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Effects of Baloxavir Marboxil Plus Neuraminidase Inhibitor vs Neuraminidase Inhibitor in High-risk Patients Hospitalized With Severe Influenza: A Post Hoc Analysis of the Flagstone Trial

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Background. Combining baloxavir with neuraminidase inhibitors (NAIs) has not demonstrated significant benefits in severe influenza. High-risk populations with impaired viral clearance may represent the optimal candidates for this combination treatment.

Methods. We conducted a post hoc analysis of the Flagstone trial (NCT03684044), including patients hospitalized with severe influenza. Eligible participants met at least 1 of the following criteria: immunosuppression, diabetes, or chronic lung disease. Time to clinical improvement (TTCI), 28-day mortality, virological outcomes, and safety end points were assessed.

Results. Among the 143 patients included in the efficacy analysis, 92 received baloxavir in combination with NAI (dual antiviral group), while 51 received NAIs alone (mono antiviral group). The median TTCI did not differ significantly between groups ($P = .48$). However, in patients infected with influenza A H3N2, the TTCI was significantly shorter in the dual compared with the mono antiviral group (median [interquartile range {IQR}], 97.53 [43.02–149.27] hours vs 172.42 [95.93–243.52] hours; $P = .013$). The dual antiviral group demonstrated significantly lower mortality compared with the mono antiviral group (2 [2.17%] of 92 vs 6 [11.76%] of 51; $P = .02$) and was associated with a shorter time to cessation of viral shedding ($P < .001$). A significantly greater reduction in the adjusted mean change in virus titer from baseline to day 2 was observed in the dual antiviral group ($P < .001$). Serious adverse events were comparable between the 2 groups ($P = .42$).

Conclusions. The combination of baloxavir and NAI demonstrated superior mortality reduction compared with NAI monotherapy, without increasing the risk of adverse events.

Keywords. baloxavir; dual antiviral therapy; high-risk; post hoc analysis; severe influenza.

While antiviral treatments have demonstrated clear benefits in nonsevere influenza [1–4], their efficacy in severe cases remains controversial [5, 6]. Combining antivirals with distinct mechanisms of action offers a promising strategy for severe influenza [7]. Influenza RNA polymerase inhibitors, particularly baloxavir, represent a novel class of antiviral agents with potent activity [8, 9]. In both uncomplicated influenza patients and high-risk outpatients, baloxavir has shown superior viral clearance compared with neuraminidase inhibitors (NAIs) [2, 3]. Though the combination of baloxavir and NAI was anticipated to benefit severe influenza patients, clinical studies have not shown advantages [6]. Drawing on findings from coronavirus disease 2019 (COVID-19) research, where early antiviral treatment reduced hospitalization and mortality risks in high-risk COVID-19 patients [10], we propose that the high-risk population with severe influenza might benefit from combination antiviral therapy.

Individuals with high-risk conditions—including, but not limited to, diabetes, chronic pulmonary disorders, and immunosuppressive states—experience a disproportionate burden of influenza-related morbidity and mortality [11–13]. Patients with a single risk factor have a 1.8-fold increased risk of hospitalization due to influenza, while those with ≥4 risk factors face

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a 6.4-fold elevation in risk compared with individuals without such factors [13]. Among hospitalized influenza patients with high-risk profiles, mortality rates range from 12% to 43%, significantly higher than the 4%–8% observed in the general hospitalized influenza population [11, 14, 15]. Impaired viral clearance in these high-risk patients positions them as prime candidates for combination antiviral therapeutic strategies [16–18]. Consequently, there is an urgent need for further research to evaluate the efficacy of combination therapy in severe influenza cases among patients with high-risk factors. To date, the Flagstone trial remains the only randomized controlled trial assessing the efficacy of baloxavir-NAI combination therapy in severe influenza patients [6], offering an opportunity for this investigation. In this post hoc analysis of the Flagstone trial, we examined the efficacy and safety of baloxavir-NAI combination therapy within the specific subgroup of high-risk patients.

METHODS

Study Design and Participants

This is a post hoc analysis of the Flagstone trial, a phase III, multicenter, double-blind randomized controlled trial that enrolled 366 patients hospitalized with severe influenza between January 8, 2019, and March 16, 2020. Inclusion criteria of the trial were as follows: age ≥12 years, hospitalization for severe influenza or prolonged hospitalization due to hospital-acquired influenza (confirmed by rapid influenza diagnostic tests or reverse transcription polymerase chain reaction [RT-PCR]). Symptom onset had to occur within 96 hours. Severe influenza was defined by a baseline National Early Warning Score 2 (NEWS2) ≥4 [19], requiring ventilation or supplemental oxygen support, or the presence of influenza-related complications necessitating hospitalization. Exclusion criteria included body weight <40 kg, expected discharge or death within 48 hours, and prior antiviral treatment for ≥48 hours before screening. The detailed study design and results have been previously published [6]. Only immunocompromised patients, patients with diabetes, or patients with chronic lung disease, including chronic obstructive lung disease (COPD), interstitial lung disease, bronchiectasis, and cystic fibrosis, were analyzed in this study. Immunocompromised patients were defined as individuals with primary immunodeficiency, solid organ transplant recipients on ongoing immunosuppression, allogeneic hematological stem cell transplant recipients on ongoing immunosuppression, individuals with HIV and a most recent CD4 <500/mm^3 within the last 6 months, those with hematologic malignancies, or individuals receiving systemic immunosuppressive therapy for at least 12 weeks before and continuing at the first time of study drug administration. Immunosuppressive therapies included steroids, cytotoxic agents, proteasome inhibitors, calcineurin inhibitors, mTOR inhibitors, immunosuppressive antibodies, monoclonal antibodies, and other immunosuppressants.

The Flagstone trial was approved by all the ethics committees of all study sites and is registered with ClinicalTrials.gov (NCT03684044). The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines. All data for the post hoc analysis were de-identified.

Randomization and Masking

All patients enrolled in the Flagstone trial were randomly assigned in a 2:1 ratio to receive either oral baloxavir combined with NAI (dual antiviral group) or NAI plus baloxavir-matched placebo (mono antiviral group). Patients were stratified by region, baseline NEWS2 score (≤7 or >7), and time from symptom onset (≤48 hours or >48 hours). Baloxavir was administered on days 1 and 4, with dosing determined by body weight (40 mg for patients weighing 40 kg to <80 kg; 80 mg for patients weighing ≥80 kg). A third dose on day 7 was administered if any of the following conditions occurred on day 5: mechanical ventilation, persistent fever, severe immunosuppression, pneumonia, or a confirmed or suspected influenza-related complication. NAIs, including oseltamivir and peramivir, were chosen by the treating physician and administered in line with local clinical practice. Participants, investigators, outcome assessors, and data analysts were blinded to the group allocations.

End Points

Efficacy end points included time to clinical improvement (TTCI), 28-day mortality, 7-day mortality, the 6-point ordinal scale at day 7, time to clinical response, ICU admission rate, mechanical ventilation rate, time to hospital discharge, and time to a sustained NEWS2 score of ≤2 for 24 hours. TTCI was defined as the time to discharge or a NEWS2 score of ≤2 maintained for 24 hours, whichever occurred first. Clinical response was defined as the time to discharge or normalization of 4 out of 5 vital signs (systolic blood pressure, oxygen saturation, respiratory status, heart rate, and body temperature) sustained for 24 hours. Virology outcomes included time to cessation of viral shedding by virus titer (TTVS), the proportion of patients with a positive viral titer each day, the mean change in virus titer from baseline, time to cessation of viral detection by viral ribonucleic acid (RNA) load, the proportion of patients with a positive viral RNA load each day, and the mean change in RNA load from baseline. The incidence of adverse events (AEs) was also assessed. AEs reported after the initial dose of the study drug, as well as those with an onset before the start of study treatment but that increased in severity beyond their initial intensity, were included in the safety analyses of this study. Serious adverse events (SAEs) were defined as any untoward medical occurrence that at any dose results in death, is

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life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

Statistical Analyses

The modified intention-to-treat infected (mITTI) population of the Flagstone trial included all the randomized participants who received at least 1 dose of the study drug and had RT-PCR-confirmed influenza at any time point. The safety population consisted of all patients who received at least 1 dose of study drug. High-risk patients (immunocompromised, diabetic, or with chronic lung disease) from the mITTI population were included in the target efficacy analysis population for the post hoc analyses, while high-risk patients from the safety population were included in the target safety analysis.

Baseline characteristics were summarized descriptively, with continuous variables presented as means (SDs) and categorical variables as numbers (proportions). Comparisons of continuous variables were performed using the Student *t* test, and categorical variables were compared using the chi-square test.

Time-to-event outcomes were reported as medians with interquartile ranges (IQRs) and compared between the dual antiviral group and mono antiviral group using the stratified, generalized Wilcoxon test based on the stratification factors at randomization and the Kaplan-Meier method. Subgroup analysis was performed based on influenza virus subtypes, comparing TTCI and TTVS between the dual and mono antiviral groups in patients infected with influenza H1N1 and H3N2 separately. Sensitivity analyses of time-to-event outcomes were conducted using the Fleming-Harrington test to compare differences between groups.

Clinical status at day 7, as assessed by the 6-point ordinal scale, along with the proportion of patients with a positive viral titer and the proportion of patients with detectable RNA each day, were compared using the stratified Cochran-Mantel-Haenszel statistic based on the randomization factors. Analysis of covariance models were used to compare the mean change from baseline in virus titer and in the amount of virus RNA, with adjustments for region, baseline NEWS2, time from symptom onset to study treatment, age, COPD comorbidity (present or absent), and immunocompromised status (yes or no).

Multivariable Cox proportional hazards models were applied to evaluate the effects of combination therapy on TTCI and TTVS. These models adjusted for baseline confounders including age, sex, and admission setting, while incorporating the stratification factors at randomization. Additionally, high-risk conditions and influenza virus subtypes were included as covariates in both TTCI and TTVS models, given their potential influence on efficacy and virology outcomes [1, 3, 20–22].

A P value <.05 was considered statistically significant. Statistical analyses were performed using SAS, version 9.4, and R, version 4.4.1.

RESULTS

Patient Characteristics

Among the 322 mITTI population of the Flagstone study, 143 high-risk patients were included in the efficacy population of this post hoc analysis, with 92 in the dual antiviral group and 51 in the mono antiviral group (Figure 1). The demographic and baseline characteristics of the included population are presented in Table 1. Overall, the mean age (SD) of the dual antiviral group was 63.65 (15.90) years, which was lower than the mono antiviral group (mean [SD], 69.95 [11.42] years; $P = .02$). Diabetes was the most common risk factor in both the dual and mono antiviral groups (49 [53.26%] of 92 vs 28 [54.90%] of 51; $P = .85$), followed by COPD (34 [36.96%] of 92 vs 27 [52.94%] of 51; $P = .06$), immunocompromise (17 [18.48%] of 92 vs 13 [25.49%] of 51; $P = .32$), and interstitial lung disease (11 [11.96%] of 92 vs 8 [15.69%] of 51; $P = .53$). Most of the patients in both groups were hospitalized for the current influenza episode (86 [93.48%] of 92 vs 46 [90.20%] of 51; $P = .49$), with the majority being recruited in general wards (74 [80.43%] of 92 vs 42 [82.35%] of 51; $P = .78$). In the post hoc efficacy population, 49.65% (71/143) were infected with influenza A H1N1, 40.56% (58/143) with influenza A H3N2, and only 4.20% (6/143) with influenza B, with no significant difference between the 2 groups ($P = .22$).

Efficacy End Points

The median (IQR) TTCI was 106.14 (57.52–184.93) hours in the dual antiviral group and 122.13 (67.73–230.02) hours in the mono antiviral group, with no significant difference between the 2 groups (Wilcoxon test, $P = .48$) (Figure 2*A*). Sensitivity analyses (Fleming-Harrington test, $P = .24$) and multivariable Cox proportional hazards models (hazard ratio, 1.20; 95% CI, 0.74–1.94; $P = .46$) (Supplementary Table 1) confirmed that the combination treatment with baloxavir plus NAI was not a risk factor for TTCI. In the influenza A H3N2 subgroup, the median (IQR) TTCI for the dual antiviral group was 97.53 (43.02–149.27) hours, significantly lower than the 172.42 (95.93–243.52) hours observed in the mono antiviral group (Wilcoxon test, $P = .01$) (Figure 2*C*). However, no significant difference in TTCI was found between the 2 groups in the influenza A H1N1 subgroup (Figure 2*B*).

The proportion of patients achieving a specified clinical status on a 6-point ordinal scale at day 7 was similar between the dual antiviral group and the mono antiviral group (Cochran-Mantel-Haenszel, $P = .99$). Specifically, 38 patients (44.19%) in the dual antiviral group and 19 patients (39.58%) in the mono antiviral group were discharged by day 7

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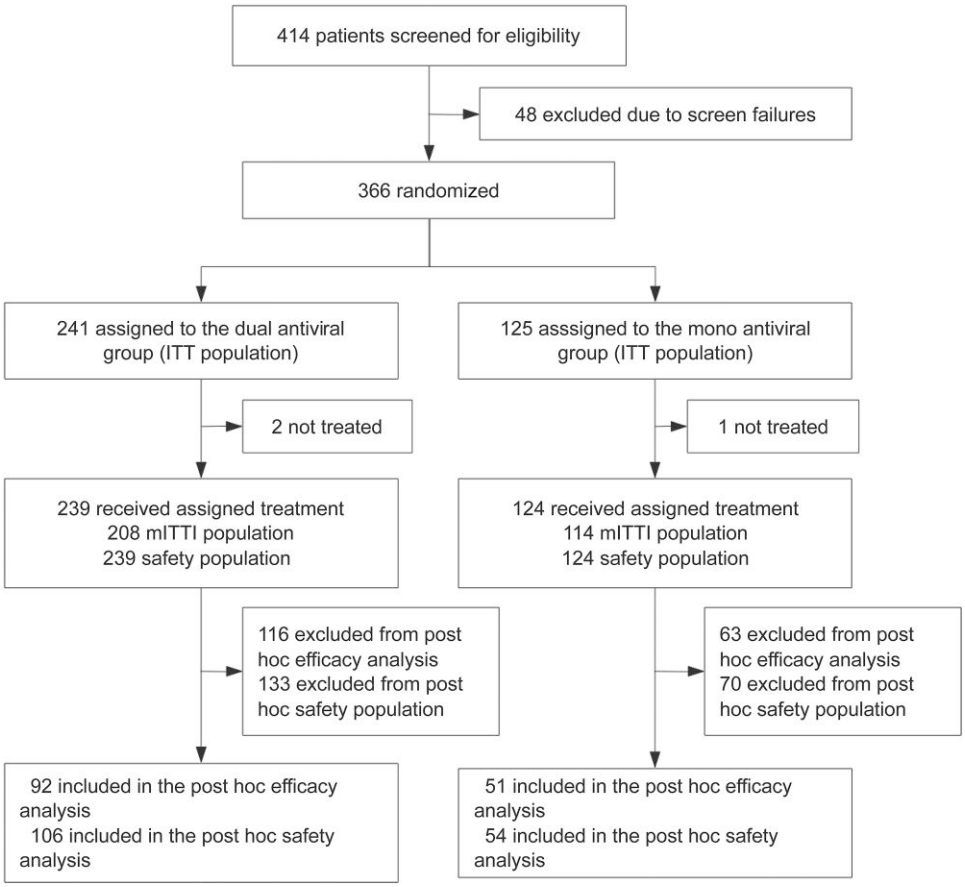

Figure 1. Flowchart of the study. Abbreviations: ITT, intention-to-treat; mITTI, modified intention-to-treat infected.

(Supplementary Table 2). Time to clinical response was also comparable between the 2 groups, with the dual antiviral group having a median (IQR) of 130.14 (76.82–234.02) hours and the mono antiviral group having 144.26 (91.30–282.27) hours (Wilcoxon test, $P = .52$; Fleming-Harrington test, $P = .35$). No significant differences were observed between the dual and mono antiviral groups regarding the proportion of patients with ICU admission, mechanical ventilation, length of hospital stay, or time to NEWS2 of ≤2 maintained for 24 hours (Table 2). Mortality in the dual antiviral group was significantly lower than in the mono antiviral group. No deaths occurred in the dual antiviral group within 7 days, while 3 patients (5.88%) died in the mono antiviral group ($P = .01$). By day 28, 2 deaths (2.17%) occurred in the dual antiviral group, compared with 6 deaths (11.76%) in the mono antiviral group ($P = .02$).

Virology End Points

The median (IQR) viral titer in the dual antiviral group was 1.25 (0.5–4.13) $\log_{10}$ $TCID_{50}$/mL, compared with 1.63 (0.53–4.00) $\log_{10}$ $TCID_{50}$/mL in the mono antiviral group at baseline, with no significant difference between the groups ($P = .90$). The median (IQR) time to cessation of viral shedding in the dual antiviral group was 24.33 (20.08–47.33) hours, which was significantly shorter than in the mono antiviral group (60.98 [36.42–92.38] hours; Wilcoxon test, $P = .002$; Fleming-Harrington test, $P = .004$) (Supplementary Figure 1). After adjusting for baseline characteristics, Cox regression analysis identified that the combination treatment of baloxavir and NAIs was an independent factor for shorter time to cessation of viral shedding (hazard ratio, 2.75; 95% CI, 1.56–4.85; $P < .001$) (Supplementary Table 3). The proportion of patients with a positive viral titer on days 2 and 3 and day 5 was significantly lower in the dual antiviral group (Supplementary Table 4), and the adjusted mean change in viral titer from baseline to day 2 was greater in the dual antiviral group than in the mono antiviral group (mean [SD], −2.20 [1.77] vs −0.79 [1.31] $\log_{10}$ $TCID_{50}$/mL; Cochran-Mantel-Haenszel, $P < .001$) (Figure 3*A*; Supplementary Table 4).

No significant difference was observed between the dual and mono antiviral groups in terms of time to cessation of viral detection by RT-PCR (median [IQR], 136.77 [68.03–211.35] hours vs 176.36 [90.42–210.52] hours; Wilcoxon test, $P = .22$; Fleming-Harrington test, $P = .33$). The baseline viral RNA load was similar between the 2 groups (median [IQR], 6.41

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Table 1. Baseline Characteristics of Patients in the Post Hoc Efficacy Analysis

	Dual Antiviral Group (n = 92), No. (%)	Mono Antiviral Group (n = 51), No. (%)	*P* Value
Age, mean (SD), y	63.65 (15.90)	69.65 (11.42)	**.02**
Sex			.46
Female	42 (45.65)	20 (39.22)	
Male	50 (54.35)	31 (60.78)	
Race			.93
Asian	22 (23.91)	13 (25.49)	
White	64 (69.57)	34 (66.67)	
Black or African American	4 (4.35)	2 (3.92)	
Unknown	2 (2.17)	2 (3.92)	
Region			
North America	17 (18.48)	5 (9.80)	.37
EMEA	43 (46.74)	25 (49.02)	
Rest of world	32 (34.78)	21(41.18)	
High-risk factors			
Chronic obstructive pulmonary disease	34 (36.96)	27 (52.94)	.06
Cystic fibrosis	1 (1.09)	0 (0.00)	1.00
Interstitial lung disease	11 (11.96)	8 (15.69)	0.53
Bronchiectasis	4 (4.35)	0 (0.00)	.06
Diabetes mellitus	49 (53.26)	28 (54.90)	.85
Immunocompromised	17 (18.48)	13 (25.49)	.32
Time to treatment from influenza onset			
Mean (SD), h	58.31 (25.58)	60.00 (24.40)	.70
≤48 h	45 (48.91)	27 (52.94)	.64
>48 h	47 (51.09)	24 (47.06)	
Antiviral treatment ≤48 h before screening			.54
Oseltamivir/oseltamivir phosphate	36/38 (96.74)	20/20 (100)	
Peramivir	2/38 (5.26)	0/20 (0.00)	
Reason for hospitalization			.49
Current influenza episode	86 (93.48)	46 (90.20)	
Other (prolonged hospitalization)	6 (6.52)	5 (9.80)	
Location of recruitment			.78
General ward	74 (80.43)	42 (82.35)	
ICU	18 (19.57)	9 (17.65)	
Requires ventilation or supplemental oxygen	68 (73.91)	43 (84.31)	.15
NEWS2 at baseline, mean (SD)	7.07 (2.31)	7.63 (2.21)	.16
Six-point ordinal scale status at day 1[a]			.11
Discharged	0/91	0/51	
Non-ICU hospital ward not requiring supplemental oxygen or noninvasive ventilation	19/91 (20.88)	8/51 (15.69)	
Non-ICU hospital ward requiring supplemental oxygen or noninvasive mechanical ventilation	51/91 (56.04)	32/51 (62.75)	
ICU without mechanical (invasive) ventilation	19/91 (20.88)	6/51 (11.76)	
Mechanical (invasive) ventilation	2/91 (2.20)	5/51 (9.80)	
Death	0/91	0/51	
Viral subtype			.22
Influenza A H1N1	45 (48.91)	26 (50.98)	
Influenza A H3N2	41 (44.57)	17 (33.33)	
Influenza B	3 (3.26)	3 (5.88)	
Mixed infection	2 (2.17)	1 (1.96)	
Unknown	1 (1.09)	4 (7.84)	

Data are No. (%) or mean (SD). Bold *P* values indicate statistical significance ($P < .05$).

Abbreviations: EMEA, Europe, Middle East, and Africa; ICU, intensive care unit; NEWS2, National Early Warning Score 2.

[a]Based on 91 patients in the dual antiviral group and 51 patients in the mono antiviral group.

[5.30–7.50] $\log_{10}$ copies/mL for the dual antiviral group vs 6.70 [5.09–7.45] $\log_{10}$ copies/mL for the mono antiviral group; $P = .91$). Although no significant difference was found in the proportion of patients with a positive viral RNA load each day, the adjusted mean change in the amount of virus RNA from baseline on day 2 to day 5 and day 10 was significantly greater in the dual antiviral group compared with the mono antiviral group (Figure 3*B*; Supplementary Table 5).

Safety Analyses

A total of 106 patients in the dual antiviral group and 54 patients in the mono antiviral group were included in the post hoc safety analysis of target high-risk patients. Overall, there were no significant differences between the dual and mono antiviral groups in the proportion of patients experiencing adverse events (60 [56.60%] of 106 vs 30 [55.56%] of 54; $P = .90$) (Table 3) or treatment-related adverse events (2 [1.89%] of 106 vs 4 [7.41%] of 54; $P = .09$) (Table 3). However, mortality was significantly lower in the dual antiviral group compared with the mono antiviral group (2 [1.89%] of 106 vs 7 [12.96%] of 54; $P = .005$). Neither group reported treatment-related serious adverse events.

DISCUSSION

In high-risk patients hospitalized with severe influenza, this study showed that combining baloxavir with NAIs significantly shortened the time to clinical improvement in the subgroup of influenza A H3N2. The combination treatment of baloxavir with NAI resulted in reduced 28-day mortality and faster cessation of viral shedding. The dual antiviral therapy showed no increase in adverse events compared with single antiviral treatment in this high-risk population.

Combination antiviral treatments for influenza have been believed to accelerate viral clearance and improve effectiveness [7, 23]. Nevertheless, several clinical trials have failed to observe

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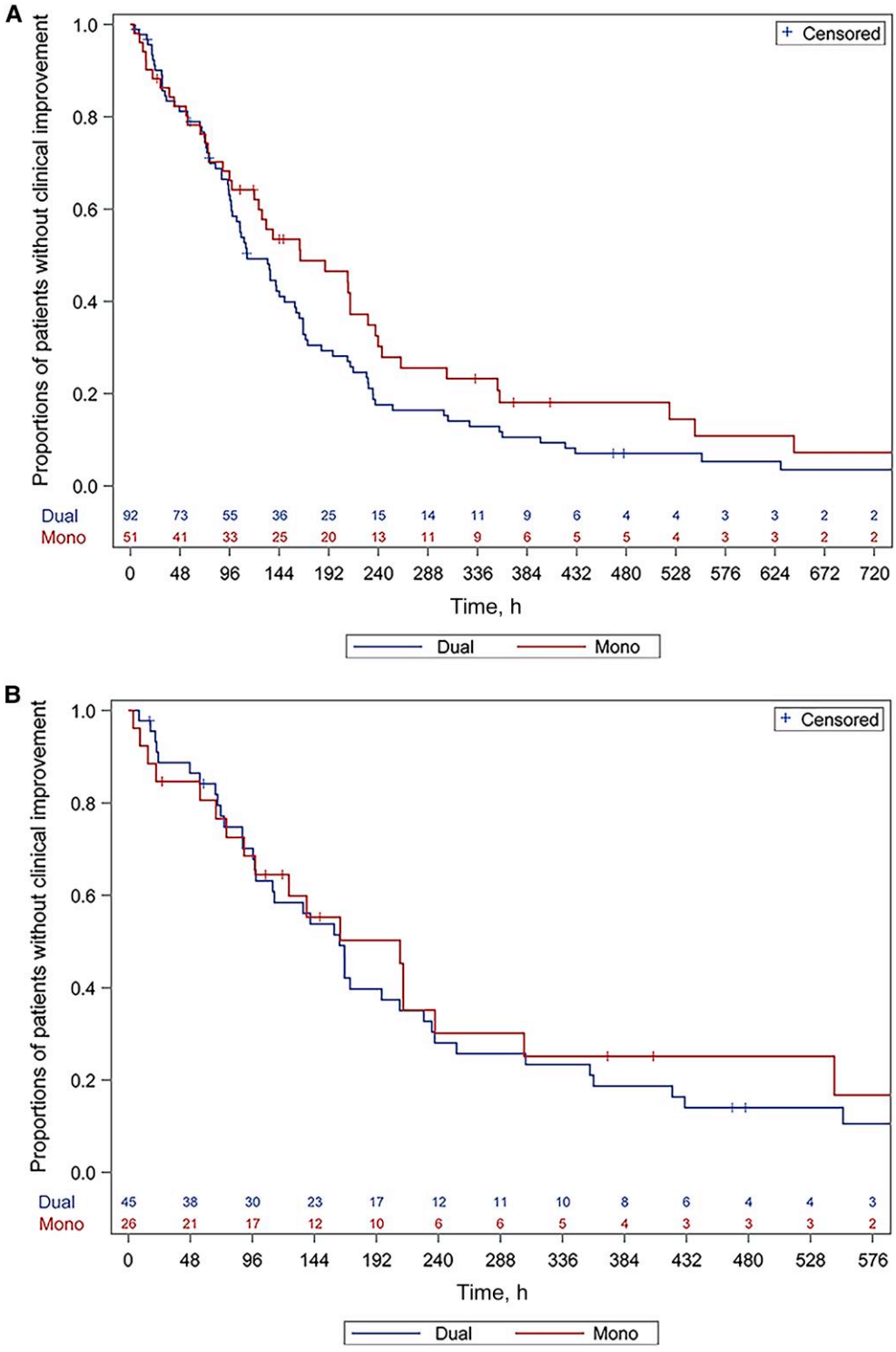

Figure 2. Kaplan-Meier curves of TTCI in the post hoc efficacy population. *A*, TTCI in the overall population. The median (IQR) TTCI was 106.14 (57.52–184.93) hours in the dual antiviral group and 122.13 (67.73–230.02) hours in the mono antiviral group ($P = .477$). *B*, TTCI in the subgroup with influenza A H1N1 infection. The median (IQR) TTCI was 126.28 (68.29–245.54) hours in the dual antiviral group, 112.74 (60.52–212.80) hours in the mono antiviral group ($P = .692$). *C*, TTCI in the subgroup with influenza A H3N2 infection. The median (IQR) TTCI was 97.53 (43.02–149.27) hours in the dual antiviral group and 172.42 (95.93–243.52) hours in the mono antiviral group ($P = .013$). Abbreviations: IQR, interquartile range; TTCI, time to clinical improvement.

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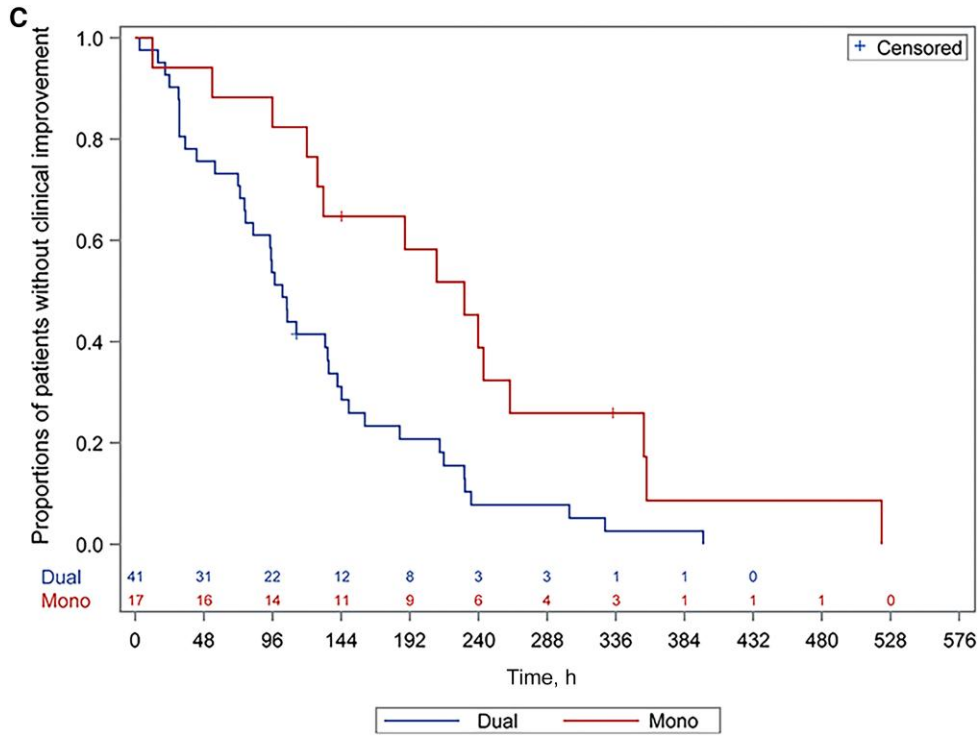

Figure 2. Continued

Table 2. Summary of Efficacy Outcome Measurements

	Dual Antiviral Group (n = 92), No. (%)	Mono Antiviral Group (n = 51), No. (%)	*P* Value
Time to clinical improvement,[a] median (IQR)	106.14 (57.52–184.93)	122.13 (67.73–230.02)	.48/.24
Time to clinical response,[a] median (IQR)	130.14 (76.82–234.02)	144.26 (91.30–282.27)	.52/.35
Incidence of ICU stay	3/70 (4.29)	1/40 (2.50)	1.00
Incidence of mechanical ventilation	8/89 (8.99)	2/46 (4.35)	.49
Time to hospital discharge,[a] median (IQR)	155.98 (97.77–236.27)	163.98 (106.22–330.10)	.77/.21
Time to NEWS2 of ≤2 maintained for 24 h,[a] median (IQR)	115.10 (67.42–303.52)	123.34 (67.73–237.35)	.69/.60
7-d mortality	0 (0.00)	3 (5.88)	**.01**
28-d mortality	2 (2.17)	6 (11.76)	**.02**

Data are expressed as No. (%) or median (IQR). Bold *P* values indicate statistical significance ($P < .05$).

Abbreviations: ICU, intensive care unit; IQR, interquartile range; NEWS2, National Early Warning Score 2.

[a]Time-to-event end points were compared between the dual antiviral group and mono antiviral group using the stratified generalized Wilcoxon test and Fleming-Harrington test based on the stratification factors at randomization, including region, baseline NEWS2 score, and time from symptom onset. The *P* values are presented as *P* values of Wilcoxon test/*P* values of Fleming test.

clinical benefits from combination antiviral therapy for influenza [6, 24, 25]. Our findings suggest that the combination of baloxavir and NAI significantly shortened the TTCI over NAI monotherapy in the influenza A H3N2 subgroup, indicating that combination therapy may offer better efficacy in specific viral subgroups. Although oseltamivir has shown potent antiviral activity against multiple influenza subtypes in vitro, its sensitivity to the H1N1 and H3N2 strains varies across studies. Several studies have found that oseltamivir exhibits higher sensitivity to influenza A H3N2 than to H1N1 [22, 26, 27], with a mean 50% inhibitory concentration (IC_{50}) of 0.73 ± 0.20 nM for H3N2, statistically lower than the 1.37 ± 0.31 nM for H1N1pdm09 ($P < .0001$) [22]. Meanwhile, some studies have shown that baloxavir exhibits greater sensitivity to the H3N2 strain [21, 28, 29]. One study assessing the susceptibility of baloxavir to influenza viruses circulating in the United States during the 2016/2017 and 2017/2018 seasons observed greater sensitivity to H3N2, with mean 50% effective concentrations

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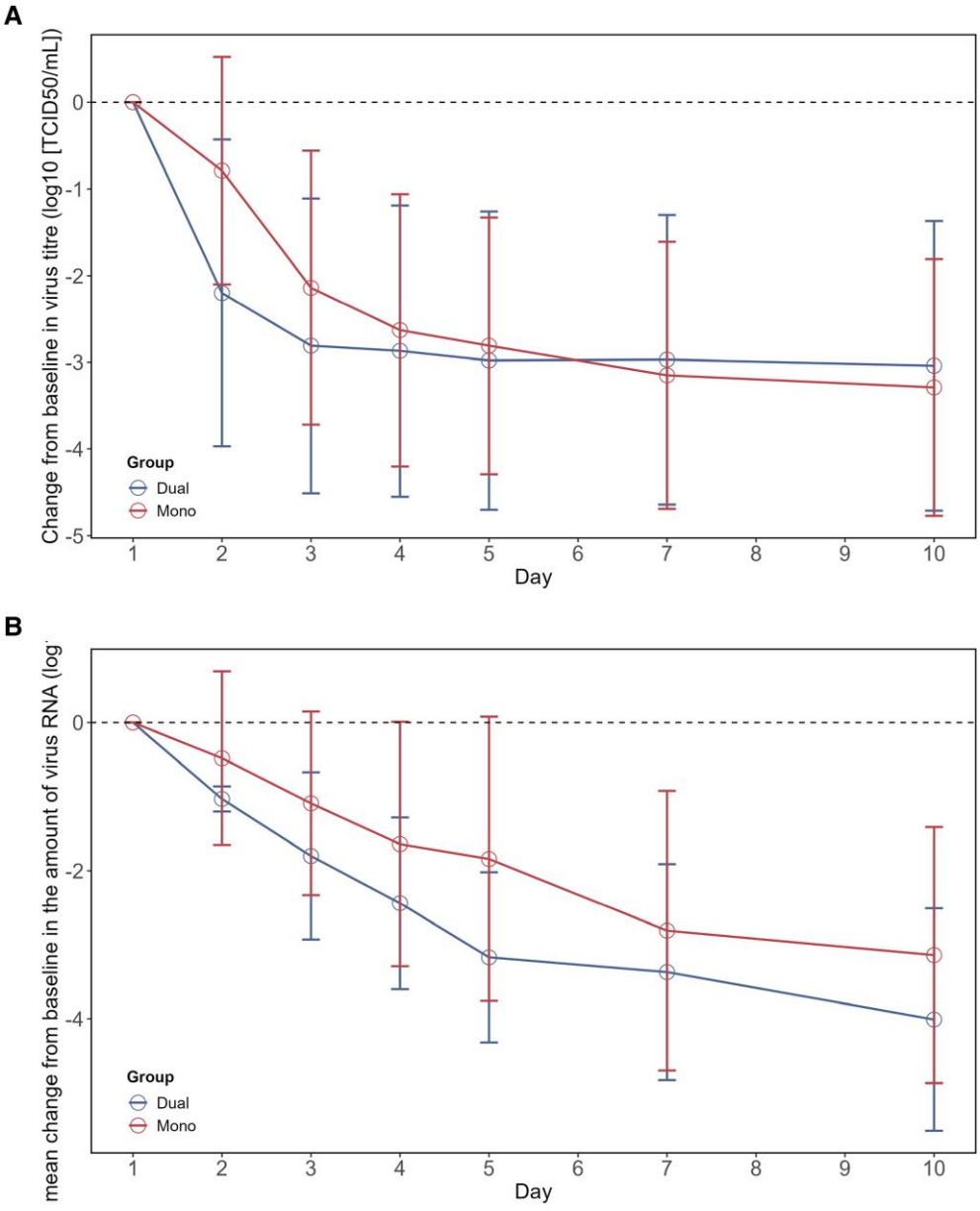

Figure 3. Change from baseline in influenza viral titers (*A*) and influenza viral RNA load (*B*) over time in the post hoc efficacy population. The circle indicates means, and the error bars indicate standard deviations in both panels.

(EC_{50}) of 0.83 ± 0.30 nM for H3N2 and 1.58 ± 0.49 nM for H1N1pdm09 [28], consistent with findings from Hickerson et al. [21]. Both influenza A H1N1 and H3N2 strains show strong synergy when treated with a combination of baloxavir and NAIs [30, 31]. The addition of baloxavir to NAI may provide the greatest antiviral effect. Therefore, severe patients with high-risk conditions infected with influenza H3N2 may benefit most from dual antiviral therapy with baloxavir and NAI. However, due to the underpowered sample size in the viral subgroups, no definitive conclusions can be drawn.

Based on the findings of this study, mortality could be a more suitable end point for assessing the efficacy of dual antiviral treatment in severe influenza patients with risk factors. Although the TTCI in the overall population did not show a significant difference between the dual and mono antiviral groups, the 28-day mortality was significantly reduced with the dual antiviral therapy in our study. Preclinical studies support this view [32, 33]. Moreover, a retrospective analysis primarily involving high-risk patients hospitalized with influenza [34] reported a 30-day mortality of 0% (0/10) in the baloxavir-peramivir combination treatment group,

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Table 3. Summary of Adverse Events and Safety in the Post Hoc Safety Population

	Dual Antiviral Group (n = 106), No. (%)	Mono Antiviral Group (n = 54), No. (%)	*P* Value
Adverse events			
Any	60 (56.60)	30 (55.56)	.90
Leading to withdrawal of study drug	0 (0.00)	2 (3.70)	.11
Serious adverse events (excluding death)	18 (16.98)	12 (22.22)	.42
Death	2 (1.89)	7 (12.96)	.005
Treatment-related adverse events			
Any	2 (1.89)	4 (7.41)	.09
Leading to withdrawal of study drug	0 (0.00)	1 (1.85)	.34
Serious treatment-related adverse events (excluding death)	0	0	
Death	0	0	

numerically lower than the 4.5% (6/132) in the peramivir monotherapy group. Clinical efficacy end points that are based mainly on symptoms or signs, such as TTCI, are suitable for assessing whether antiviral treatment accelerates disease resolution. However, the mechanism of action of antiviral agents is primarily aimed at inhibiting the replication or release of the influenza virus, thereby reducing viral-induced lung damage, rather than promoting lung repair [8, 35]. Combination antiviral treatment accelerates viral clearance in severe influenza patients, potentially preventing disease progression. This suggests that mortality, as an indicator of disease progression, may serve as a more appropriate end point for evaluating the efficacy of antiviral therapy in severe influenza. Further research with larger sample sizes is needed to evaluate the potential of using mortality as a primary end point for dual antiviral therapy in severe influenza patients with high-risk conditions and may yield positive results.

This study has several limitations. As a post hoc secondary analysis, the investigation was not predefined, leading to differences in baseline characteristics, particularly age distribution, between the 2 groups. To address this limitation, we prospectively registered the study protocol on the Vivli, Inc., data sharing platform before study initiation. Moreover, in our analytical approach, we performed Cox regression analyses with comprehensive adjustment for baseline characteristics for selected key outcomes. Additionally, being a subgroup analysis of the Flagstone trial, this study was constrained by a relatively small sample size, which prevented subgroup analyses stratified by different high-risk conditions. The heterogeneity in antiviral immunity, responses to preventive measures such as vaccination, and the varying risks of adverse outcomes across different high-risk populations may collectively influence study outcomes. Future studies should consider stratifying outcomes by these distinct high-risk populations. Furthermore, our study population consisted predominantly of high-risk patients with immunosuppression, diabetes, or chronic lung diseases, with a mean age >60 years. Consequently, the generalizability of our findings to other high-risk populations may be limited. Another limitation arose from the limited number of ICU patients, and therefore the findings regarding this population require further validation. Potential residual confounding, including factors such as vaccination status and other comorbidities, was not available in this study. If the dual antiviral group had higher vaccination rates or fewer comorbidities, the observed benefits of combination therapy might be overestimated. Future studies should rigorously document vaccination status and comorbidities to further validate these findings and address potential confounding factors.

This study suggests that severe influenza patients with high-risk conditions may benefit from the combination of baloxavir and NAI, with a safety profile comparable to that of NAI monotherapy. Additionally, patients infected with influenza A H3N2 are more likely to benefit from this dual antiviral treatment. Further research, particularly focusing on mortality outcomes, is needed to validate the therapeutic advantages of this combination in severe influenza patients with risk factors.

Supplementary Data

Supplementary materials are available at *Open Forum 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.

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Author contributions. All authors had full access to the complete study data and contributed to the critical revision and writing of the manuscript. All authors are responsible for the submission and publication. Y.W. and B.C. designed the study, X.G. and M.Y. conducted the analysis. M.Y. wrote the first draft of the manuscript. Y.W., X.G., and B.C. provided critical revisions on the manuscript.

Patient consent. This study is a post hoc analysis of the Flagstone trial. The Flagstone trial was approved by all the ethics committees of all study sites and is registered with ClinicalTrials.gov (NCT03684044). Before enrollment, written informed consent was obtained from all participants or their legally authorized representatives. All data used in this post hoc analysis were de-identified.

Data sharing. The data used in this study were obtained by requesting access from Roche through the global clinical research data sharing platform Vivli, Inc. (https://search.vivli.org/). Qualified researchers may apply for individual patient-level data from Roche via the Clinical Study Data Request platform (www.clinicalstudydatarequest.com) in accordance with Roche's data sharing policy (https://www.roche.com/innovation/process/clinical-trials/data-sharing).

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Potential conflicts of interest. B.C. is the leading PI from China for the transmission study initiated by F. Hoffmann-La Roche. All other authors report no potential conflicts.

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