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MAJOR ARTICLE

Efficacy and Safety of WXSH0208 Tablets in Treatment of Acute Uncomplicated Influenza Infection in Adults: A Multicenter Randomized, Double-Blind, Placebo-Controlled Phase 2 Trial

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Background. WXSH0208 is a selective inhibitor of influenza RNA polymerase subunit, demonstrating antiviral activity in preclinical studies against influenza A and B virus infections. The purpose of this study was to investigate the efficacy and safety of WXSH0208 in adult outpatients with uncomplicated influenza.

Methods. We conducted a multicenter phase 2 trial based on a randomized, double-blind, placebo-controlled design at 23 research centers in China from November 2023 to March 2024. Participants were randomized 1:1:1:1 to receive one of the following treatments within 48 hours of symptom onset: WXSH0208 10 mg once daily for 5 days, 20 mg once daily for 5 days, 30 mg once daily for 3 days, or placebo. The primary outcome was the time to negative detection of viral load by reverse transcriptase quantitative polymerase chain reaction in the intention-to-treat infected population.

Results. Of 240 randomized patients, 209 were included in the intention-to-treat infected analysis. The median time to negative detection of viral load was 49.3 hours in the WXSH0208 10 mg group, 48.0 hours in the 20 mg group, and 48.2 hours in the 30 mg group, as compared with 95.6 hours in the placebo group ($P < .001$). Time to alleviation of influenza symptoms was comparable among all groups. Treatment-emergent adverse events were reported in 48.3% to 51.7% of WXSH0208 recipients and 58.3% of placebo recipients, with most being mild or moderate in severity.

Conclusions. WXSH0208 showed no evident safety concerns and was superior to placebo in reducing viral load in adult outpatients with uncomplicated influenza.

Clinical Trials Registration. CTR20233250 (www.chinadrugtrials.org.cn).

Keywords. influenza symptoms; safety; uncomplicated influenza; viral load; WXSH0208.

Seasonal influenza remains a global health challenge and a major cause of considerable morbidity and mortality [1, 2]. Currently, 3 types of antiviral drugs are available for influenza treatment: M2 ion channel inhibitors, neuraminidase inhibitors, and RNA polymerase subunit inhibitors. However, widespread resistance to M2 ion channel inhibitors has precluded

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their clinical use [3]. There have also been reports of antiviral resistance to neuraminidase inhibitors, including the widely prescribed oseltamivir [4, 5].

The RNA polymerase subunits of influenza virus have garnered considerable attention as highly promising targets for the development of antiviral drugs. Several drugs targeting these subunits—polymerase basic protein 1 (PB1), polymerase basic protein 2 (PB2), and polymerase acidic protein (PA)—have been studied in clinical trials [6]. The PB1 inhibitor favipiravir [7], approved in Japan in 2014 for treating influenza viruses that are unresponsive or insufficiently responsive to other antiviral agents, has shown inconsistent clinical efficacy and antiviral effects in phase 3 randomized controlled trials of uncomplicated influenza [8]. The PB2 inhibitor pimodivir, whether administered as monotherapy or in combination with oseltamivir, has shown significant virologic improvements for uncomplicated influenza A but failed to add clinical and virologic benefit to the standard-of-care treatment in the interim analysis of a phase 3 trial [9, 10]. Baloxavir marboxil, a selective PA inhibitor, has demonstrated substantial antiviral and clinical efficacy against influenza A and B viruses in adult outpatients with uncomplicated influenza [11]. Comparable benefits were also observed in healthy children aged 1 to 12 years with acute influenza and in outpatients aged ≥12 years who were at high risk [12, 13]. However, variant viruses with I38T/M/F PA substitutions that confer reduced susceptibility to baloxavir have been detected [11–15]. Evidence has been reported indicating the occurrence of infections with these emerging resistant variants in patients who had not undergone treatment with baloxavir, potentially suggesting transmission from individuals who had been treated with baloxavir [13]. The emergence of resistance variants emphasizes the ongoing necessity for continuous research into novel and effective anti-influenza agents.

WXSH0208, an oral small molecule anti-influenza agent inhibiting the selective PA subunit, has demonstrated antiviral activity against influenza A and B viruses in vitro, including strains resistant to baloxavir (unpublished preclinical study data, available in the supplementary clinical trial protocol). In an ascending single-dose study involving healthy participants, no evident safety concerns were noted with the highest-tested dosage of WXSH0208 (60 mg). WXSH0208 showed linear pharmacokinetic characteristics and a plasma elimination half-life of 14.7 hours. The aim of the current study was to evaluate the efficacy and safety of 3 WXSH0208 dosing regimens as compared with placebo in adult outpatients with uncomplicated influenza A and B virus infections.

METHODS

Study Design

This multicenter phase 2 trial based on a randomized, double-blind, placebo-controlled design was conducted at 23 clinical centers in China. The trial enrolled adult participants aged 18 to 64 years with influenza-like illness from November 2023 through March 2024. Participants were randomly assigned in a 1:1:1:1 ratio to receive a once-daily oral dose as follows: WXSH0208 10 mg for 5 days, WXSH0208 20 mg for 5 days, WXSH0208 30 mg for 3 days plus placebo for 2 days, and placebo for 5 days. The 3 dosing regimens of WXSH0208 in our study were based on the pharmacodynamic, pharmacokinetic, and safety findings in the preclinical study (supplementary protocol 4.3). Randomization was completed via an interactive web response system generated by SAS software (version 9.4; SAS Institute). All patients, study team, and data analysts were masked by medication allocation. The active drugs were identical to the placebo tablets in appearance, smell, and outer packaging. Patients in all 4 groups received 3 pills per day: 5 mg × 2 pills and 20 mg × 1 pill of WXSH0208, placebo, or both. To minimize the impact of food consumption on drug absorption as demonstrated in phase 1 studies, patients were instructed to take the drug at least 2 hours before or 2 hours after meals. The study protocol and amendments were reviewed and approved by institutional review board and ethics committee at each study site. This study was conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines of the International Conference on Harmonization. The trial was registered with the Center for Drug Evaluation of the National Medical Products Administration in China (www.chinadrugtrials.org.cn; CTR20233250). Written informed consent was obtained from each participant. Data were analyzed by a statistician employed by the research sponsor.

Patients

Patients who were eligible had a documented axillary temperature ≥37.3 °C, at least 1 respiratory symptom (cough, nasal congestion, or sore throat), and at least 1 systemic symptom of moderate or worse severity (headache, muscle or joint pain, feverishness or chills, and fatigue) within 48 hours of symptom onset (see supplementary material for assessment of influenza symptom severity). A positive test result for influenza A or B virus by rapid antigen test or reverse transcriptase quantitative polymerase chain reaction (RT-qPCR) was another entry criterion. Participants self-assessed the severity of influenza symptoms twice daily from enrollment to day 9 and once daily from days 10 through 14 using a 4-point scale (0, none; 1, mild; 2, moderate; 3, severe). Patients were required to assess their health status on a scale from 0 (worst) to 10 (normal) each evening from days 1 through 14. In addition, patients measured their body temperature 4 times daily from days 1 to 3 and twice daily from days 4 through 14. Patients with the following underlying conditions were excluded: a body mass index ≥30 kg/m^2, pregnancy, major comorbidities, severe illness resulting in hospitalization, or receipt of anti-influenza medication within 4 weeks prior to enrollment. During the

study, patients were allowed to use acetaminophen as needed. Participants were assessed by medical investigators on day 1 (before the first dose of the trial drug) and days 2, 3, 5, 6, 9, and 15. Routine laboratory tests, including blood examination, chemical tests, and thyroid function tests, were performed on days 1, 6, and 15. Nasopharyngeal swab specimens were obtained on day 1 (before first dose) and days 2, 3, 5, 6, 9, and 15 to measure influenza virus load and viral titer by RT-qPCR and viral culture, respectively. Full details of the trial design are available in the supplementary protocols.

Outcomes

The primary outcome was to evaluate the time to negative detection of viral load by RT-qPCR in the intention-to-treat infected (ITTI) population. The key secondary outcomes included the time to negative detection of viral titer, the change from baseline to day 15 in viral RNA load and titer, the mean viral load and titer area under the curve (AUC) from baseline to day 15, and the time to alleviation of influenza symptoms. Other secondary end points were the percentage of patients with measurable viral load and influenza symptom relief at each time point. All secondary end points are listed in the supplementary protocols. The safety end points included the frequencies and severity of treatment-emergent adverse events, defined as those reported after the first dose of study drug. Severity assessment was based on the Common Terminology Criteria for Adverse Events (version 5.0).

Statistical Analysis

Based on the phase 2 clinical trial of baloxavir marboxil [11], the estimated median time to negative detection of viral load by RT-qPCR was 5 days in the placebo group, and the estimated hazard ratio (HR) for the treatment group vs the placebo group was 0.56. The comparison was made by a 2-sided, 2-sample log-rank test with $\alpha = .05$ and $\beta = .80$, with a follow-up of 14 days. The number of required participants was determined to be 54 in each group. Considering a dropout rate of 5%, this trial planned to enroll 240 in the ITTI population, with 60 per group.

The intention-to-treat population and safety set population included all randomized participants who received at least 1 dose of the investigational drug. The ITTI population included all participants who received the investigational drug with confirmed influenza virus infection based on RT-qPCR, serving as the primary analysis population. The per-protocol set population included all participants from the ITTI population who did not experience a major protocol deviation that affected the analysis of the primary end point. Time to negative detection of viral RNA load by RT-qPCR—defined as the time between the initiation of study treatment and the first instance when viral RNA by RT-qPCR fell below the limit of detection—was compared between each of the 3 WXSH0208 trial groups and the placebo group with a log-rank test. Considering that this is a phase 2 exploratory study, the log-rank test was used separately for comparisons between each WXSH0208 dosage group and placebo, without corrections for multiple comparisons. Patients whose virus RNA had not reached cessation by the last observation time point were treated as censored at that time point. The HRs of each treatment group vs the placebo group and their 95% CIs were calculated by a Cox proportional hazards model. Kaplan-Meier curves were plotted, and the median time to negative detection of viral load by RT-qPCR and its 95% CI were calculated for all groups. The 95% CIs were estimated via the log-log transformed Brookmeyer-Crowley method. A similar approach was applied to the secondary end point of time to alleviation of influenza symptoms. The Clopper-Pearson method and other necessary statistics were also applied. Additionally, sensitivity analysis was conducted in per-protocol set and ITTI populations. The type and number of any adverse events, treatment-emergent adverse events, and patients with serious adverse events were reported for each intervention group. All statistical analyses were performed with SAS (version 9.4; SAS Institute).

RESULTS

Patient Disposition and Baseline Characteristics

A total of 240 patients underwent randomization, of whom 232 completed the trial and 209 were included in the ITTI population (Figure 1). The overall population was 45.0% male (n = 94), with a median age of 26 years (IQR, 22–33). No significant differences in demographic or clinical characteristics were noted between those assigned to WXSH0208 treatment groups and those assigned to the placebo group (Table 1). In the ITTI population, 28.7% of patients initiated the trial regimen within 24 hours of symptom onset and 69.4% within 24 to 48 hours. The influenza A virus was the predominant virus type, accounting for 70.8% to 87.3% of infections in the 4 trial groups.

Virologic and Clinical Efficacy

In the ITTI population, the median time to negative detection of viral load by RT-qPCR in the 3 WXSH0208 dose groups was significantly shorter than that in the placebo group: 49.3 hours in the 10-mg group, 48.0 in the 20-mg group, and 48.2 in the 30-mg group vs 95.6 in the placebo group, corresponding to differences of −46.3 hours (HR, 1.68; 95% CI, 1.14–2.49; $P = .0390$), −47.6 (HR, 1.93; 95% CI, 1.30–2.86; $P = .0163$), and −47.4 (HR, 2.20; 95% CI, 1.47–3.29; $P = .0089$), respectively (Figure 2, Supplementary Table 1). The risk of detectable viral load in the 3 WXSH0208 dosing regimens vs placebo was reduced by 40.5%, 48.2%, and 54.5%. Sensitivity analysis confirmed the significant shortening of time to negative detection of viral load in the WXSH0208 groups as compared with the

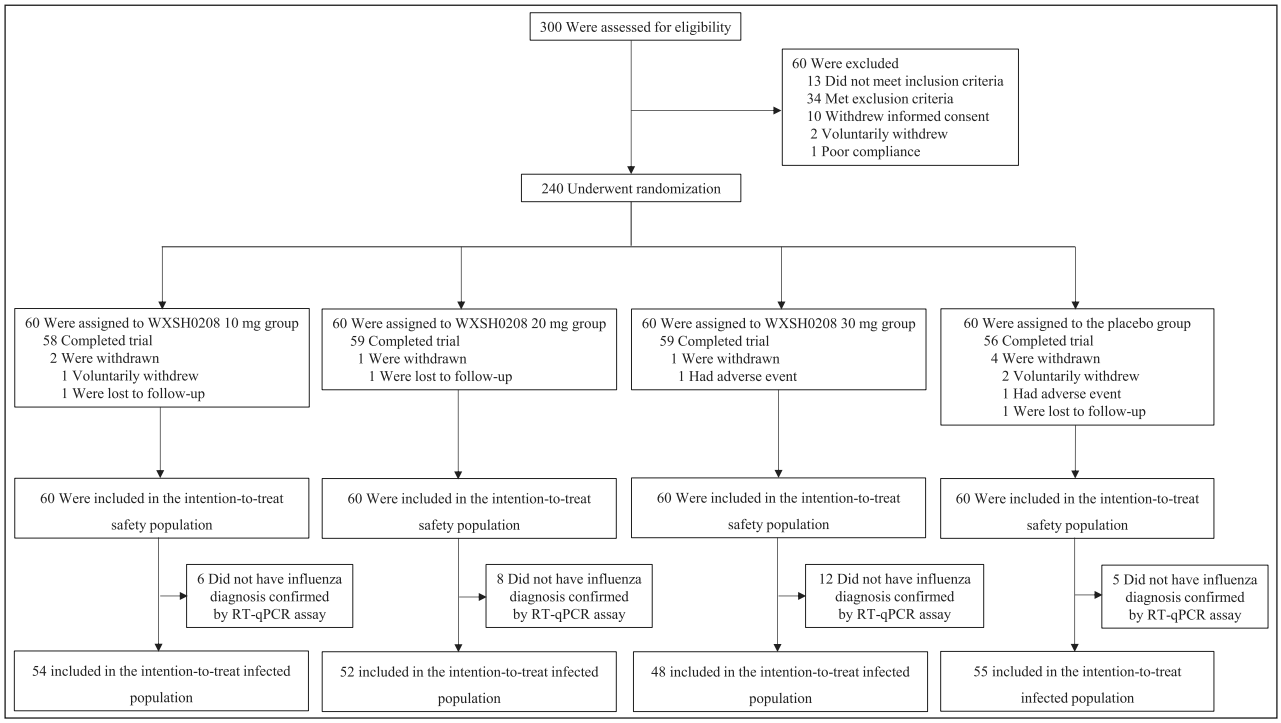

Figure 1. Trial profiles. The intention-to-treat infected population included the patients who were originally randomized, received at least 1 dose of the investigational drug, and had a positive RT-qPCR test result at baseline. The safety set population was defined as all patients who were randomized and received the drugs at least once. RT-qPCR, reverse transcriptase quantitative polymerase chain reaction.

Table 1. Baseline Demographic and Clinical Characteristics

	WXSH0208 10 mg (n = 54)	WXSH0208 20 mg (n = 52)	WXSH0208 30 mg (n = 48)	Placebo (n = 55)
Age, y	25.5 (20.0–32.0)	25.5 (23.0–33.0)	26.0 (21.0–35.0)	27.0 (23.0–32.0)
Weight, kg				
Mean	61.3 ± 11.4	63.9 ± 12.6	64.7 ± 11.8	62.0 ± 12.0
>80	3 (5.6)	6 (11.5)	3 (6.3)	6 (10.9)
BMI, kg/m^2	21.9 ± 2.8	22.7 ± 3.5	23.0 ± 3.4	22.7 ± 3.0
Male sex	26 (48.1)	25 (48.1)	20 (41.7)	23 (41.8)
Current smoker	8 (14.8)	3 (5.8)	5 (10.4)	10 (18.2)
Total score of influenza symptoms at baseline	12.4 ± 3.0	12.4 ± 2.8	11.8 ± 3.1	11.6 ± 2.8
Body temperature, °C	38.0 ± 0.5	38.0 ± 0.6	38.0 ± 0.7	38.1 ± 0.6
Time from symptom onset to initiation of the trial regimen, h				
<24	15 (27.8)	17 (32.7)	15 (31.3)	13 (23.6)
24–48	37 (68.5)	35 (67.3)	33 (68.7)	40 (72.7)
>48	2 (3.7)	0	0	2 (3.6)
Influenza virus type on RT-qPCR assay at enrollment				
A, uncertain subtype	41 (75.9)	43 (82.7)	34 (70.8)	48 (87.3)
B	13 (24.1)	9 (17.3)	14 (29.2)	7 (12.7)
Influenza viral load, $\log_{10}$ copies/mL	5.03 ± 1.16	5.01 ± 0.97	5.11 ± 1.04	4.99 ± 1.00
Influenza vaccination	0	0	0	0

Data are presented as median (IQR), mean ± SD or No. (%) unless noted otherwise.

Abbreviations: BMI, body mass index; RT-qPCR, reverse transcriptase quantitative polymerase chain reaction.

placebo group (Supplementary Table 2). Further analyses of the time to negative detection of viral load by RT-qPCR within subgroups revealed significant differences among the WXSH0208 groups and the placebo group: treatment initiated 24 to 48 hours after symptoms onset (median, 48.5 hours [95% CI, 44.8–52.9] vs 47.2 [25.1–49.3] vs 48.0 [25.1–49.7] vs 96.2

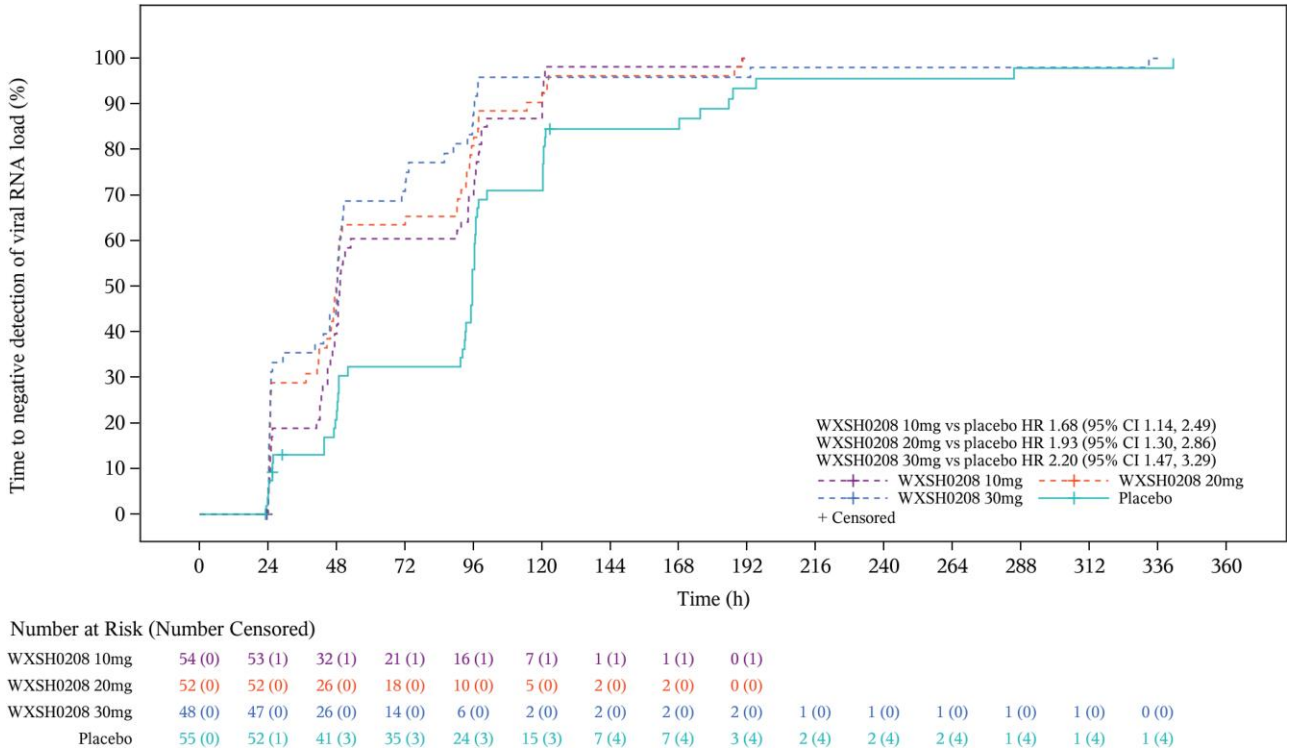

Figure 2. Kaplan-Meier curve of time to negative detection of viral load by reverse transcriptase quantitative polymerase chain reaction in the intention-to-treat infected population. The median time to negative detection of viral load in the 3 WXSH0208 dose groups was significantly shorter than in the placebo group: 49.3 hours in the WXSH0208 10-mg group, 48.0 hours in the WXSH0208 20-mg group, and 48.2 hours in the WXSH0208 30-mg group vs 95.6 hours in the placebo group. HR, hazard ratio.

[93.1–97.2]), influenza A infection (median, 48.8 hours [95% CI, 45.9–91.6] vs 48.9 [42.0–91.8] vs 48.0 [25.1–50.4] vs 95.7 [93.1–97.2]), and baseline weight <80 kg (median, 49.2 hours [95% CI, 46.5–91.6] vs 48.7 [46.1–90.4] vs 48.1 [29.2–49.7] vs 95.6 [91.5–96.9]; Supplementary Table 3).

The mean virus load AUC measured with RT-qPCR from baseline to day 15 was lower for the WXSH0208 treatment groups than the placebo group ($P < .0001$; Supplementary Table 4), with the average changes from the placebo group being 7.92 day × $\log_{10}$ copies/mL (95% CI, 3.19–12.65), 8.42 (3.65–13.20), and 8.90 (4.03–13.77) for the WXSH0208 10-, 20-, and 30-mg groups, respectively. Similarly, the mean virus titer AUC (viral culture method) from baseline to day 15 was lower for the WXSH0208 treatment groups than the placebo group ($P < .0001$; Supplementary Table 4).

WXSH0208 was associated with a significantly more rapid decline in viral load and titer than placebo. By 24 hours after initiation of the treatment regimen, the mean reductions in viral load from baseline were 1.70, 1.80, 2.05, and 1.21 $\log_{10}$ copies/mL in the 3 WXSH0208 dosing regimen groups and the placebo group, respectively (Figure 3, Supplementary Table 5). Meanwhile, the mean reductions in viral titer from baseline were 2.16, 1.78, 2.01, and 1.60 $\log_{10}$ $TCID_{50}$/mL (50% tissue-culture infective dose per milliliter) in the 3 WXSH0208 dosing regimen groups and the placebo group (Supplementary Table 6). The proportion of patients with measurable viral load and titer also declined more rapidly in each WXSH0208 group vs the placebo group (Supplementary Tables 7 and 8).

The median time to alleviation of influenza symptoms among the 3 WXSH0208 dosing regimen groups was not significantly shorter than that of the placebo group (62.1 hours in the 10-mg group, 53.4 in the 20-mg group, and 62.9 in the 30-mg group vs with 65.6 in the placebo group). No significant differences were observed in comparisons of time to alleviation of respiratory or systemic symptoms between the 3 WXSH0208 groups and the placebo group (Figure 4, Supplementary Table 9). The WXSH0208 20-mg group had a significantly shorter median time to fever relief than the placebo group (15.5 hours [95% CI, 8.2–18.1] vs 18.1 [13.2–23.1], $P = .0254$; Supplementary Table 10). No significant difference in time to return to routine daily activities was observed between the WXSH0208 groups and the placebo group (Supplementary Table 11).

Any treatment-emergent adverse events were reported in 53.3%, 48.3%, and 51.7% of WXSH0208 recipients and 58.3% of placebo recipients (Table 2). The severity of most adverse events was grade 1 or 2. The most frequent treatment-emergent adverse

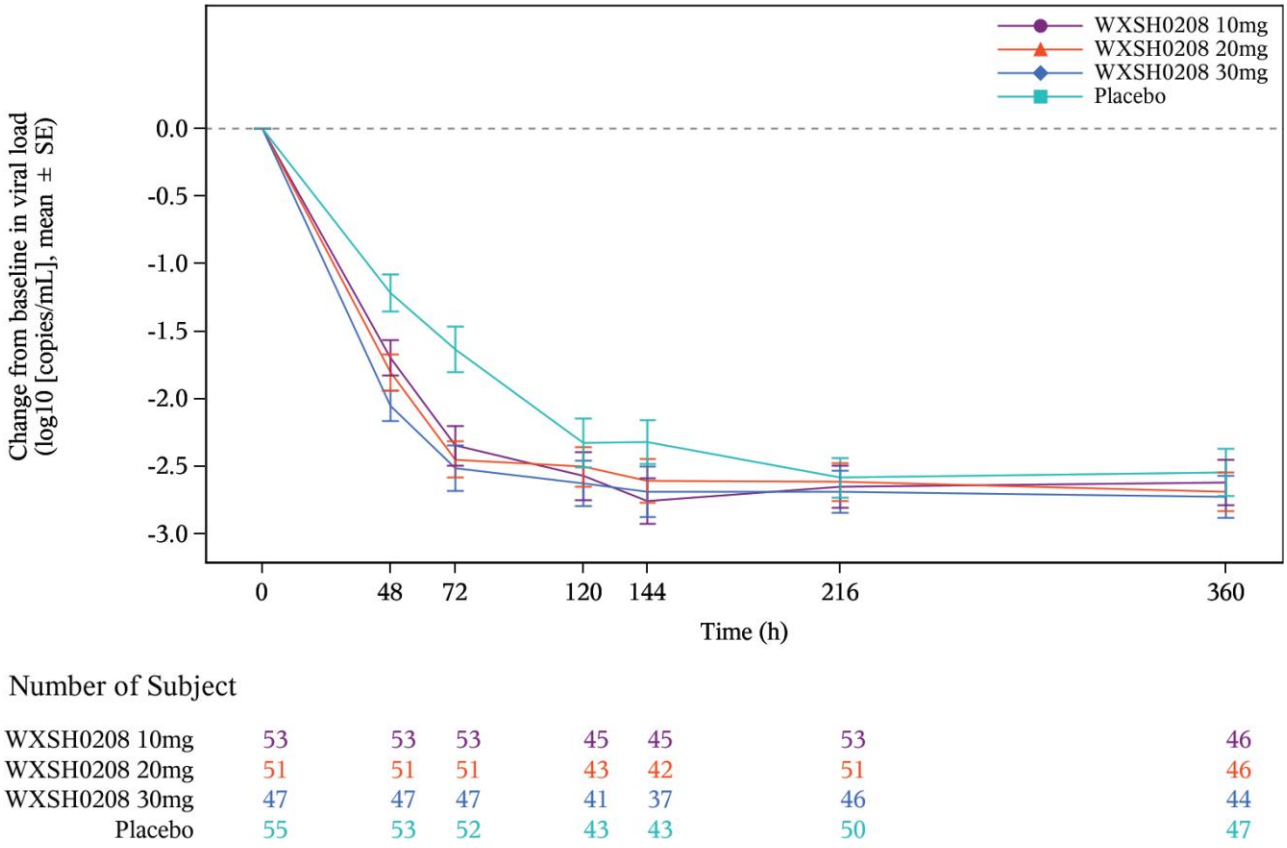

Figure 3. Change from baseline in viral load at each time point. By 1 day after initiation of the treatment regimen, the mean reductions of viral load from baseline were −1.70, −1.80, −2.05, and −1.21 $\log_{10}$ copies/mL in the 3 WXSH0208 dosing regimen groups (10, 20, and 30 mg) and the placebo group, respectively.

events (by >5% of participants in any group), including vomiting, hematuria, hypertriglyceridemia, and sinus bradycardia, were mild or moderate in severity and resolved rapidly. Four events of grade ≥3 laboratory abnormalities, specifically elevated triglyceride levels that were absent at enrollment, were observed in the WXSH0208 20-mg, WXSH0208 30-mg, and placebo groups. Two serious treatment-emergent adverse events reported as grade 3 were noted in WXSH0208 30-mg recipients (acute bronchitis and bacterial pneumonia); however, neither was identified by the investigators as being associated with the trial medication, and both patients eventually recovered after further adequate treatment. The incidence of complications due to influenza, such as bronchitis and otitis, was low in the 4 trial groups (Supplementary Table 12). No deaths were reported during this phase 2 study.

DISCUSSION

In this phase 2 study, 3 WXSH0208 dose regimens were administered within 48 hours of symptom onset in adult outpatients with uncomplicated influenza, which resulted in a statistically significant reduction in the time to negative detection of viral RNA load by RT-qPCR as compared with the placebo group. Other observations included a shorter time to negative detection of viral titer and a lower mean viral load AUC from baseline to day 15 for the WXSH0208 trial groups relative to the placebo group. WXSH0208 had a remarkable antiviral effect, albeit without an accompanying acceleration in the alleviation of influenza symptoms.

The virologic efficacy of WXSH0208 in the current study corresponds well with findings from earlier studies in adult patients with uncomplicated influenza. Among the antiviral agents targeting the influenza virus RNA polymerase subunits, favipiravir and pimodivir showed substantial antiviral effects in phase 3 trials, although no satisfying clinical efficacy was demonstrated [8, 10]. The clinical and antiviral efficacy of baloxavir in phase 2 and 3 trials has led to its application as a first-line medication [11–13]. The phase 2 clinical trial on baloxavir for adult and adolescent outpatients with uncomplicated influenza showed that baloxavir had a shorter median duration of virus RNA load detection than placebo, with a significant difference of −48 hours in the ITTI population. Onradivir, a novel PB2 subunit inhibitor, also had a strong antiviral effect with a shorter median time to negative detection of viral RNA load

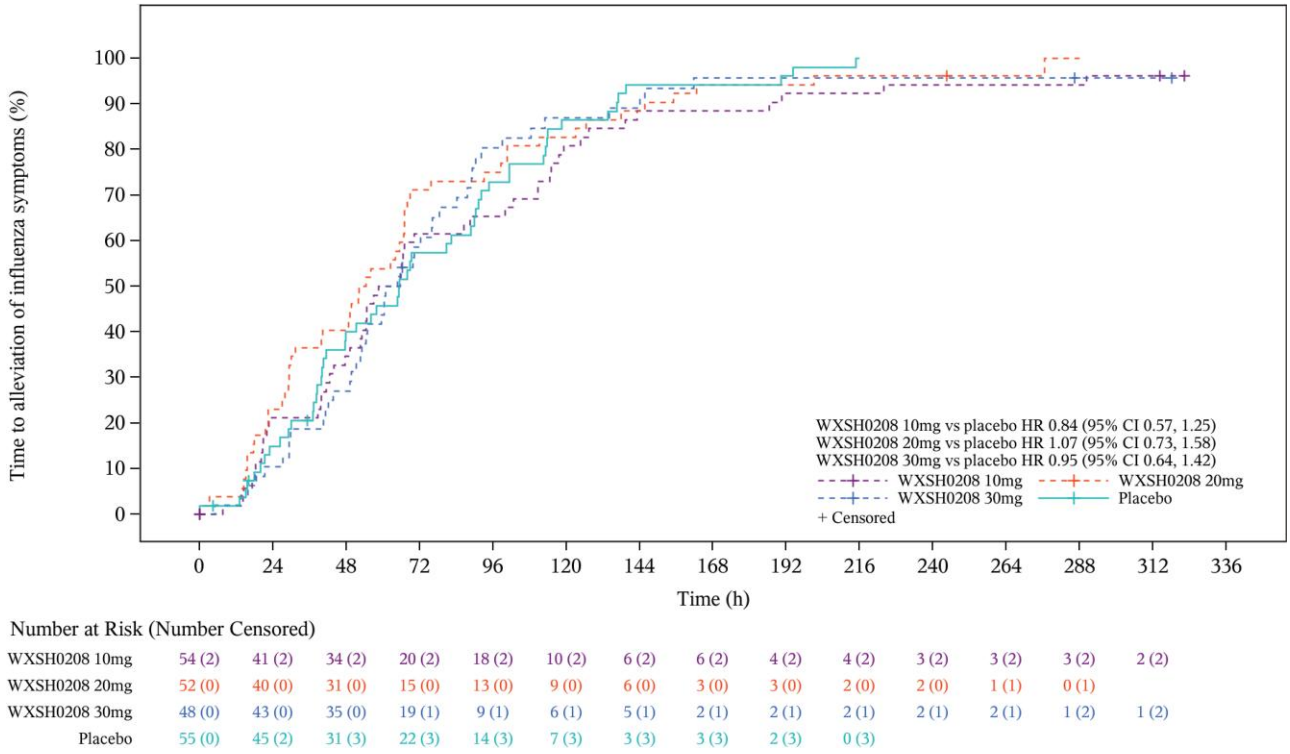

Figure 4. Time to alleviation of influenza symptoms by dose group (patient diary card record). The median time to alleviation of influenza symptoms among the 3 WXSH0208 dosing regimen groups was not significantly shorter than that of the placebo group: 62.1 hours in the WXSH0208 10-mg group, 53.4 hours in the WXSH0208 20-mg group, and 62.9 hours in the WXSH0208 30-mg group vs 65.6 hours in the placebo group. HR, hazard ratio.

in a phase 2 trial [16]. Our current study of WXSH0208 in adult patients with uncomplicated influenza revealed superior antiviral efficacy as compared with a previous study of oseltamivir [17].

A significant decrease in median time to alleviation of influenza symptoms was also observed in the onradivir or baloxavir treatment group as compared with the placebo group in phase 2 studies [11, 16]. It remains unclear why the greater antiviral activity of WXSH0208 in our study brings no significant benefit of influenza symptoms when compared with placebo. The small sample size limited the conclusions that could be drawn. A phase 3 clinical trial with a sufficiently large number of patients who initiated the trial drug early is expected. In addition, WXSH0208 10-mg once-daily therapy led to a similar time to negative detection of viral RNA load vs placebo in the subgroup that initiated treatment within 24 hours of symptom onset, indicating that low-dose WXSH0208 cannot effectively suppress the early replication of the influenza virus.

An additional observation is the enrollment of a larger cohort of participants infected with influenza A virus in our study. In the subgroup analysis, WXSH0208 showed no significant antiviral efficacy in patients with influenza B infection in comparison with those with influenza A. This finding corresponds with previous studies reporting that oseltamivir was less efficacious in the treatment of influenza B as compared with influenza A [11, 18, 19]. Notably, the phase 3 trial of baloxavir marboxil revealed clinical and virologic benefits over placebo in patients at high risk with uncomplicated influenza B (CAPSTONE-2) [13]. However, the observed difference in antiviral efficacy between influenza A and B subtypes in the present study may be attributable to the relatively limited sample size of patients with influenza B, highlighting the need for further investigation in a phase 3 trial with larger cohorts.

A favorable safety profile was identified for WXSH0208 in our study. Adverse events in the treatment groups were well tolerated and soon relieved. Vomiting, the most common treatment-emergent adverse event in the WXSH0208 groups, was mild and transient, occurring more frequently in the WXSH0208 30-mg regimen.

There are several limitations in this study. We did not assess patients for the emergence of resistant variants with a reduced susceptibility to WXSH0208. Based on previous studies investigating novel antiviral agents such as baloxavir and onradivir, the development of resistant variants appears to be an inevitable outcome of their therapeutic use. Whether the strong antiviral effect of WXSH0208 would be associated with a lower risk of resistant variants requires further study. Our trial was also

Table 2. Adverse Events in the Phase 2 Study of WXSH0208: Safety Population

	WXSH0208 10 mg (n = 60)	WXSH0208 20 mg (n = 60)	WXSH0208 30 mg (n = 60)	Placebo (n = 60)
Any adverse event	34 (56.7)	30 (50.0)	31 (51.7)	35 (58.3)
Any treatment-emergent adverse event	32 (53.3)	29 (48.3)	31 (51.7)	35 (58.3)
Treatment-related adverse events reported in at least 2% of patients in any group				
Sinus bradycardia	4 (6.7)	1 (1.7)	0	3 (5.0)
Hypertriglyceridemia	3 (5.0)	4 (6.7)	4 (6.7)	4 (6.7)
Urinary tract infection	3 (5.0)	0	0	5 (8.3)
White blood cell decreased	3 (5.0)	1 (1.7)	0	4 (6.7)
Neutrophil decreased	3 (5.0)	2 (3.3)	2 (3.3)	2 (3.3)
Diarrhea	2 (3.3)	1 (1.7)	1 (1.7)	1 (1.7)
Hematuria	2 (3.3)	0	0	4 (6.7)
Vomiting	1 (1.7)	0	4 (6.7)	2 (3.3)
Epistaxis	1 (1.7)	0	3 (5.0)	3 (5.0)
Chest discomfort	1 (1.7)	2 (3.3)	0	0
AST increased	2 (3.3)	1 (1.7)	0	1 (1.7)
ALT increased	0	2 (3.3)	0	1 (1.7)
Adverse events leading to discontinuation of trial	0	0	1 (1.7)	1 (1.7)
Serious treatment-emergent adverse events	0	0	2 (3.3)	0
Worst adverse events				
Grade 3	0	1 (1.7)	3 (5.0)	1 (1.7)
Grade 4	0	0	1 (1.7)	0

Data are presented as No. (%). Adverse events include those of any grade unless noted otherwise.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

limited by the enrollment of a relatively small number of patients with influenza B infection, as well as the lack of determination of influenza A subtypes (H1N1 or H3N2). Consequently, the conclusions regarding the efficacy of WXSH0208 against distinct influenza subtypes are constrained.

In conclusion, this phase 2 trial demonstrated the antiviral efficacy and favorable safety profile of WXSH0208 among adult outpatients with uncomplicated influenza. While no significant benefits of influenza symptoms were observed, a phase 3 study is warranted to conclusively determine the extent of its clinical benefit. WXSH0208 has the potential to be another effective antiviral agent for the clinical treatment of influenza.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Author contributions. B. C., Y. W., and W. C. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: B. C. and Y. W. Acquisition, analysis, or interpretation of data: all authors. Writing–original draft: W. C. Writing–review and editing: B. C. and Y. W. Statistical analysis: W. C. and Y. W.

Data sharing. The study protocol is provided in the supplementary material. Additional data will be made available on reasonable requests directed to the corresponding author. Proposals will be reviewed and approved by the sponsor, investigator, and collaborators based on scientific merit.

Role of the funder/sponsor. The trial was designed by principal investigators independently without the participation of sponsors. Data were collected by the investigators and site personnel, analyzed by statisticians from a third party, and interpreted by investigator team.

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Potential conflicts of interest. The clinical trial titled "Severe Influenza Trial of Arbidol" (ClinicalTrials.gov: NCT03787459) led by B. C. has received support from Shijiazhuang No. 4 Pharmaceutical. 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.

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