent kit NA Star (Applied Biosystems) to obtain a 50% inhibitory concentration for pimodivir and oseltamivir were performed, respectively.

Efficacy

FLU-iiQ influenza PRO questionnaire evaluated symptom severity [17]. Patients completed questionnaires in their native language or a language in which they were fluent and literate. Incidence and severity of symptoms (individual and composite) were evaluated twice daily (preferably morning and evening) from day 1 to 14 and once daily from day 15 to the final study visit (preferably in the evening).

Hospital Recovery Scale

The Hospital Recovery Scale end point used here was adapted from a previous scale with similar categories (Supplementary Material) [18]. The worst category each calendar day was recorded for each patient. Analysis was performed on day 8 using a proportional odds model, modeling the common odds ratio (OR) of the improvement of pimodivir plus oseltamivir versus placebo plus oseltamivir. Baseline Hospital Recovery Scale and age group were added to the model.

Time to Hospital Discharge

Length of overall hospital stay was calculated from the date of first study drug(s) intake to the date of discharge. Patients still hospitalized at the end of the study were censored at last contact.

Statistical Analysis

Based on clinical insights and sensitivity analysis, 72 and 96 hours since symptom onset are the most relevant cutoffs to identify subgroups for additional analyses. To evaluate these cutoffs, exploratory analyses of viral load over time, time to viral negativity (based on qRT-PCR and/or viral culture from nasal midturbinate swabs and, if applicable, PCR-based rapid molecular testing from nasal midturbinate swabs) and Hospital Recovery Scale were performed.

A sample size of ≥60 patients was estimated to lead to acceptable precision for primary pharmacokinetics parameters. Descriptive statistics were performed for the pharmacokinetics-evaluable population (patients from whom at least 1 pharmacokinetic parameter was obtained).

The study was not powered to show statistically significant differences in virologic parameters or clinical end points, but exploratory analyses were performed. The cutoff for viral titer negativity was <0.75 $\log_{10}$ $TCID_{50}$/mL (further defined in the Supplementary Material). Time to influenza A viral negativity was summarized using a Kaplan-Meier curve. AUC was estimated for each treatment arm and compared using a mixed model for repeated measurements, containing treatment group, age group, visit, and their interactions as model parameters.

Descriptive statistics were used for all efficacy end points presented by treatment arm, age cohort, and time since symptom onset. All time-to-clinical-outcome end points and time to hospital discharge were presented using Kaplan-Meier curves. For treatment arm comparisons, time-to-event end points were analyzed using an accelerated failure time model, including age group and applicable baseline characteristics as model parameters.

RESULTS

Patient Disposition and Baseline Characteristics

Patients were recruited at 40 centers in 11 countries between January 2016 and March 2017. Of 194 patients screened, 102

patients were randomized to treatment, 3 of which withdrew consent prior to treatment start. Therefore, the safety set of patients who received ≥1 dose of study drug(s) comprised 99 patients (pimodivir plus oseltamivir, n = 64; placebo plus oseltamivir, n = 35). In 4 of these patients influenza A infection was not confirmed by virology data and the results were excluded from the full analysis set (FAS), which comprised 95 patients (pimodivir plus oseltamivir, n = 63; placebo plus oseltamivir, n = 32), comprising 39 elderly patients and 56 nonelderly patients. Of the 95 patients, 86.3% (82/95) completed treatment with 85.3% (81/95) completing the study (Supplementary Figure 1).

Reasons for treatment discontinuation included AEs (n = 6), protocol violation (n = 1), consent withdrawal (n = 4), and loss to follow-up (n = 2). No relevant differences in study and treatment discontinuations were observed between elderly and nonelderly subgroups, or between pimodivir plus oseltamivir and placebo plus oseltamivir.

Demographics between treatment groups for the FAS were generally similar, with imbalances in some categories (eg, time since onset of symptoms, race, tobacco use; Table 1). The median age was 61 (range, 19–85) years, with 41.1% (39/95) elderly patients. The time from the onset of influenza symptoms to enrollment in the trial was ≤72 hours for

Table 1. Patient Demographic Characteristics at Baseline (Full Analysis Set)

Characteristic	Pimodivir 600 mg + Oseltamivir 75 mg (n = 63)	Placebo + Oseltamivir 75 mg (n = 32)	All Patients (N = 95)
Sex female, n (%)	26 (41.3)	15 (46.9)	41 (43.2)
Age, y, median (range)	60.0 (19–85)	61.0 (26–80)	61.0 (19–85)
Age categories, n (%)			
18–≤ 64 y	38 (60.3)	18 (56.3)	56 (58.9)
65–85 y	25 (39.7)	14 (43.8)	39 (41.1)
Weight, kg, median (range)	80.0 (38.0–142.4)	75.0 (48.0–128.0)[a]	76.7 (38.0–142.4)[b]
Race, n (%)			
American Indian or Alaska Native	1 (1.6)	0	1 (1.1)
Asian	5 (7.9)	7 (21.9)	12 (12.6)
Black or African American	6 (9.5)	6 (18.8)	12 (12.6)
Multiple	0	1 (3.1)	1 (1.1)
Other	2 (3.2)	1 (3.1)	3 (3.2)
Unknown	2 (3.2)	0	2 (2.1)
White	47 (74.6)	17 (53.1)	64 (67.4)
BMI, mean kg/m^2 (SD)	27.9 (6.4)	28.1 (5.3)	28.0 (6.0)
Tobacco user, n (%)	15 (23.8)	4 (12.5)	19 (20.0)
Influenza subtype category, n (%)			
H1N1	19 (30.2)	10 (31.3)	29 (30.5)
H3N2	42 (66.7)	22 (68.8)	64 (67.4)
Unknown subtype	2 (3.2)	0	2 (2.1)
Influenza A viral load by qRT-PCR, $\log_{10}$ vp/mL			
Mean (SD)	5.45 (1.74)	5.90 (1.51)	5.60 (1.67)
Median (range)	5.64 (0.0–8.4)	5.83 (3.1–9.1)	5.75 (0.0–9.1)
Influenza A viral titer, $\log_{10}$ $TCID_{50}$/mL			
Mean (SD)	1.82 (1.51)[c]	2.13 (1.76)[d]	1.92 (1.60)[e]
Median (range)	1.38 (0.4–5.3)[c]	1.75 (0.4–6.3)[d]	1.50 (0.4–6.3)[e]
Time since onset of influenza symptoms, n (%)			
≤72 h	21 (34.4)	15 (46.9)	36 (38.7)
>72 h	40 (65.6)	17 (53.1)	57 (61.3)
≤96 h	34 (55.7)	21 (65.6)	55 (59.1)
>96 h	27 (44.3)	11 (34.4)	38 (40.9)
Unknown	2 (3.2)	0	2 (2.1)
Hospital recovery scale category			
Non-ICU + no supplemental oxygen, n (%)	31 (49.2)	19 (59.4)	50 (52.6)
Non-ICU + supplemental oxygen, n (%)	32 (50.8)	13 (40.6)	45 (47.4)

Abbreviations: BMI, body mass index; ICU, intensive care unit; qRT-PCR, quantitative reverse transcription polymerase chain reaction; $TCID_{50}$, 50% tissue culture infective dose.

[a]n = 32.

[b]n = 94.

[c]n = 58.

[d]n = 30.

[e]n = 88.

38.7% (36/93) of patients and ≤96 hours for 59.1% (55/93) of patients.

Pimodivir Pharmacokinetics

Of the 63 patients treated with pimodivir plus oseltamivir (FAS), pharmacokinetics of pimodivir were obtained in 35 patients (elderly, n = 15; nonelderly, n = 20; Table 2). Appreciable between-patient variability was observed in pharmacokinetic parameters and concentration-time profiles (Figure 2) for both elderly and nonelderly patients. Point estimates of the geometric mean ratio for minimum concentration (C_{min}), maximum concentration (C_{max}), and AUC_{12h} between elderly and nonelderly patients were 105%, 112%, and 116%, respectively, with similar range of variability (Table 2).

Exposure in 1 patient was approximately 2.5 standard deviations above the mean exposure in the elderly group (C_{max}, 17 300 ng/mL; AUC_{12h}, 90 355 ng.h/mL); this patient was an 80-year-old woman weighing 38 kg, and study drugs were discontinued due to hyperbilirubinemia (see section "Safety") (Supplementary Table 1). Sensitivity analyses performed excluding this patient (Supplementary Table 2 and Figure 2) had similar results.

Safety

Safety profiles were generally similar between the treatment groups, including grade 3 or 4 TEAEs, severe or life-threatening TEAEs and serious AEs (SAEs) (Table 3 and Supplementary Table 3). The most frequently reported TEAE was diarrhea, typically mild and transient.

Irrespective of grade, there were no clinically relevant differences in laboratory parameters between treatment groups or elderly and nonelderly subgroups. In some instances, influenza-related complications were treated with concomitant antibiotics or corticosteroids.

Differences by Treatment Received

TEAEs resulting in permanent discontinuation of study drug(s) were reported by 1 patient (1.6% [1/64]) in the pimodivir plus oseltamivir group (hyperbilirubinemia) and in 14.3% (5/35) of patients who received placebo plus oseltamivir (headache, glomerular filtration rate decreased, liver function test increased, blood creatinine increased, and stroke).

At least 1 SAE was reported by 17.2% of patients treated with pimodivir plus oseltamivir and 11.4% of patients who received placebo plus oseltamivir (Table 3). Each SAE was experienced by only 1 patient. Worst grade 3 or 4 AEs were reported in 9/64 and 6/35 patients who received pimodivir plus oseltamivir and placebo plus oseltamivir, respectively. Each individual grade 3 or 4 AE term was reported in a maximum of 1 patient. One patient experienced a grade 3 hypersensitivity reaction, which was the only SAE considered to be at least possibly related to pimodivir treatment by the investigator. One death was reported in the pimodivir plus oseltamivir group—a cardiac arrest during follow-up considered doubtfully related to the study drug(s) by the investigator.

Differences by Age Group

In patients who were treated with pimodivir plus oseltamivir, diarrhea was more frequent in elderly patients versus nonelderly patients (24% [6/25] vs 17.9% [7/38], respectively). Diarrhea was more frequent in elderly patients treated with pimodivir plus oseltamivir than those who received placebo plus oseltamivir (7.1% [1/14]), but similar in both nonelderly treatment groups. No other significant differences were observed.

Viral Kinetics

Pimodivir Plus Oseltamivir Group Versus Placebo Plus Oseltamivir Group

At baseline, in the FAS, overall median viral load (qRT-PCR) was 5.7 log_{10} virus particles (vp)/mL, and median viral titer (viral culture) was 1.5 log_{10} $TCID_{50}$/mL. The estimated difference in viral load AUC of pimodivir plus oseltamivir treatment versus placebo plus oseltamivir treatment in the overall dataset was small (0.7 log_{10} vp/mL*day; 95% confidence interval [CI], −3.0 to 4.3); results were similar for the elderly and nonelderly subgroups. The difference in AUC for the ≤72-hour and ≤96-hour subgroups was −2.2 (95% CI, −8.0 to 3.7) log_{10} vp/mL*day and −0.9 (95% CI, −5.4 to 3.6) log_{10} vp/mL*day, respectively, with similar results in the elderly and nonelderly subgroups.

Table 2. Pimodivir Pharmacokinetic Parameters in Patients Administered Pimodivir at 600 mg Twice Daily in Combination With Oseltamivir at 75 mg Twice Daily in Elderly and Nonelderly Subjects With Influenza A Infection (Pharmacokinetics Data Analysis Set)

Pharmacokinetic Parameter	Elderly Adults, 65 to ≤85 y, Mean (SD) (n = 15)	Nonelderly Adults, 18 to ≤64 y, Mean (SD) (n = 20)[a]	Geometric Mean Ratio of Elderly to Nonelderly, %	90% CI	CV, %	Overall (n = 35)[b]
C_{min}, ng/mL	738 (892)	507 (414)	104.9	62.1–177.3	112.9	603 (655)
C_{max}, ng/mL	5933 (4427)	5378 (3888)	111.7	70.7–176.5	93.3	5616 (4074)
AUC_{12h}, ng.h/mL	27 386 (25 191)	20 101 (11 063)	116.1	76.5–176.2	82.7	23 224 (18 522)

Abbreviations: AUC_{12h}, area under the plasma concentration-time curve from time 0–12 h after dosing; CI, confidence interval; C_{max}, maximum observed analyte concentration; C_{min}, minimum observed analyte concentration; CV, coefficient of variation.

[a]n = 21 for C_{min}.

[b]n = 36 for C_{min}.

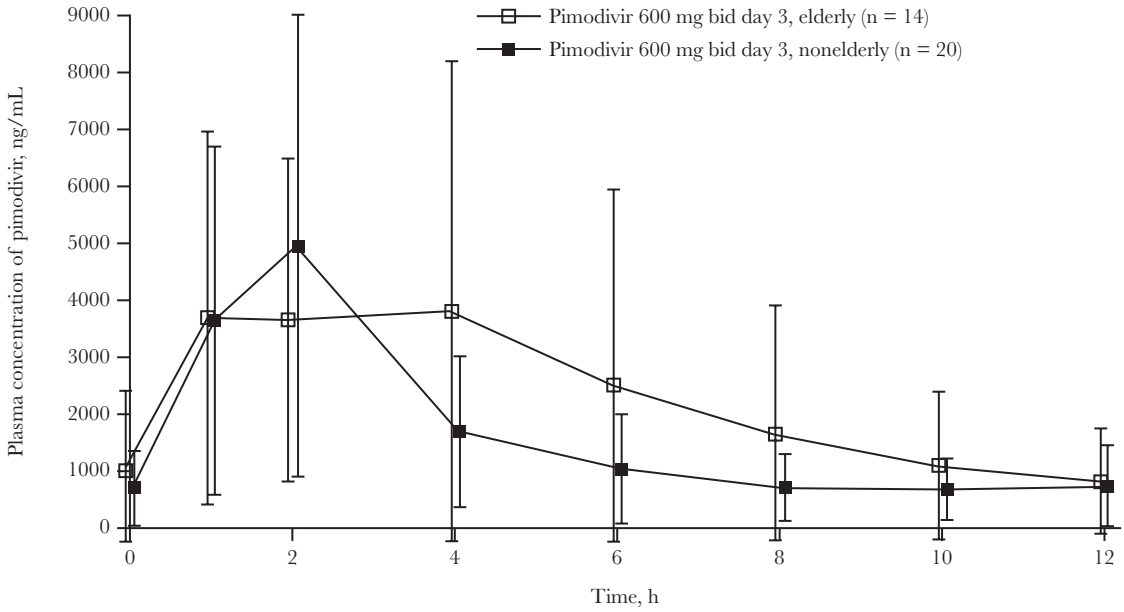

Figure 2. Mean (SD) plasma concentration-time profiles for pimodivir after administration of pimodivir (600 mg, twice daily) plus oseltamivir (75mg, twice daily) in all patients.

The estimated difference in viral titer over time by culture (AUC) was small between pimodivir plus oseltamivir and placebo plus oseltamivir groups (−0.5 $\log_{10}$ $TCID_{50}$/mL*day; 95% CI, −2.0 to 1.0). In the ≤72-hour and ≤96-hour subgroups, estimated difference in viral titer over time (AUC) was −1.2 (95% CI, −4.2 to 1.8) and −0.9 (95% CI, −3.0 to 1.3) $\log_{10}$ $TCID_{50}$/mL*day, respectively, with pimodivir plus oseltamivir than with placebo plus oseltamivir. There was no meaningful difference between age groups. Pimodivir plus oseltamivir treatment resulted in, on average, 36% and 28% faster time to viral negativity than placebo plus oseltamivir in the ≤72-hour and ≤96-hour subgroups, respectively (Figure 3).

Efficacy

Unless otherwise noted, efficacy in the elderly and nonelderly subgroups was similar.

Incidence of Influenza Complications

The incidence of investigator-determined influenza-related complications in the FAS in patients treated with pimodivir plus oseltamivir was 7.9% (5/63) versus 15.6% (5/32) in patients who received placebo plus oseltamivir; the corresponding OR adjusted for age strata was 0.470 (95% CI, .131–1.692). Influenza-related complications in patients treated with pimodivir plus oseltamivir versus placebo plus oseltamivir in both the ≤72-hour and ≤96-hour subgroups were 4.8% (1/21) versus 26.7% (4/15) and 5.9% (2/34) versus 23.8% (5/21), respectively.

Hospital Recovery Scale

Both treatment groups had similar Hospital Recovery Scale profiles at baseline. All patients were admitted to the hospital ward; 50.8% (32/63) received supplemental oxygen in the pimodivir plus oseltamivir group and 40.6% (13/32) in the placebo plus oseltamivir group. Seven days of treatment with pimodivir plus oseltamivir or placebo plus oseltamivir resulted in similar clinical outcomes on the Hospital Recovery Scale at day 8, as expressed by a common OR of 1.06 (95% CI, .43–2.47) (adjusted for baseline clinical outcome category and age strata, FAS). Proportional odds model assumptions were not violated. At day 8, the same common OR for the ≤72-hour subgroup was 0.40 (95% CI, .09–1.71) and for the ≤96-hour subgroup was 0.50 (95% CI, .16–1.56), indicating a 60% and 50% improvement, respectively, on the odds of a better clinical outcome after treatment with pimodivir plus oseltamivir versus placebo plus oseltamivir (Figure 4).

Patient-Reported Outcomes

In the FLU-iiQ assessment, the median time to resolution of influenza symptoms was defined as time of first 2 evaluations in which symptom scores were none or mild for each of 7 primary influenza symptoms (cough, sore throat, headache, nasal congestion, feeling feverish, body ache, and fatigue). Median time to resolution with pimodivir plus oseltamivir was 72.45 hours (95% CI, 39.05–110.77 hours) compared with 94.15 hours with placebo plus oseltamivir (95% CI, 51.68–145.00 hours) in the FAS (Supplementary Figure 3).

Median time to resumption of usual activities in the FAS was 124.8 (95% CI, 85.9–207.5) hours in the pimodivir plus oseltamivir group versus 162.2 (95% CI, 58.1–386.4) hours for placebo plus oseltamivir.

Time to Hospital Discharge

The pimodivir plus oseltamivir group showed a similar estimated median time to hospital discharge versus the placebo

Table 3. Adverse Events Reported in at Least ≥10% of Patients Within Any Treatment Group

MedDRA System Organ Class Dictionary-derived Term	Pimodivir 600 mg + Oseltamivir 75 mg, n (%) (n = 64)	Placebo + Oseltamivir 75 mg, n (%) (n = 35)
TEAEs		
Any AE	48 (75.0)	25 (71.4)
Severe AE	5 (7.8)	3 (8.6)
Life-threatening AE	4 (6.3)	4 (11.4)
Any AE with fatal outcome	1 (1.6)[a]	0
Worst grade 1 or 2 AE	39 (60.9)	19 (54.3)
Worst grade 3 AE	5 (7.8)	2 (5.7)
Worst grade 4 AE	4 (6.3)	4 (11.4)
Gastrointestinal disorders	29 (45.3)	12 (34.3)
Diarrhea	13 (20.3)	4 (11.4)
Nausea	9 (14.1)	5 (14.3)
General disorders and administration site conditions	12 (18.8)	2 (5.7)
Respiratory, thoracic, and mediastinal disorders	12 (18.8)	6 (17.1)
Cough	4 (6.3)	4 (11.4)
Nervous system disorders	11 (17.2)	5 (14.3)
Headache	7 (10.9)	3 (8.6)
Infections and infestations	7 (10.9)	3 (8.6)
Musculoskeletal and connective tissue disorders	7 (10.9)	5 (14.3)
Metabolism and nutrition disorders	5 (7.8)	4 (11.4)
Abnormal laboratory investigations	4 (6.3)	7 (20.0)
SAEs		
Any SAE	11 (17.2)	4 (11.4)
Any SAE among elderly patients (65–85 y)	6 (24)	3 (7.1)
Any SAE among nonelderly patients (18–64 y)	8 (12.8)	5 (14.3)
Any SAE at least possibly related to treatment	1 (1.6)[b]	0

Abbreviations: AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

[a]Death was considered doubtfully related to pimodivir.

[b]Serious TEAE was hypersensitivity and considered possibly related to pimodivir + oseltamivir.

plus oseltamivir group (4.00 [95% CI, 3.00–5.00] days and 4.00 [95% CI, 3.00–4.00] days, respectively); similar results were seen for the same comparisons within the ≤72-hour and ≤96-hour subgroups.

Treatment Resistance

No *PB2* mutations at any of the positions of interest were observed in post baseline samples from patients treated with pimodivir plus oseltamivir. Emergence of the oseltamivir

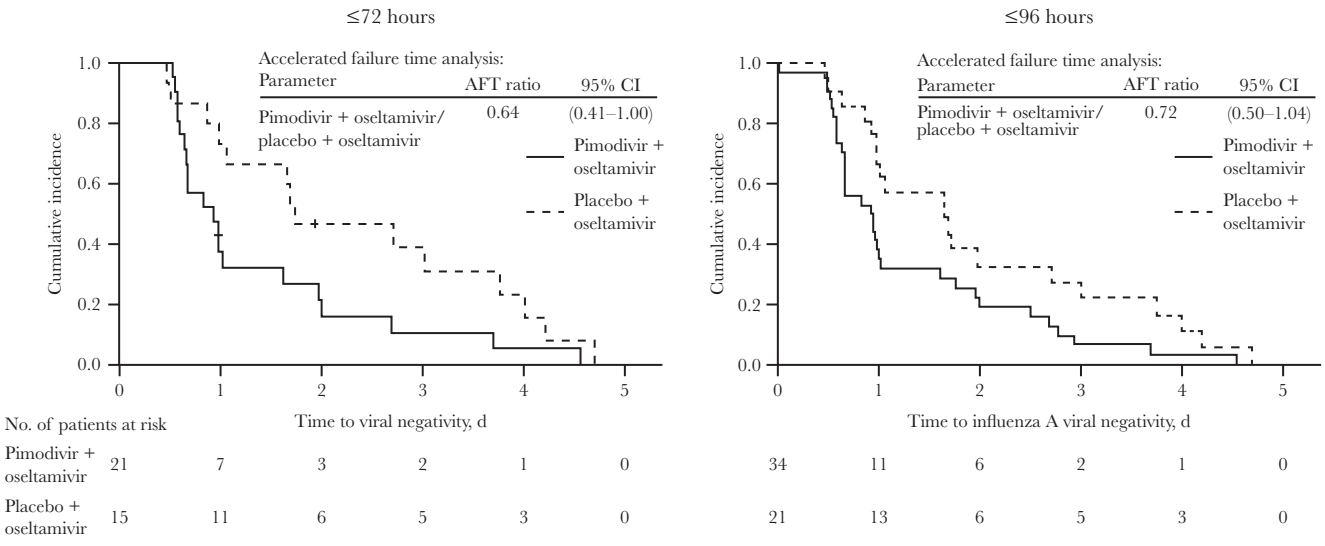

Figure 3. Time to viral negativity determined by viral culture in patients treated with pimodivir plus oseltamivir compared with placebo plus oseltamivir. Abbreviations: AFT, accelerated failure time; CI, confidence interval.

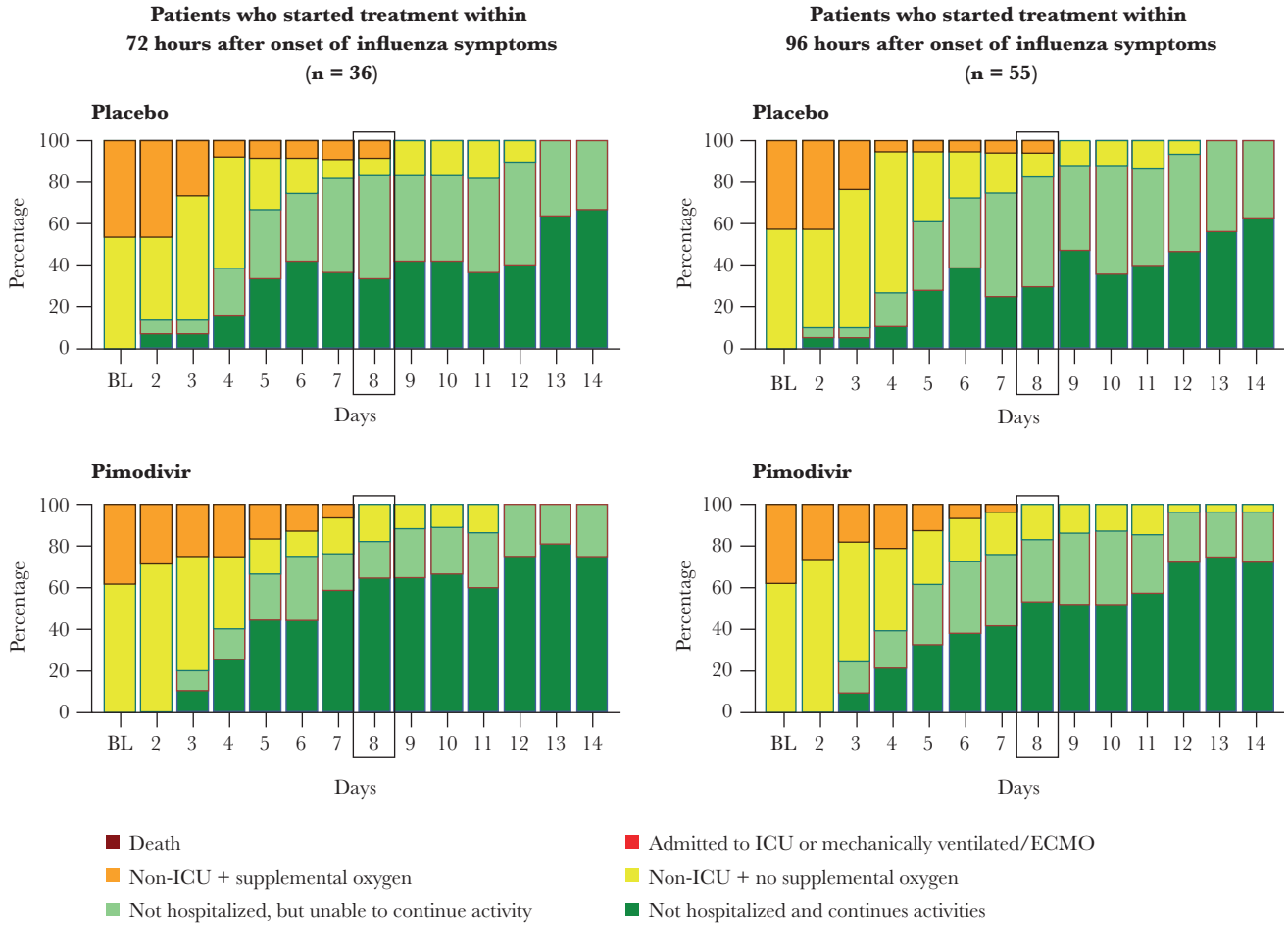

Figure 4. Changes in patient status determined by the Hospital Recovery Scale in patients who started treatment within ≤72 hours (n = 36) or ≤96 hours (n = 55) after onset of influenza symptoms. Abbreviations: BL, baseline; ICU, intensive care unit; ECMO, extra corporeal membrane oxygenation.

mutation H275Y was observed in 1 patient in the placebo plus oseltamivir group.

DISCUSSION

In this study, pharmacokinetics in elderly patients were not different from those in nonelderly patients. Pimodivir plus oseltamivir was generally well tolerated upon repeated dosing in hospitalized patients, with diarrhea being the most common AE which was typically mild and transient. Our results are consistent with those from the phase 1 study which found no safety concerns between pimodivir and oseltamivir in healthy volunteers [19], and also with another phase 2 study (TOPAZ) in high-risk influenza A-infected patients, where plasma concentrations of pimodivir 600 mg were similar with and without oseltamivir 75 mg, with good tolerability [13].

In the subgroups of patients who initiated treatment at ≤72 or ≤96 hours after the onset of symptoms, the pimodivir plus oseltamivir group appeared to have faster time to viral negativity than the oseltamivir plus placebo group. This highlights the potential for a longer treatment window than oseltamivir alone; this is important because patients typically present later in the course of their illness [20, 21]. Larger studies are needed to confirm this.

Patients in the pimodivir plus oseltamivir group experienced a 21.7-hour shorter time to resolution of the 7 primary influenza symptoms and 37.4-hour shorter time to resumption of usual activity compared with placebo plus oseltamivir. However, as the trial was not powered for time to viral negativity of symptom resolution, statistical analyses were not performed. Although the study was not powered to detect between-group differences, there was a trend towards a lower incidence of influenza-related complications in the pimodivir plus oseltamivir group. However, no clear differences were observed for time to hospital discharge. This could be due to factors that were not assessed within the study, such as individual patient factors (eg, underlying conditions) or physician opinion on the suitability of patients to be discharged.

The absence of emerging pimodivir resistance aligns with observations from the TOPAZ study, where pimodivir 600 mg plus oseltamivir resulted in a lower frequency of pimodivir

resistance (1/57 patients had an emerging pimodivir resistance-associated *PB2* substitution) versus pimodivir alone (10/115 patients with an emerging *PB2* resistance in the 300 mg and 600 mg dose groups combined) [13]. In contrast, treatment-emergent amino acid substitutions in the polymerase acidic protein inducing reduced susceptibility to baloxavir have been observed in 2%–20% of cases in clinical trials; the impact of dual therapy with baloxavir and oseltamivir on resistance emergence has not been prospectively studied [22]. Additionally, the sole H275Y mutation that emerged on therapy was in the placebo plus oseltamivir group. This further supports the development of combination therapy for influenza treatment.

This study has several limitations. Small sample size and large between-patient variability in pimodivir pharmacokinetics limit our conclusions. Because hospitalized patients underwent intensive pharmacokinetic sampling on day 3, no pharmacokinetic data were available for patients who were discharged before day 3 (ultimately 45% of enrolled patients); hence, the pharmacokinetics evaluable dataset is smaller than the safety and FAS datasets. This was due to the rate of patient withdrawal and reflects the real-life situations within hospitals.

To aid development of agents in hospitalized adults with influenza, an ordinal scale has been proposed as a way of analyzing multiple factors simultaneously [23] because no single best end point for evaluating new treatments in these populations has been determined. This study suggests that a Hospital Recovery Scale may be a useful end point for clinical studies of influenza antivirals, by capturing the clinical status of patients each day from baseline to end of treatment, representing the full spectrum of severity after initial infection—improvement on this scale is of clear relevance to patients and providers. A phase 3 hospital-based study (SAPPHIRE; clinicaltrials.gov, NCT03376321; EudraCT, 2017-002156-84) will use an updated version of the Hospital Recovery Scale as the primary end point, aiming to simultaneously capture clinically meaningful outcomes and meet regulatory standards. A phase 3 outpatient study of high-risk adults with influenza (DIAMOND study; clinicaltrials.gov, NCT03381196; EudraCT, 2017-002217-59) will use time to symptom resolution as the primary end point.

Addressing influenza public health challenges requires novel agents with the ability to expand the treatment window from symptom onset until treatment initiation [24, 25]. In this study, oral pimodivir plus oseltamivir showed a favorable safety profile, with pharmacokinetic profiles unaffected by age. This preliminary exploratory efficacy trial demonstrated promising antiviral and clinical benefits in at-risk, hospitalized influenza A-infected patients.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. We wish to thank all the patients, family members, and staff from all the centers who participated in the study. Laboratory support was provided by ***Covance***, ***Viroclinics Biosciences***, ***Kinesis***, and ***PRA Health Sciences***. Medical writing support was provided by ***Christopher Whittaker*** (Zoetic Science, an Ashfield company, part of UDG Healthcare plc, Macclesfield, UK), and funded by ***Janssen Pharmaceuticals***.

Financial support. This work was supported by Janssen Research and Development.

Potential conflicts of interest. B. O'N. reports personal fees from Seqirus. M. G. I. reports personal fees from Celltrion, Genentech/Roche, GlaxoSmithKlein, Janssen, Seqirus, Shionogi, Viracor Eurofins, and VirBio; grants from Emergent BioSolutions, Genentech/Roche, and Janssen; payments to Northwestern University by AiCuris, Chimerix, Gilead, and Shire for research; and he was a nonpaid consultant for GlaxoSmithKlein, Romark, and Vertex. A. C. N. reports payments to Skåne University Hospital by Janssen. W. v. D., I. V. D., D. A., S. D., T. K., J. V., S. R., and L. L. are employees of Johnson & Johnson and may be stock holders. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Taubenberger JK, Kash JC. Influenza virus evolution, host adaptation, and pandemic formation. Cell Host Microbe **2010**; 7:440–51.
2. Grohskopf LA, Sokolow LZ, Broder KR, Walter EB, Fry AM, Jernigan DB. Prevention and control of seasonal influenza with vaccines: recommendations of the advisory committee on immunization practices-United States, 2018–19 Influenza Season. MMWR Recomm Rep **2018**; 67:1–20.
3. Mertz D, Kim TH, Johnstone J, et al. Populations at risk for severe or complicated influenza illness: systematic review and meta-analysis. BMJ **2013**; 347:f5061.
4. Budd AP, Wentworth DE, Blanton L, et al. Update: influenza activity - United States, October 1, 2017-February 3, 2018. MMWR Morb Mortal Wkly Rep **2018**; 67:169–79.
5. Panatto D, Signori A, Lai PL, Gasparini R, Amicizia D. Heterogeneous estimates of influenza virus types A and B in the elderly: results of a meta-regression analysis. Influenza Other Respir Viruses **2018**; 12:533–43.
6. Oh DY, Hurt AC. A review of the antiviral susceptibility of human and avian influenza viruses over the last decade. Scientifica **2014**; 2014:430629.

7. Hayden FG, Sugaya N, Hirotsu N, et al; Baloxavir Marboxil Investigators Group. Baloxavir marboxil for uncomplicated influenza in adults and adolescents. N Engl J Med **2018**; 379:913–23.
8. Genentech, Inc. XOFLUZA prescribing information, **2018**. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210854s000lbl.pdf. Accessed May 2020.
9. de Jong MD, Ison MG, Monto AS, et al. Evaluation of intravenous peramivir for treatment of influenza in hospitalized patients. Clin Infect Dis **2014**; 59:e172–85.
10. Marty FM, Vidal-Puigserver J, Clark C, et al. Intravenous zanamivir or oral oseltamivir for hospitalised patients with influenza: an international, randomised, double-blind, double-dummy, phase 3 trial. Lancet Respir Med **2017**; 5:135–46.
11. Centers for Disease Control and Prevention. Influenza antiviral medications: summary for clinicians. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm. Accessed September 2019.
12. Clark MP, Ledeboer MW, Davies I, et al. Discovery of a novel, first-in-class, orally bioavailable azaindole inhibitor (VX-787) of influenza PB2. J Med Chem **2014**; 57:6668–78.
13. Finberg RW, Lanno R, Anderson D, et al. Phase 2b study of pimodivir (JNJ-63623872) as monotherapy or in combination with oseltamivir for treatment of acute uncomplicated seasonal influenza A: TOPAZ trial. J Infect Dis **2019**; 219:1026–34.
14. Roche. Oseltamivir—summary of product characteristics. https://www.hpra.ie/docs/default-source/Safety-Notices/tamiflu-6mg-ml-powder-for-oral-suspension-smpc-version-10sept2012.pdf?sfvrsn=0. Accessed September 2019.
15. Powers JH, Guerrero ML, Leidy NK, et al. Development of the Flu-PRO: a patient-reported outcome (PRO) instrument to evaluate symptoms of influenza. BMC Infect Dis **2016**; 16:1.
16. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Medical Dictionary for Regulatory Activities, Version 19.1. https://www.meddra.org/sites/default/files/guidance/file/intguide_19_1_english.pdf. Accessed September 2019.
17. Osborne RH, Norquist JM, Elsworth GR, et al. Development and validation of the influenza intensity and impact questionnaire (FluiiQ™). Value Health **2011**; 14:687–99.
18. National Institute of Allergy and Infectious Diseases. Anti-influenza hyperimmune intravenous immunoglobulin pilot study (INSIGHT 005: Flu-IVIG Pilot). ClinicalTrials.gov. Identifier NCT02008578. https://clinicaltrials.gov/ct2/show/NCT02008578. Accessed September 2019.
19. Deleu S, Kakuda TN, Spittaels K, et al. Single- and multiple-dose pharmacokinetics and safety of pimodivir, a novel, non-nucleoside polymerase basic protein 2 subunit inhibitor of the influenza A virus polymerase complex, and interaction with oseltamivir: a phase 1 open-label study in healthy volunteers. Br J Clin Pharmacol **2018**; 84:2663–72.
20. Ison MG. Influenza in hospitalized adults: gaining insight into a significant problem. J Infect Dis **2009**; 200:485–8.
21. Nguyen-Van-Tam JS, Venkatesan S, Muthuri SG, Myles PR. Neuraminidase inhibitors: who, when, where? Clin Microbiol Infect **2015**; 21:222–5.
22. Gubareva LV, Mishin VP, Patel MC, et al. Assessing baloxavir susceptibility of influenza viruses circulating in the United States during the 2016/17 and 2017/18 seasons. Euro Surveill **2019**; 24:1800666.
23. Peterson RL, Vock DM, Powers JH, et al; INSIGHT FLU-IVIG Study Group. Analysis of an ordinal endpoint for use in evaluating treatments for severe influenza requiring hospitalization. Clin Trials **2017**; 14:264–76.
24. Li TC, Chan MC, Lee N. Clinical implications of antiviral resistance in influenza. Viruses **2015**; 7:4929–44.
25. Shen Z, Lou K, Wang W. New small-molecule drug design strategies for fighting resistant influenza A. Acta Pharm Sin B **2015**; 5:419–30.