Early treatment with baloxavir marboxil in high-risk adolescent and adult outpatients with uncomplicated influenza (CAPSTONE-2): a randomised, placebo-controlled, phase 3 trial

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Summary

Background Baloxavir marboxil (hereafter baloxavir), a selective inhibitor of influenza cap-dependent endonuclease, was approved in 2018 in the USA and Japan for the treatment of uncomplicated influenza in otherwise healthy individuals aged 12 years and older. We aimed to study the efficacy of baloxavir in outpatients at high risk of developing influenza-associated complications.

Methods We did a double-blind, placebo-controlled and oseltamivir-controlled trial in outpatients aged 12 years and older in 551 sites in 17 countries and territories. Eligible patients had clinically diagnosed influenza-like illness, at least one risk factor for influenza-associated complications (eg, age older than 65 years), and a symptom duration of less than 48 h. Patients were stratified by baseline symptom score (≤14 *vs* ≥15), pre-existing and worsened symptoms at onset of illness compared with pre-influenza (yes or no), region (Asia, North America and Europe, or southern hemisphere), and weight (<80 kg *vs* ≥80 kg), and randomly assigned (1:1:1) via an interactive web-response system to either a single weight-based dose of baloxavir (40 mg for patients weighing <80 kg and 80 mg for patients weighing ≥80 kg; baloxavir group), oseltamivir 75 mg twice daily for 5 days (oseltamivir group), or matching placebo (placebo group). All patients, investigators, study personnel, and data analysts were masked to treatment assignment until database lock. The primary endpoint was time to improvement of influenza symptoms (TTIIS) in the modified intention-to-treat population, which included all patients who received at least one dose of study drug and had RT-PCR-confirmed influenza virus infection. Safety was assessed in all patients who receved at least one dose of study drug. This trial is registered with ClinicalTrials.gov, NCT02949011.

Findings 2184 patients were enrolled from Jan 11, 2017, to March 30, 2018, and randomly assigned to receive baloxavir (n=730), placebo (n=729), or oseltamivir (n=725). The modified intention-to-treat population included 1163 patients: 388 in the baloxavir group, 386 in the placebo group, and 389 in the oseltamivir group. 557 (48%) of 1163 patients had influenza A H3N2, 484 (42%) had influenza B, 80 (7%) had influenza A H1N1, 14 patients had a mixed infection, and 28 had infections with non-typable viruses. The median TTIIS was shorter in the baloxavir group (73·2 h [95% CI 67·2 to 85·1]) than in the placebo group (102·3 h [92·7 to 113·1]; difference 29·1 h [95% CI 14·6 to 42·8]; p<0·0001). The median TTIIS in the oseltamivir group was 81·0 h (95% CI 69·4 to 91·5), with a difference from the baloxavir group of 7·7 h (–7·9 to 22·7). Adverse events were reported in 183 (25%) of 730 patients in the baloxavir group, 216 (30%) of 727 in the placebo group, and 202 (28%) of 721 in the oseltamivir group. Serious adverse events were noted in five patients in the baloxavir group, nine patients in the placebo group, and eight patients in the oseltamivir group; one case each of hypertension and nausea in the placebo group and two cases of transaminase elevation in the oseltamivir group were considered to be treatment related. Polymerase acidic protein variants with Ile38Thr, Ile38Met, or Ile38Asn substitutions conferring reduced baloxavir susceptibility emerged in 15 (5%) of 290 baloxavir recipients assessed for amino acid substitutions in the virus.

Interpretation Single-dose baloxavir has superior efficacy to placebo and similar efficacy to oseltamivir for ameliorating influenza symptoms in high-risk outpatients. The safety of baloxavir was comparable to placebo. This study supports early therapy for patients at high risk of complications of influenza to speed clinical recovery and reduce complications.

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Introduction

Influenza causes considerable morbidity and mortality, with the greatest incidence of influenza-associated complications, hospital admissions, and death in high-risk groups, including people aged 50 years and older and those with underlying medical conditions.[1,2] Until 2018, treatment of influenza has been limited to two classes of antiviral medication. Widespread resistance to M2

Research in context

Evidence before this study

Influenza causes considerable morbidity and mortality, with the greatest incidence of influenza-associated complications, admissions to hospital, and death in high-risk patients, including older patients and those with underlying medical conditions. We searched PubMed with terms including "baloxavir marboxil" "influenza," "antiviral therapy," and "neuraminidase inhibitor" for articles published in any language between Dec 1, 2009, and Dec, 1, 2019. Antiviral therapy for influenza is limited to neuraminidase inhibitors that have been generally studied in acute uncomplicated influenza and are associated with reduced duration of symptoms. To date, only one study has reported on the use of baloxavir marboxil (hereafter referred to as baloxavir). In that study, baloxavir shortened the median time to alleviation of symptoms by 26·5 h compared with placebo in adults with acute uncomplicated influenza.

Added value of this study

We compared a single dose of baloxavir with oseltamivir or placebo given for 5 days for improving clinical and virological outcomes of patients with influenza who were at high risk of influenza-associated complications. Baloxavir was similar to oseltamivir but clinically superior to placebo for influenza A and clinically superior to both oseltamivir and placebo for influenza B. We report one of the first prospective studies to enrol sufficient numbers of patients with influenza A and B to assess clinically meaningful differences of antiviral therapy by virus type. Antiviral therapy was associated with lower frequency of influenza-associated complications than was placebo. This finding suggests that antiviral therapy is an efficacious treatment for influenza in patients at high risk of complications.

Implications of all the available evidence

These data support current guidelines recommending early antiviral therapy in high-risk patients infected with influenza. Furthermore, early antiviral therapy reduced the incidence of complications, and baloxavir was effective clinically and virologically against influenza B. These data should provide a case for increasing early therapy for influenza to speed recovery and reduce the risk of complications in high risk patients.

ion-channel inhibitors and emergence of resistance to neuramindase inhibitors (particularly to oseltamivir) in treated patients and community clusters—including global circulation of oseltamivir-resistant seasonal influenza A H1N1 in 2008–09—emphasise the need for new drugs with different mechanisms of antiviral action.[3–6] Furthermore, oseltamivir is less active in vitro against influenza B than influenza A viruses, and it appears to be less effective in treating infections with influenza B virus than it is in treating infections with influenza A virus.[7,8] Although observational studies—some including high-risk groups—have found that timely oseltamivir therapy is associated with reduced risks of influenza-associated pneumonia, cardiovascular events, admission to hospital, and mortality, few randomised, placebo-controlled trials of neuramindase inhibitors in high-risk patients have been published.[9–14]

See Online for appendix

Several new influenza antiviral drugs that target different protein subunits of the influenza polymerase complex are undergoing clinical studies.[15] Baloxavir marboxil (hereafter referred to as baloxavir) is the small-molecule prodrug of baloxavir acid that has antiviral activity against influenza A and B viruses, including those resistant to current antivirals.[16] Baloxavir was licensed in 2018 in otherwise healthy outpatients with uncomplicated influenza after studies showed that a single dose of the drug shortened the median time to alleviation of symptoms by 26·5 h compared with placebo, an effect that was similar to that of oseltamivir.[17] Moreover, baloxavir was associated with more rapid reductions in infectious virus titres than were placebo or oseltamivir, although variant viruses with polymerase acidic protein Ile38Thr, Ile38Met, or Ile38Phe substitutions conferring reduced susceptibility to baloxavir were identified in 2·2–9·7% of patients treated with baloxavir.[17]

In this study, we aimed to assess the efficacy and tolerability of single-dose baloxavir treatment compared with placebo and oseltamivir in adult and adolescent outpatients with uncomplicated influenza who were at high risk of influenza-related complications.

Methods

Study design and participants

The CAPSTONE-2 study was a double-blind, double-dummy, phase 3, randomised controlled trial done at 551 study sites in 17 countries and territories (appendix pp 3–7). The sites included hospitals and clinics in Japan, South Korea, the Philippines, Taiwan, the USA, Europe (Belgium, Bulgaria, Germany, Spain, the UK, Hungary, Latvia, Poland, and Romania), and areas in the southern hemisphere (Australia, New Zealand, and South Africa). Eligible patients were outpatients aged 12 years or older with suspected influenza A or influenza B virus infection who were considered at high risk of developing influenza-associated complications. The definition of patients at high risk of complication was adapted from US Centers for Disease Control and Prevention (CDC) criteria. Other inclusion criteria were clinically diagnosed influenza-like illness as defined by a fever (axillary temperature ≥38·0°C), at least one systemic symptom and at least one respiratory symptom of at least moderate severity, and a symptom duration of 48 h or less. Patients also had to have at least one risk factor defined by

the CDC as placing the patient at increased risk of complications, including asthma or chronic lung disease, endocrine disorders, heart disease, age 65 years or older, and metabolic disorders.[18] Some patients at high risk, including pregnant women or women who were breastfeeding, patients with hepatic impairment, patients with cancer within 5 years (unless non-melanoma skin cancer), patients with untreated HIV or a CD4 count of less than 350 cells per µL in the past 6 months, patients on immunosuppressive treatment for organ or bone marrow transplantation, and patients receiving at least 20 mg prednisolone, were excluded from the trial.

Patients with severe influenza requiring inpatient treatment and patients with a known allergy to oseltamivir were also excluded. A full list of inclusion and exclusion crtieria is presented in the appendix (pp 8–10).

The trial was done in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol was approved by the institutional review boards at each study site and can be found online All participants provided written informed consent (or assent for adolescents).

Randomisation and masking

Participants were enrolled into the study by the investigator and randomly assigned (1:1:1) to either the baloxavir group, the oseltamivir group, or the placebo group with an interactive web response system. Before randomisation, patients were stratified by baseline Influenza Symptom Severity Scale (≤14 or ≥15), pre-existing and worsened symptoms at onset of illness compared with pre-influenza (yes or no), region (Asia, North America and Europe, or southern hemisphere), and weight (<80 kg or ≥80 kg).

All patients, investigators, study personnel, and data analysts were masked to the treatment assigned at randomisation until database lock. The placebo tablets were composed of the same non-pharmacological fillers and were visually identical to the active drugs. To maintain blinding, patients in the baloxavir group received oseltamivir-matched placebo and patients in the oseltamivir group received baloxavir-matched placebo.

Procedures

Patients in the baloxavir group received a single oral dose of baloxavir at baseline (40 mg for patients weighing <80 kg and 80 mg for those weighing ≥80 kg) and oseltamivir-matched placebo twice daily for 5 days. Patients in the oseltamivir group received oseltamivir 75 mg twice daily for 5 days and a single oral dose of baloxavir-matched placebo at baseline. Patients in the placebo group received a single oral dose of baloxavir-matched placebo at baseline and oseltamivir-matched placebo twice daily for 5 days. Paracetamol (acetaminophen; maximum 3000 mg per day) could be given for severe discomfort or fever, but no other symptomatic therapies, antiviral drugs for the treatment of influenza, or antibiotics were permitted, except for the treatment of suspected bacterial infections that developed after randomisation.

Participants self-assessed the severity of seven influenza-associated symptoms (cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue) on a four-point scale (with 0 indicating no symptoms, 1 mild symptoms, 2 moderate symptoms, and 3 severe symptoms) twice daily from enrolment (day 1) until day 9 and once daily on days 10–14 Participants recorded their results in the patient eDiary (electronic diary). Axillary temperature was measured four times a day until day 3 and twice daily until day 14. Additionally, patients assessed their overall health status on a scale of 0 (worst possible) to 10 (normal) each evening until day 14. On days 1, 5 or 6, 15, and 22, safety laboratory tests (haematology, blood chemistry, and urinalysis) were done.

Serum samples for influenza-neutralising antibody testing (with focus-reduction neitralisation test) were collected on days 1 and 22. Nasopharyngeal swabs (or throat swabs, if nasopharyngeal swabbing was not feasible) were collected on days 1, 2, 3, 4 (optional visit), 5, 6 (optional visit), and 9 for viral quantitation (with a cell-based assay and RT-PCR) and susceptibility testing with Sanger sequencing; optional visits were at the discretion of the study patient (appendix pp 12–13). Enrolment RT-PCR results for influenza virus were included in the database after completion of the study and were used to identify the population infected with influenza, but were not available to the study team at the time of enrolment.

Patients in the modified intention-to-treat population who had paired baseline and follow-up samples both confirmed as influenza positive by RT-PCR were included in the analysis of polymerase acidic protein Ile38Thr amino acid substitutions. Polymerase acidic sequencing was done in patients taking baloxavir and randomly selected patients taking placebo, selected to keep balance of type and subtype of virus and region (USA, Asia, EU, southern hemisphere). The polymerase acidic sequencing procedure is described in the appendix (p 13).

Outcomes

The primary objective was to compare baloxavir with placebo, with a secondary objective to compare it with oseltamivir. The primary efficacy endpoint was time to improvement of influenza symptoms (TTIIS), which was defined as time from the start of treatment to patient-reported improvement in all seven influenza-associated symptoms. For patients without symptoms before the onset of illness, all symptoms had to be rated as mild or absent; for patients with symptoms that were present before development of influenza symptoms, symptoms had to improve by at least one level (ie, from severe to moderate; a full definition of improvement measures is presented in the appendix, pp 16–17). Secondary clinical endpoints included time to alleviation of symptoms,

For more on the **protocol** see https://clinicaltrials.gov/ct2/show/NCT02949011?term=baloxavir&draw=2&rank=9

defined as time from the start of treatment to patient-reported alleviation of all seven influenza symptoms (with alleviation defined as absent or mild symptoms); time to patient-reported resolution of fever; number of influenza-associated complications meeting pre-defined diagnostic criteria assessed by investigator (appendix p 10); number of antibiotic prescriptions (reported by investigator); and patient-reported time to return to pre-illness health status. Secondary virology endpoints included the duration of infectious virus detection and changes from baseline in viral titres and viral RNA load over time. A full list of secondary endpoints, including reasons for not reporting some in this Article, is provided in the appendix (pp 18–19).

As an exploratory virology endpoint we assessed the frequency of emergence of amino acid substitutions in polymerase acidic protein Ile38Thr, which have been associated with reduced susceptibility of influenza to baloxavir.[19] We tested for the substitutions by sequencing the polymerase acidic region in the viral genome.

Details of additional post-hoc analyses are described in the appendix (p 20).

Safety endpoints included the frequencies and severities of adverse clinical and laboratory events. A comprehensive list of endpoints is included in the appendix (pp 16–20)

Statistical analysis

The primary efficacy analysis was done in the modified intention-to-treat population, which included all patients who received at least one dose of the study drug and had a confirmed diagnosis of influenza virus infection on the basis of RT-PCR positivity on day 1 and who were enrolled at sites with GCP compliance. Assuming that 55% of randomly assigned participants had confirmed influenza virus infection (on the basis of the previous oseltamivir study in high risk patients),[14,20] we calculated that we needed to enrol 2157 participants (719 per group) to have at least 90% power to detect a 36 h difference in median TTIIS between the baloxavir and placebo groups at a two-sided significance level of 0·05. This assumption would yield 1185 patients in the modified intention-to-treat analysis (395 patients per treatment group).

The safety population included all randomised patients who received at least one dose of the study drug. The population was analysed according to the initial treatment that patients actually received.

A generalised Wilcoxon test, with stratification according to composite symptom score at baseline, pre-existing and worsened symptoms, and region, was used to compare the TTIIS between the baloxavir and placebo groups as a primary analysis, between the baloxavir and oseltamivir groups as a secondary analysis, and for subgroups of interest (both pre-specified and post-hoc; appendix pp 17–18). Confidence intervals for median differences are bootstrap estimates from 10 000 bootstraps. For analysis of the primary endpoint, patients who did not experience improvement of symptoms were treated as censored at the last observation timepoint. Missing data were not imputed for any endpoints. Kaplan-Meier curves were used to to estimate TTIIS.

The details of the pre-specified subgroups and other analyses of the various secondary endpoints are provided in the appendix (pp 17–20). We set the significance level at 0·05 except for the analysis of the frequency of paracetamol use, for which a two-sided significance level of 0·15 was used. The significance level was different for this analysis because it was done not for confirmation of efficacy but to assess the comparability among treatment groups.

An independent data monitoring committee was used to assess safety. This trial is registered with ClinicalTrials.gov, NCT02949011.

Role of the funding source

The sponsor of the study was involved in the study design, data collection, data analysis, and preparation of the manuscript. Data were compiled by the sponsor and analysed by a statistician employed by the sponsor. All authors had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Jan 11, 2017, and March 30, 2018, 2592 patients provided consent and 2184 were randomly assigned to either the baloxavir group (n=730), the placebo group (n=729), or the oseltamivir group (n=725; figure 1). Although 1195 (55%) of 2178 patients received at least one dose of study drug and had influenza confirmed by RT-PCR, only 1163 (53%) were included in the modified intention-to-treat population because 32 patients who were enrolled at sites that were not compliant with Good Clinical Practice guidelines were excluded (figure 1).

No relevant differences in demographic or clinical characteristics were observed across the treatment groups (table 1). In the modified intention-to-treat population, 557 (48%) of 1163 patients had influenza A H3N2, 484 (42%) had influenza B, 80 (7%) had influenza A H1N1pdm, and 42 had mixed infection or other (PCR test did not identify which type of influenza A infection). 526 (45%) patients initiated treatment with study drugs within 24 h after onset of symptoms. The most common risk factors for influenza complications were asthma or chronic lung disease (456 [39%] of 1163 patients), endocrine disorders (382 [33%] of 1163 patients), and age 65 years or older (319 [27%] of 1163 patients). During the study, paracetamol was used less by patients in the baloxavir group than in the placebo group (p=0·066) and to a similar extent in the baloxavir and oseltamivir groups (p=0·71); 178 (46%) of 388 patients in the baloxavir group, 154 (40%) of 386 in the placebo group, and 168 (43%) of 389 in the oseltamivir group did not use paracetamol (appendix p 43).

In the primary efficacy analysis, the median TTIIS was shorter in the baloxavir group than in the placebo group

(73·2 h [95% CI 67·2–85·1] *vs* 102·3 h [92·7–113·1]; p<0·0001), corresponding to a difference between groups of 29·1 h (95% CI 14·6–42·8; figure 2A). This difference was significant in patients with influenza A H3N2 (25·0 h [95% CI 4·7–45·2]; p=0·014; figure 2B), influenza B (26·0 h [2·7–43·6]; p=0·014; figure 2C), and asthma or chronic lung disease (35·6 h [95% CI not estimated]; p=0·0038; appendix p 21). Patients in the baloxavir group had a shorter TTIIS than did those in the placebo group in all regions (except for the southern hemisphere, p=0.31; appendix pp 25–26). The TTIIS was significantly shorter in the baloxavir group than in the placebo group in patients who initiated the trial regimen within 12 h, 12–24 h, or 24–36 h after onset of symptoms, but not in those who started the regimen within 36–48 h (appendix pp 40–42). In a post-hoc analysis, there was no difference between the baloxavir group and the placebo group in median TTIIS in patients without influenza virus infection (100·4 h [95% CI 92·9 to 106·2] in the baloxavir group *vs* 96·1 h [87·1 to 105·0] in the placebo group; median difference –4·3 [–17·5 to 8·7]).

The median TTIIS in the oseltamivir group (81·0 h [95% CI 69·4 to 91·5]) was similar to that in the baloxavir group in all patients (median difference 7·7 h [95% CI –7·9 to 22·7]; figure 2A) and in those infected with influenza A H3N2 virus (–7·2 h [–31·5 to 14·5]; figure 2B), but was significantly shorter in the baloxavir group than in the oseltamivir group in those with influenza B virus (27·1 h [6·9–42·3]; p=0·025; figure 2C).

In 1158 patients who rated all seven symptoms as mild or absent, the median time to alleviation of symptoms in the baloxavir group (77·0 h [95% CI 68·4–88·3]) was shorter

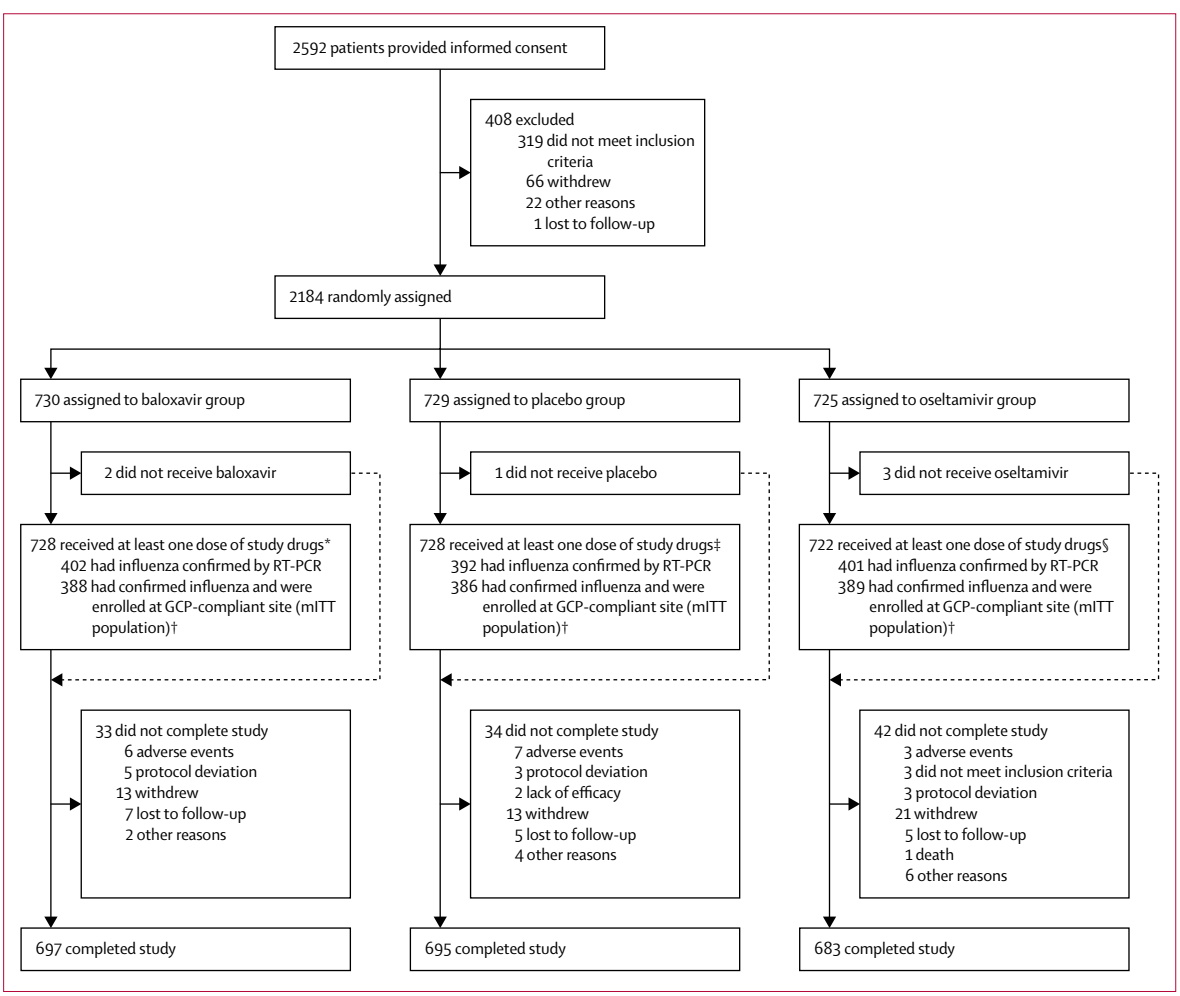

Figure 1: **Trial profile**

GCP=Good Clinical Practice. mITT=modified intention-to-treat. *730 patients were included in the baloxavir safety population, including two patients randomly assigned to other treatment groups who received at least one dose of baloxavir. †727 patients were included in the placebo safety population; one patient randomly assigned to the placebo group received at least one dose of baloxavir and was included in the baloxavir group for safety assessment. ‡721 patients were included in the oseltamivir safety population; one patient randomly assigned to the oseltamivir group received at least one dose of baloxavir and was included in the baloxavir group for safety assessment. §14 patients in the baloxavir group, six in the placebo group, and 12 in the oseltamivir group were excluded from the mITT population because of GCP compliance issues at their enrolment sites, with repeated protocol deviations or deviations related to informed consent at two sites discovered at audit during the study.

	Baloxavir group (n=388)	Placebo group (n=386)	Oseltamivir group (n=389)
Age, years	52·3 (16·8)	51·9 (16·7)	51·1 (17·0)
Maximum	84	86	89
Age group			
12–19	19 (5%)	17 (4%)	22 (5·7)
20–64	256 (66%)	266 (69%)	264 (68%)
≥65	113 (29%)	103 (27%)	103 (26%)
Weight, kg	77·7 (21·6)	79·0 (23·8)	79·5 (23·4)
Maximum	158·2	165·6	167·4
Weight group			
<80	239 (62%)	232 (60%)	233 (60%)
≥80	149 (38%)	154 (40%)	156 (40%)
Sex			
Male	193 (50%)	180 (47%)	191 (49%)
Female	195 (50%)	206 (53%)	198 (51%)
Region			
Asia	159 (41%)	151 (39%)	152 (39%)
North America or Europe	212 (55%)	216 (56%)	220 (57%)
Southern hemisphere*	17 (4%)	19 (5%)	17 (4%)
Current smoker			
Yes	59 (15%)	58 (15%)	66 (17%)
No	329 (85%)	328 (85%)	323 (83%)
Composite symptom score	14·3 (3·7)	14·4 (3·6)	14·2 (3·5)
≤14	188 (48%)	188 (49%)	201 (52%)
≥15	200 (52%)	198 (51%)	188 (48%)
Body temperature, °C	38·4 (0·4)	38·4 (0·4)	38·4 (0·4)
Time to treatment from influenza onset†, h			
0 to ≤12	27 (7%)	42 (11%)	37 (10%)
>12 to ≤24	151 (39%)	150 (39%)	119 (31%)
>24 to ≤36	114 (29%)	120 (31%)	141 (36%)
>36 to ≤48	95 (24%)	74 (19%)	92 (24%)
Influenza vaccination			
Yes	91 (23%)	99 (26%)	104 (27%)
No	297 (77%)	287 (74%)	285 (73%)
Influenza virus subtype based on RT-PCR			
A H1N1pdm	28 (7%)	17 (4%)	35 (9%)
A H3N2	182 (47%)	185 (48%)	190 (49%)
B	167 (43%)	168 (44%)	149 (38%)
Mixed infection	4 (1%)	5 (1%)	5 (1%)
Other‡	7 (2%)	11 (23%)	10 (3%)
Risk factor§			
Asthma or chronic lung disease	151 (39%)	157 (41%)	148 (38%)
Endocrine disorder	123 (32%)	131 (34%)	128 (33%)
Age ≥65 years	113 (29%)	103 (27%)	103 (26%)
Heart disease	46 (12%)	49 (13%)	53 (14%)
Metabolic disorder	51 (13%)	50 (13%)	56 (14%)
Morbid obesity (body mass index ≥40 kg/m^2)	36 (9%)	39 (10%)	48 (12%)

Data are n (%) or mean (SD), unless otherwise specified. *Australia, New Zealand, South Africa. †Data from one patient in baloxavir group missing. ‡Subtype of influenza A not identified. §Risk factors present in at least 10% of patients in any group; enrolled patients could have one or more risk factors.

Table 1: **Baseline characteristics of patients in the modified intention-to-treat population**

than in the placebo group (102·8 h [93·2–113·4]; p<0·0001) and similar to that in the oseltamivir group (85·6 h [71·5–94·8]; p=0·91; appendix p 57). Similarly, the median time to resolution of fever in 1148 patients was shorter in the baloxavir group than in the placebo group (30·8 h [95% CI 28·2–35·4] *vs* 50·7 [44·6–58·8] h; p<0·0001) but not significantly different between the baloxavir group and the oseltamivir group (34·3 [30·0–38·9] h; p=0·24).

Influenza-associated complications were observed in 11 (3%) of 388 patients in the baloxavir group compared with 40 (10%) of 386 patients in the placebo group (p<0·0001) and 18 (5%) of 389 patients in the oseltamivir group (p=0·26; appendix pp 44–45). The significant difference between the baloxavir and placebo groups was due to fewer patients in the baloxavir group than in the placebo group having sinusitis or bronchitis or requiring antibiotics for suspected or proven secondary infections (appendix pp 44–45).

The median time to return to pre-influenza health status was assessed in 274 patients in the baloxavir group, 274 in the placebo group, and 286 in the oseltamivir group. The time did not differ between the baloxavir group (126·4 h [95% CI 104·6–153·4]) and the placebo group (149·8 h [124·7–175·7]; difference 23·4 h [95% CI −21·8 to 52·2]; p=0·46) or the oseltamivir group (126·9 h [104·9 to 152·7]; 0·6 h [−30·6 to 29·0]; p=0·64). One (<1%) of 388 patients in the baloxavir group, five (1%) of 386 in the placebo group, and four (1%) of 389 in the oseltamivir group were admitted to hospital (baloxavir *vs* placebo, p=0·50; baloxavir *vs* oseltamivir, p=1·00).

Baloxavir was associated with a significantly faster decline in infectious virus titres than were placebo and oseltamivir, a finding that was also observed for the subgroups with influenza A H3N2 or B virus infections (figure 3; appendix p 56). By 1 day after initiation of the trial regimen, the mean reduction in virus titre from baseline in the modified intention-to-treat population was 3·36 $\log_{10}TCID_{50}$/mL in the baloxavir group, 1·76 $\log_{10}TCID_{50}$/mL in the oseltamivir group, and 1·25 $\log_{10}TCID_{50}$/mL in the placebo group (figure 3). The reductions in viral RNA load were also faster in the baloxavir group than in the placebo and oseltamivir groups (appendix pp 59–60). In a post-hoc analysis, the median time to sustained cessation of infectious virus detection was shorter in the baloxavir group (48·0 h [95% CI not estimated]) than in the placebo group (96·0 h [95% CI not estimated]; p<0·0001) and the oseltamivir group (96·0 h [95% CI 72·0–96·0]; p<0·0001; appendix pp 46–47, 61). The frequencies and magnitude of neutralising antibody responses were similar across the three treatment groups (appendix pp 48–49).

290 patients in the baloxavir group had paired baseline and follow-up samples both confirmed as influenza positive by RT-PCR and were included in the analysis of amino acid substitutions in polymerase acidic protein. Substitutions at Ile38 were detected in 15 (5%) patients after baloxavir treatment (13 [9%] of 141 with influenza A

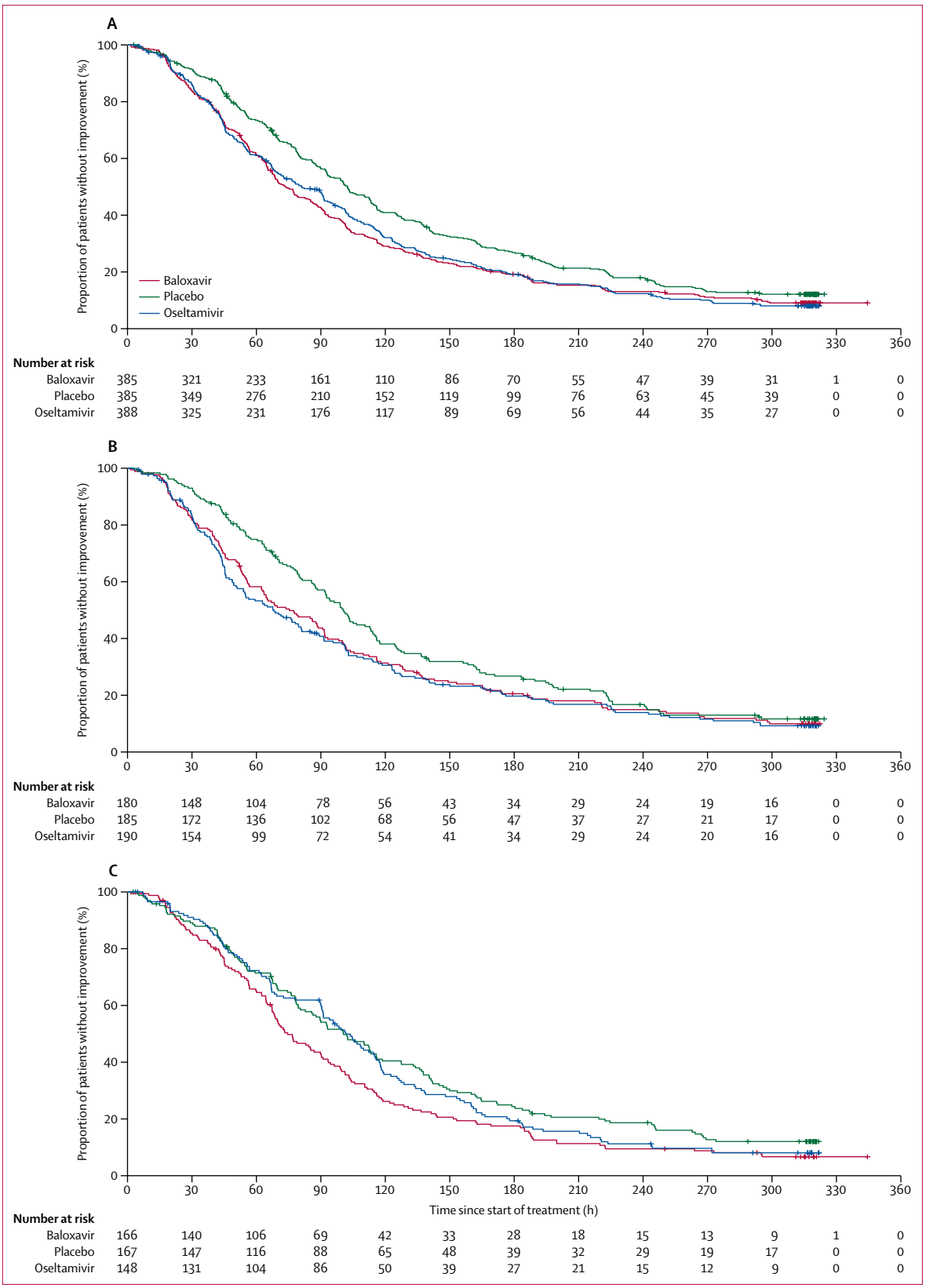

***Figure 2*: Kaplan-Meier curves of TTIIS in the modified intention-to-treat population**
(A) TTIIS in the overall population. (B) TTIIS in the subgroup with influenza A H3N2 virus infection; the median TTIIS was 75·4 h (95% CI 62·4–91·6) in the baloxavir group, 100·4 h (88·4–113·4) in the placebo group, and 68·2 h (53·9–81·0) in the oseltamivir group. (C) TTIIS in the subgroup with influenza B virus infection; the median TTIIS was 74·6 h (95% CI 67·4–90·2) in the baloxavir group, 100·6 h (82·8–115·8) in the placebo group, and 101·6 h (90·5–114·9) in the oseltamivir group. TTIIS=time to improvement of influenza symptoms.

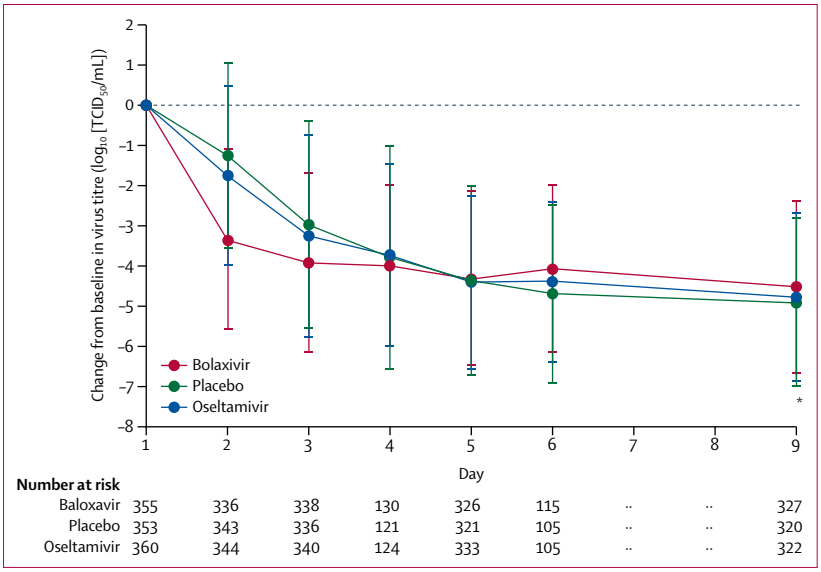

Figure 3: **Change from baseline in virus titre in the modified intention-to-treat population**
Data are mean reduction with error bars indicating SD. Days 4 and 6 were optional visits, and there were no visits on days 7 and 8 Day 2: p<0·0001 for baloxavir versus placebo and p<0·0001 for baloxavir versus oseltamivir. Day 3: p<0·00001 for baloxavir versus placebo and p<0·0024 for baloxavir versus oseltamivir. $TCID_{50}$=50% tissue culture infectious dose.

	Baloxavir group (n=730)	Placebo group (n=727)	Oseltamivir group (n=721)
Adverse events			
Any	183 (25%)	216 (30%)	202 (28%)
Reported in ≥2% of participants in any treatment group			
Bronchitis	21 (3%)	33 (5%)	30 (4%)
Sinusitis	14 (2%)	21 (3%)	22 (3%)
Diarrhoea	20 (3%)	21 (3%)	23 (3%)
Nausea	20 (3%)	29 (4%)	34 (5%)
Leading to withdrawal of study drug	5 (1%)	5 (1%)	4 (1%)
Serious adverse events (excluding death)	5 (1%)	9 (1%)	8 (1%)
Death*	0	0	1 (<1%)
Treatment-related adverse events			
Any	41 (6%)	60 (8%)	57 (8%)
Reported in ≥2% of participants in any treatment group			
Nausea	16 (2%)	20 (3%)	23 (3%)
Leading to withdrawal of study drug	2 (<1%)	2 (<1%)	3 (<1%)
Serious treatment-related adverse events (excluding death)	0	2 (<1%)	2 (<1%)
Death	0	0	0

Data are n (%). *One patient treated with oseltamivir developed pneumonia on study day 12, which resulted in death on day 38.

Table 2: **Summary of adverse events and treatment-related adverse events in safety population**

H3N2, one [6%] of 18 with influenza A H1N1, and one [1%] of 131 with influenza B), but were not detected in any baseline samples from these patients nor in samples from 78 randomly selected patients in the placebo group (exploratory analysis). The 78 patients were selected to keep balance of type and subtype of virus and region (USA, Asia, EU, southern hemisphere). Polymerase acidic Ile38X variants were detected most commonly on study day 5 or day 9 (0 of 61 patients on day 2, 0 of 97 on day 3, one (6%) of 18 on day 4, ten (13%) of 76 on day 5, 0 of 12 on day 6, and four (16%) of 25 on day 9). Substitutions in the polymerase gene outside the Ile38 position were detected in 39 (13%) of 290 patients in the baloxavir group and in five (6%) of 78 patients in the placebo group. The median time to sustained cessation of virus shedding was longer in baloxavir recipients with polymerase acidic Ile38X-substituted viruses than in those without, those with viruses with polymerase acidic substitutions other than Ile38X, and those who received placebo (appendix p 50). The proportion of patients positive for infectious virus on day 5 was higher in baloxavir recipients with polymerase acidic Ile38 amino acid-substituted viruses (ten [71%] of 14) than in those without (34 [16%] of 212), those with viruses with amino acid substitutions elsewhere in the polymerase acidic protein (five [14%] of 36), those in the placebo group (99 [31%] of 322), and those in the oseltamivir group (68 [20%] of 333). The median TTIIS in baloxavir recipients was similar in those with polymerase acidic Ile38X-substituted viruses, those without, and those with viruses with polymerase acidic substitutions other than Ile38X, and was shorter than in patients who received placebo (appendix pp 50, 62).

A post-hoc multivariate analysis identified a significant association between time from symptom onset to treatment and emergence of polymerase acidic I38X-substituted viruses in baloxavir-treated patients infected with influenza A H3N2 virus who had paired sequencing data available (appendix p 51). A higher proportion (ten [15%] of 67 patients; eight with Ile38Thr, one with Ile38Met, and one with Ile38Thr and Ile38Ile) of patients who started baloxavir treatment early (within 24 h) had emergence of polymerase acidic Ile38X-substituted viruses than did those who started treatment after 24 h (three [4%] of 73; two with Ile38Thr and one with both Ile38Thr and Ile38Ile). However, no significant associations were found with other factors (appendix p 51).

Adverse events were reported in 183 (25%) of 730 patients who received baloxavir, 216 (30%) of 727 patients who received placebo, and 202 (28%) of 721 patients who received oseltamivir; the most frequently identified adverse events were bronchitis, sinusitis, diarrhoea, and nausea (table 2). Few adverse events led to cessation of the trial regimen (1% in each group; table 2). Adverse events leading to withdrawal of study drug occurring in more than one patient in any treatment group were pneumonia (two patients in the baloxavir group and one in the oseltamivir group), vomiting (two patients in the baloxavir group), and bronchitis (two patients in the placebo group only). Serious adverse events were noted in five patients in the baloxavir group, nine patients in the placebo group, and eight patients in the oseltamivir group; one case of hypertension and one case of nausea in the placebo group

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and two cases of transaminase elevations in the oseltamivir group were considered to be treatment related; all other serious adverse events were not considered to be treatment related (table 2). One patient in the oseltamivir group developed pneumonia on study day 12, which resulted in death on day 38.

Discussion

A single dose of baloxavir started within 48 h of symptom onset resulted in more rapid improvement of symptoms, fewer influenza-associated complications, and faster reduction in viral replication in high-risk adolescent and adult outpatients with uncomplicated influenza than did placebo. Symptom improvement was faster when the therapy was initiated early after onset of symptoms (appendix p 40), consistent with previous studies of baloxavir and neuraminidase inhibitors in uncomplicated influenza.[17,21–23] Overall, time to return to pre-influenza health status was about 1 day shorter in the baloxavir group than in the placebo group. Furthermore, baloxavir was generally well tolerated, with adverse event occurrences similar to those observed with placebo. The study builds on previous studies[17] of baloxavir by demonstrating its ability to reduce influenza-associated complications compared with placebo and improve clinical and virological outcomes compared with both placebo and oseltamivir in patients infected with influenza B virus.

Outpatients with underlying conditions are at increased risk of influenza-associated complications, admission to hospital, and death.[1] Observational studies of oseltamivir have shown that timely antiviral therapy can reduce the risk of these complications.[10,24] In this study, both baloxavir and oseltamivir reduced the incidence of influenza-related complications and antibiotic use compared with placebo (appendix p 44–45). The reduction in antibiotic use with oseltamivir in this trial confirms results of earlier reports, including an individual patient-level meta-analysis of oseltamivir randomised controlled trials, which also found that oseltamivir treatment reduced the risk of admission to hospital.[10] Admissions to hospitals and death were rare in our study population, and future studies with much larger sample sizes will be needed to understand the effect of antiviral treatment on these outcomes.

We enrolled a sufficiently large number of influenza B virus-infected patients in the current study to asess both antiviral and clinical efficacy of baloxavir over oseltamivir against influenza B. Both antivirals show less potent inhibition of influenza B than of influenza A viruses in vitro,[25] and oseltamivir has been associated with longer symptom durations, especially of fever, and sustained viral replication in patients with influenza B than in those with influenza A infections.[8,16,25,26] In our study, baloxavir showed both clinical and virological benefits over placebo, whereas oseltamivir did not show these benefits in patients with influenza B in a previous study.[26]

The efficacy of baloxavir in this study corresponds well with results from previous studies in otherwise healthy adults and adolescents.[17] High-risk patients generally take longer to recover from influenza illness than do patients without risk factors; median duration of illness (based on time to alleviation of symptoms) in otherwise healthy placebo recipients was 80·2 h in our earlier trial compared with 102·8 h in high-risk patients receiving placebo in this study.[11] Patients treated with baloxavir recovered about 1 day faster than did patients who received placebo in both trials (median difference between baloxavir and placebo in time to alleviation of symptoms was 26·5 h in our previous study and 25·8 h in this study). Symptom reduction was significantly greater with baloxavir than with placebo among patients with asthma or chronic lung disease (appendix p 21). Baloxavir was associated with more rapid cessation of infectious virus detection than either placebo or oseltamivir in both trials. Further studies in high-risk patients, particularly patients in hospital and those who are immunocompromised, who have longer durations of viral replication, higher incidences of complications, and greater risk of death than patients enrolled in this study are needed to determine the clinical utility of rapid reductions in viral replication.

We detected treatment-emergent variant viruses with amino acid substitutions in polymerase acidic Ile38 conferring reduced susceptibility to baloxavir in 9% of patients infected with influenza A H3N2 virus, but in only 1% of patients infected with influenza B virus. A further 13% of patients in the baloxavir group had polyamerase acidic substitutions at positions other than Ile38, but the importance of such changes to drug susceptibility remains to be determined. In patients with emergence of polyamerase acidic Ile38X–substituted viruses, increases in virus titres on days 6 and 9 were found in most, although without an associated increase in symptoms (data not shown). Because these variants were typically detected at a time of waning drug concentrations, whether additional baloxavir doses might reduce their frequency remains to be determined. In a post-hoc multvariate analysis, we found that treatment-emergent variant viruses with polyamerase acidic Ile38 substitutions developed more frequently in patients whose therapy started within the first 24 h of symptom onset than in those with later onset of therapy, a finding that was not noted in previous baloxavir studies.[27,28] In the CAPSTONE-1 trial[27] and a study in children with uncomplicated influenza,[28] a lower baseline neutralising antibody titre was associated with increased risk of variant emergence, indicating that lower virus-specific immunity at enrolment increased the risk of resistance emergence. The reasonably high prevalence of variant emergence in our study population raises concerns about use of a single dose of baloxavir in patients with influenza with prolonged viral replication—in particular, infants, immunocompromised patients, and patients with severe illness who are in hospital. An open-label study in Japanese children aged 0–12 years, which used a lower dose than is planned for an oseltamivir-controlled trial in

children (NCT03629184), reported that 23·4% of patients had emergence of viruses with polymerase acidic Ile38Thr or Ile38Met variants after baloxavir treatment, and that emergence was associated with prolonged illness.[29] Owing to reports of infection with polymerase acidic Ile38Thr-substituted viruses in three patients who were not treated with baloxavir, probably representing transmission from patients treated with baloxavir, monitoring and surveillance to determine the extent of transmission is ongoing.[30,31] Previous studies of other antivirals have shown combination therapy to be associated with reductions in the emergence of drug-resistant viruses on therapy.[32,33] Future trials should study combinations of baloxavir with antiviral drugs with different mechanisms of action to assess whether additional clinical efficacy can be provided or the emergence of drug-resistant variants can be reduced.[32,33] An ongoing study (NCT03684044) in patients in hospital will determine whether additional doses of baloxavir combined with neuramindase inhibitors might achieve these outcomes.

This study has several limitations. Because we excluded some patients with immunosuppression, pregnant women, and patients with hepatic dysfunction, the safety and efficacy of baloxavir in these populations will need to be defined in future studies. Although we had similar numbers of patients infected with influenza A H3N2 and influenza B, few patients had influenza A H1N1 infection, which limits conclusions that can be made about the efficacy of baloxavir in these patients, particularly when subtypes of influenza can vary from year to year. However, time to illness alleviation was significantly shortened and antiviral effects were found to be potent in a phase 2 randomised controlled trial of single-dose baloxavir in Japanese adults with uncomplicated influenza, 61–71% of whom had influenza A H1N1.[17,34] Ongoing studies are expected to provide additional data on baloxavir efficacy against influenza A H1N1. Another observation is that regional differences were identified in the TTIIS between baloxavir-treated and placebo groups, which might lead to different outcomes. We observed differences between patients enrolled in Asia and those enrolled in North America and Europe in baseline composite symptom scores (≥15 in 25% of patients in Asia *vs* 67% of patients in North America and Europe—Belgium, Germany, Hungary, Latvia, Poland, Romania, and Spain), time to treatment from influenza onset (≤24 h in 55% of patients in Asia *vs* 39% of patients in North America and Europe), and incidence of metabolic disorders (24% of patients in Asia *vs* 7% of patients in North America and Europe; data not shown). Each of these factors are associated with differences in TTIIS and probably explain many of the regional differences observed. Patients typically present for evaluation earlier and therefore begin treatment earlier in Asia (especially in Japan) than do patients in North America and Europe (appendix p 25). Another limitation was that the study was not powered for comparisons with oseltamivir, by influenza type, or by subgroup, and so the findings of these analyses should be interpreted with caution.

Baloxavir is the first drug to be approved by the US Food and Drug Administration for treatment of patients at risk of influenza-associated complications.[35] We showed that antiviral therapy is associated with reduction of influenza-associated complications, which should drive clinicians to identify and provide early treatment to high-risk patients.

Contributors

All authors participated in the interpretation of data and in the drafting and critical revision of the manuscript. SP, YY, TS, MM, KT, and TU were involved in the study design. MM, KT, and TU were involved in data collection. YY did the statistical analysis. All authors approved the final version of the manuscript.

Declaration of interests

MGI is a paid member of the Data Safety Monitoring Board for GlaxoSmithKline and Shionogi; reports personal consulting fees from Celltrione, Genentech/Roche, Janssen, Seqirus, Shionogi, Viracor Eurofins, and VirBio; reports payments to Northwestern University by AiCuris, Chimerix, Emergent BioScience, Genentech/Roche, Gilead, Janssen, and Shire for research; and has served as an unpaid consultant for GlaxoSmithKline, Romark, and Vertex. SP, TS, MM, and TU are employed by Shionogi; YY and KT are employed by, and hold stock in, Shionogi. FGH reports travel support from Shionogi and Roche; reports personal fees from WHO and the University of Alabama Antiviral Drug Discovery and Development Consortium; donations to the Ford Haitian Orphanage and School from Cidara, resTORbio, Seqirus, and Shionogi for consulting; payments to the University of Virginia from GlaxoSmithKline, Celltrion, and Vaccitech for Data Safety Monitoring Board work; has served as an unpaid consultant to various companies (CoCrystal, Farmak, FujiFilm/Toyama, Gilead Sciences GlaxoSmithKline, Janssen, MedImmune, Regeneron, Roche/Genentech), and as an unpaid member of the Scientific Advisory Board for SAB Biotherapeutics, Vir, and Visterra that are developing investigational therapeutics for influenza.

Data sharing

Qualified researchers may request access to individual patient-level data through the clinical study data request platform (www.clinicalstudydatarequest.com). Further details on Roche's criteria for eligible studies are available at https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx. For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm.

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References

1 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.

2 Molinari NA, Ortega-Sanchez IR, Messonnier ML, et al. The annual impact of seasonal influenza in the US: measuring disease burden and costs. *Vaccine* 2007; **25:** 5086–96.

3 Memoli MJ, Athota R, Reed S, et al. The natural history of influenza infection in the severely immunocompromised *vs* nonimmunocompromised hosts. *Clin Infect Dis* 2014; **58:** 214–24.

4 Hurt AC, Chotpitayasunondh T, Cox NJ, et al. Antiviral resistance during the 2009 influenza A H1N1 pandemic: public health, laboratory, and clinical perspectives. *Lancet Infect Dis* 2012; **12:** 240–48.

5 Li TC, Chan MC, Lee N. Clinical implications of antiviral resistance in influenza. *Viruses* 2015; **7:** 4929–44.

6 Hu Y, Lu S, Song Z, et al. Association between adverse clinical outcome in human disease caused by novel influenza A H7N9 virus and sustained viral shedding and emergence of antiviral resistance. *Lancet* 2013; **381:** 2273–79.

7 Lee N, Hui DS, Zuo Z, et al. A prospective intervention study on higher-dose oseltamivir treatment in adults hospitalized with influenza A and B infections. *Clin Infect Dis* 2013; **57:** 1511–19.

8 Sugaya N, Mitamura K, Yamazaki M, et al. Lower clinical effectiveness of oseltamivir against influenza B contrasted with influenza A infection in children. *Clin Infect Dis* 2007; **44:** 197–202.

9 Madjid M, Curkendall S, Blumentals WA. The influence of oseltamivir treatment on the risk of stroke after influenza infection. *Cardiology* 2009; **113:** 98–107.

10 Dobson J, Whitley RJ, Pocock S, Monto AS. Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials. *Lancet* 2015; **385:** 1729–37.

11 Lalezari J, Campion K, Keene O, Silagy C. Zanamivir for the treatment of influenza A and B infection in high-risk patients: a pooled analysis of randomized controlled trials. *Arch Intern Med* 2001; **161:** 212–17.

12 Murphy KR, Evindson A, Pauksens K, et al. Efficacy and safety of inhaled zanamivir for the treatment of influenza in patients with asthma or chronic obstructive pulmonary disease: a double-blind, randomised, placebo-controlled, multicentre study. *Clin Drug Invest* 2000; **20:** 337–49.

13 Johnston SL, Ferrero F, Garcia ML, Dutkowski R. Oral oseltamivir improves pulmonary function and reduces exacerbation frequency for influenza-infected children with asthma. *Pediatr Infect Dis J* 2005; **24:** 225–32.

14 Kaiser L, Wat C, Mills T, Mahoney P, Ward P, Hayden F. Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalizations. *Arch Intern Med* 2003; **163:** 1667–72.

15 Hayden FG, Shindo N. Influenza virus polymerase inhibitors in clinical development. *Curr Opin Infect Dis* 2019; **32:** 176–86.

16 Uehara T, Shishido T, Ishibashi T, et al. S-033188, a small molecule inhibitor of cap-dependent endonuclease of influenza A and B virus, leads to rapid and profound viral load reduction. Options IX for the Control of Influenza Chicago, Illinois; Aug 24–28, 2016. (abstr LBO-1). https://www.isirv.org/site/images/conferences/OptionsIX/Options_IX_Final_Programme.pdf (accessed April 30, 2020).

17 Hayden FG, Sugaya N, Hirotsu N, et al. Baloxavir marboxil for uncomplicated influenza in adults and adolescents. *N Engl J Med* 2018; **379:** 913–23.

18 Centers for Disease Control and Prevention. People at high risk for flu complications. https://www.cdc.gov/flu/highrisk/index.htm (accessed April 18, 2020).

19 Omoto S, Speranzini V, Hashimoto T, et al. Characterization of influenza virus variants induced by treatment with the endonuclease inhibitor baloxavir marboxil. *Sci Rep* 2018; **8:** 9633.

20 Herman MA, Lipsitch M. Oseltamivir and risk of lower respiratory tract complications in patients with flu symptoms: a meta-analysis of eleven randomized clinical trials. *Clin Infect Dis* 2011; **53:** 277–79.

21 Aoki FY, Macleod MD, Paggiaro P, et al. Early administration of oral oseltamivir increases the benefits of influenza treatment. *J Antimicrob Chemother* 2003; **51:** 123–29.

22 Treanor JJ, Hayden FG, Vrooman PS, et al. Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: a randomized controlled trial. *JAMA* 2000; **283:** 1016–24.

23 Nicholson KG, Aoki FY, Osterhaus AD, et al. Efficacy and safety of oseltamivir in treatment of acute influenza: a randomised controlled trial. *Lancet* 2000; **355:** 1845–50.

24 Hsu J, Santesso N, Mustafa R, et al. Antivirals for treatment of influenza: a systematic review and meta-analysis of observational studies. *Ann Intern Med* 2012; **156:** 512–24.

25 Burnham AJ, Baranovich T, Govorkova EA. Neuraminidase inhibitors for influenza B virus infection: efficacy and resistance. *Antiviral Res* 2013; **100:** 520–34.

26 Kawai N, Ikematsu H, Iwaki N, et al. A comparison of the effectiveness of oseltamivir for the treatment of influenza A and influenza B: a Japanese multicenter study of the 2003–2004 and 2004–2005 influenza seasons. *Clin Infect Dis* 2006; **43:** 439–44.

27 Uehara T, Hayden FG, Kawaguchi K, et al. Treatment-emergent influenza variant viruses With reduced baloxavir susceptibility: impact on clinical and virologic outcomes in uncomplicated influenza. *J Infect Dis* 2019; **221:** 346–55.

28 Hirotsu N, Sakaguchi H, Sato C, et al. Baloxavir marboxil in Japanese pediatric patients with influenza: safety and clinical and virologic outcomes. *Clin Infect Dis* 2019; published online Sept 20. DOI:10.1093/cid/ciz908.

29 Sugaya N. Cap-dependent endonuclease inhibitor baloxavir marboxil for the treatment of influenza: results from a phase 3, open- label study in otherwise healthy pediatric patients with seasonal influenza. 2nd International Meeting on Respiratory Pathogens 2018; Singapore; March 7–9, 2018.

30 Takashita E, Kawakami C, Ogawa R, et al. Influenza A(H3N2) virus exhibiting reduced susceptibility to baloxavir due to a polymerase acidic subunit I38T substitution detected from a hospitalised child without prior baloxavir treatment, Japan, January 2019. *Euro Surveill* 2019; **24:** 12.

31 Takashita E, Ichikawa M, Morita H, et al. Human-to-human transmission of influenza A(H3N2) virus with reduced susceptibility to baloxavir, Japan, February 2019. *Emerg Infect Dis* 2019; **25:** 11.

32 Ison MG, Gnann JW Jr, Nagy-Agren S, et al. Safety and efficacy of nebulized zanamivir in hospitalized patients with serious influenza. *Antivir Ther* 2003; **8:** 183–90.

33 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.

34 Watanabe A, Ishida T, Hirotsu N, et al. Baloxavir marboxil in Japanese patients with seasonal influenza: dose response and virus type/subtype outcomes from a randomized phase 2 study. *Antiviral Res* 2019; **163:** 75–81.

35 Center for Drug Evaluation and Research. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/210854Orig1s001.pdf (accessed April 20, 2020).