Original article

Intravenous peramivir for treatment of influenza in hospitalized patients

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Background: Influenza causes over 200,000 hospitalizations a year in the United States, but few antiviral treatment studies have focused on patients hospitalized with influenza. This open-label, randomized study was initiated during the 2009 H1N1 pandemic to help assess the antiviral activity, safety and tolerability of 5–10 days treatment with two different dosing regimens of the intravenous neuraminidase inhibitor, peramivir, in hospitalized subjects with influenza.

Methods: Quantitative virology was done on nasopharyngeal swab specimens from subjects ≥6 years of age to measure change from baseline in tissue culture infective dose (primary end point) and quantitative viral RNA levels by real-time PCR. Clinical end points included time to clinical resolution, a composite end point of four vital signs and oxygen saturation.

Results: A total of 234 hospitalized patients were randomized to peramivir 300 mg twice daily or 600 mg once daily; 127 had laboratory confirmed influenza. In those with detectable virus at baseline, viral titres declined without differences between regimens. There were no significant differences in clinical or virological end points between treatment arms, and apparent differences were explained by baseline disease severity differences in the groups. Peramivir was generally safe and well tolerated for treated patients hospitalized with pandemic influenza with outcomes similar to those described in the literature.

Conclusions: This open-label trial of intravenous peramivir in subjects hospitalized predominantly with 2009 influenza A (H1N1) demonstrated that once- or twice-daily administration was associated with decreases in viral shedding and clinical improvement. ClinicalTrials.gov number NCT00957996.

Introduction

The burden of seasonal influenza is high, with over 200,000 hospitalizations and an average of 25,470 influenza-associated deaths annually in the United States [1,2]. In the 2009 influenza A/H1N1 pandemic, rates of hospitalization and death significantly increased in children and working adults [3–6]. Many people hospitalized with influenza require intensive care because of serious illness, including pneumonia, respiratory failure, acute respiratory distress syndrome (ARDS), shock, renal failure and gastrointestinal distress [7]. To date, no parenteral product is approved for hospitalized patients. In addition, currently available

oral therapy may not be adequately absorbed in some critically ill patients with gut dysfunction and inhaled products may result in ventilator dysfunction, resulting in compromised effectiveness in severely ill patients. Furthermore, widespread drug resistance to the adamantanes has been reported for all currently circulating influenza A strains and to oseltamivir for seasonal A/H1N1 in 2008–2009 [8–10]. For these reasons, new antivirals, particularly those with the option of intravenous delivery, are needed to treat influenza.

Peramivir is an intravenous neuraminidase inhibitor (NAI) currently approved in Japan, South Korea and China to treat influenza. Like other NAIs, peramivir can be used to treat both influenza A and B and has demonstrated clinical efficacy and tolerability superior to placebo and similar to oral oseltamivir in randomized controlled trials [11–14]. Peramivir has *in vitro* activity superior to oseltamivir and zanamivir against wild-type strains of influenza [15,16]. During the 2009 influenza A (H1N1) pandemic, investigational peramivir was made available to severely ill influenza patients initially under individual emergency investigational new drug applications [17] and later under an emergency use authorization (EUA) by the US FDA [18], because preclinical data suggested that the 2009 H1N1 influenza A virus isolates were highly susceptible to peramivir, and no approved intravenous antiviral was available [19,20].

We initiated this open-label clinical study during the 2009 H1N1 pandemic to assess the antiviral activity of two dosing regimens of intravenous peramivir in hospitalized subjects with influenza and, secondarily, to assess safety and tolerability and explore other efficacy end points. This study was designed to study the safety and efficacy of peramivir at higher doses than the previously completed study in hospitalized adults [14]. Based on the safety and tolerability of peramivir in more than 2,000 healthy subjects and patients with influenza, and the suggestion from this prior study that the maximum antiviral effect in influenza B may not have been reached, a study of higher doses as well as twice daily dosing was selected [14]. Additionally, data from studies conducted in Asia suggest that higher doses of peramivir, up to 600 mg, are generally well tolerated and efficacious in both ambulatory and seriously ill patients [11,13]. An open-label design was favoured to collect clinical data and outcomes of individuals who were severely ill given that patients would otherwise likely have accessed the compound via the peramivir EUA mechanism whereby no outcomes data would be collected.

Methods

Design

This open-label, randomized study (NCT00957996) was conducted at 59 hospitals with local influenza activity in the US, Canada, Mexico, Australia and New Zealand between October 2009 and October 2010. The study protocol was approved by independent ethics committees or institutional review boards at each study site. An independent Data Monitoring Committee assessed safety on an ongoing basis.

Subjects

All subjects provided written informed consent. Eligible subjects were males or non-pregnant females ≥6 years old with clinical signs and/or symptoms consistent with influenza, temperature ≥38.0°C (oral) or ≥38.6°C rectal or tympanic, and recent onset of respiratory symptoms (exact duration was not specified in the protocol), with severity of illness requiring hospitalization as judged by the investigator. Treatment with other antivirals was permitted prior to study drug initiation (73% of subjects had received an antiviral [oseltamivir] at baseline based upon the investigators' prior clinical or laboratory diagnosis of influenza). The protocol did not require PCR confirmation of infection for entry, or to continue dosing with study drug. Subjects were excluded if they required peritoneal dialysis, had altered neurological status, were undergoing systemic chemotherapy or radiotherapy, had a recent hematopoietic stem cell or solid organ transplant, had an uncontrolled HIV infection, had a pre-existing chronic infection, had cystic fibrosis, had a confirmed acute non-influenza infection, or had pre-specified abnormalities on laboratory testing. Subjects with reduced creatinine clearance were not excluded.

Treatments

Adult subjects ≥18 years of age were randomized 1:1 to receive intravenous peramivir (BioCryst Pharmaceuticals, Durham, NC, USA) 600 mg once daily or 300 mg twice daily for 5 days; if patients were on oseltamivir prior to enrolment, this was discontinued. Children and adolescents received either 10 mg/kg once daily or 5 mg/kg twice daily to a maximum of 600 mg/day. Child and adolescent doses were based on adult pharmacokinetic studies and a paediatric renal maturation model [21]. Peramivir doses were adjusted in subjects with moderate or worse renal impairment. Randomization was stratified by duration of illness, ≤48 h versus >48 h. Subjects not meeting the protocol-defined criteria of clinical resolution on day 5 of treatment (Table 1) or with detectable virus by local real-time PCR (RT-PCR) on day 4 could continue 600 mg once daily for 5 more days, for a total of 10 days.

Treatment continued for the planned 5 or 10 days. All subjects discharged per hospital criteria before the conclusion of their protocol-specified course received peramivir 600 mg once daily as outpatients, and all subjects returned for a day 14 clinic visit. On day 28,

Table 1. Clinical resolution parameters

Sign of clinical resolution	Resolution criteria
Temperature	≤37.2°C oral or ≤37.8°C rectal or tympanic
Oxygen saturation	≥92%
Respiration rate	≤24/min
Heart rate	≤100/min
Systolic blood pressure	≥90 mmHg

a follow-up assessment was conducted by telephone or clinic visit.

Concomitant use of antivirals during the first 5 days of study drug was prohibited as were high-dose corticosteroids (≥10 mg prednisone/day or equivalent) during peramivir administration. The use of oral or parenteral antibiotics and antipyretics or analgesics was permitted at the discretion of the patient's primary provider.

Virology

Nylon flocked swab from each nare and the posterior pharynx were collected at screening/baseline, at 12, 24, 36, 48, 60, 72, 84, 96 and 108 h after initiation of study drug on day 1, and once at the day 10 follow-up visit. For subjects who received peramivir >5 days, samples were also collected once daily on days 6–10. Samples were placed in 3.0 ml Universal Transport Medium (Copan Diagnostics, Murrieta, CA, USA) containing albumin, agitated and were transported to a central laboratory, frozen at -70°C and then sent for influenza detection – confirmed by quantitative RT-PCR and viral culture using Madin–Darby canine kidney (MDCK) cells (calculated as $\log_{10}$ tissue culture infective dose $[TCID]_{50}$/ml of viral transport medium; ViroClinics Biosciences, Rotterdam, the Netherlands). Acute and convalescent sera were tested for influenza-specific antibodies with a haemagglutination inhibition assay (61 subjects in the Southern Hemisphere only, following a protocol amendment). Local evidence of influenza infection by any FDA-approved method was also accepted as confirmation. Change in influenza virus titre was analysed by both viral culture and RT-PCR from baseline and all available post-treatment specimens. Influenza type/subtype was assessed by RT-PCR, and *in vitro* susceptibility to peramivir, oseltamivir and zanamivir was assessed by 2′-(4-methylumbelliferyl)-α-D-*N*-acetylneuraminic acid (MUNANA) for the first and last positive culturable viral isolate from individual patients [22].

Clinical assessments

Vital signs and oxygen saturation by transcutaneous oximetry were measured once at screening/baseline and three times daily while hospitalized. Following discharge, subjects or caregivers measured temperature once daily ≥4 h after administration of antipyretic medication using an electronic thermometer provided by the sponsor. Subjects rated influenza symptoms (cough, sore throat, nasal congestion, myalgia, headache, feverishness and fatigue) on a four-point scale twice daily beginning pre-dose on day 1 through day 9 and thereafter once daily through day 14, and rated their ability to perform daily activities on a visual analogue scale once daily.

Safety assessments

Adverse events were assessed daily during the period of study drug administration and at each follow-up visit. During physical examinations at screening/baseline, day 5, day 10 and day 14, clinicians used a checklist to evaluate the subject for the presence of sinusitis, otitis, bronchitis and pneumonia. Influenza-related complications and influenza symptoms were not reported as adverse events unless they worsened or were serious adverse events. Urinalysis and blood samples for clinical chemistry and haematology were collected at screening/baseline, day 3, day 5, day 10, day 14 and hospital discharge, and sent to a central laboratory for analysis.

Pharmacokinetics

Blood samples for assessment of peramivir concentrations were collected from all subjects before and 30 min after the first dose on day 5. At a subset of sites, samples were also obtained pre-dose, at 30 min, 4 h, 8 h, 12 h, 24 h, 48 h and 72 h after the end of the first infusion on day 5. Measurement of peramivir was conducted at BioCryst using solid phase extraction and high-performance liquid chromatography with tandem mass spectrometry detection as previously described [23].

Statistical analyses

The safety population included all randomized subjects who received ≥1 dose of study treatment. The intent-to-treat infected (ITTI) population included all randomized subjects who received ≥1 dose of study treatment and had confirmed influenza from the central laboratory by viral culture, PCR, paired serology specimens with ≥4-fold increase in influenza antibody titre, or documentary evidence from a local laboratory. The ITTI population was used to assess baseline characteristics and primary and secondary efficacy end points.

The primary end point was the time-weighted change in influenza virus titre from screening/baseline to 48 h measured by $\log_{10}$ $TCID_{50}$. Confidence intervals (CI) were created around change from baseline results in each treatment group. Due to the absence of an external control group, no formal hypothesis testing was

planned or conducted. The study was not powered to demonstrate non-inferiority between the two arms. Descriptive statistics were planned.

Sample size calculations were based on results of a previous study [14]. Using a change from baseline in viral titres ($\log_{10}$ $TCID_{50}$) of -1.7 ±0.79, the probability was 0.97 that a sample size of 300 would produce a two-sided 95% CI with a width ≤0.24.

Secondary end points included other virology measures: change in virus titre by quantitative RT-PCR and number (%) of subjects shedding virus. Efficacy was also assessed using secondary objective and subject-rated clinical end points. Time to clinical resolution (TTCR) was defined as the time from initiation of study treatment until resolution and 24-h maintenance of ≥4 of 5 sign abnormalities (Table 1), 2 of which had to be temperature and oxygen desaturation [24], and was estimated by the Kaplan–Meier method.

Other objective clinical end points included time to hospital discharge, incidence of influenza-related complications, incidence and duration of ICU admission after treatment initiation, and survival at days 14 and 28. Subject-rated end points included time to alleviation of symptoms and time to resumption of usual activities.

Following database lock, post-hoc analyses were conducted to investigate whether baseline characteristics were predictive of change in influenza titre and TTCR (univariate and multiple regression statistical modelling) and 28-day mortality (χ^2 test). Furthermore, a secondary analysis of the time to clinical resolution was conducted to determine factors important in determining outcome. For this analysis, univariate Cox regression models were constructed for each combination of the dependent variable, time to clinical resolution and its relevant independent variables. Additionally, the stepwise selection method was used to choose the final predictive multiple Cox regression model. In building the stepwise selection model, a 10% significance level was required to add variables to the model and a 15% significance level was required to keep a variable in the model. Variables were added in order based on the univariate model results. Factors considered for inclusion in the model were duration of hospitalization prior to start of study participation, ICU status at baseline, presence of grade 3 or 4 albumin at screening, use of supplemental oxygen at baseline, vaccination status at screening, age, BMI, presence of abnormal chest X-ray at screening, corticosteroid use at baseline, duration of illness at randomization (≤48 h versus >48 h), duration of antiviral use prior to study participation, gender, ethnicity, influenza season, presence of moderate renal impairment (creatinine clearance rate [CrCl] 30–49 ml/min), presence of grade 3 or 4 lymphopenia at screening, presence of grade 3 or 4 neutropenia at screening and treatment.

Results

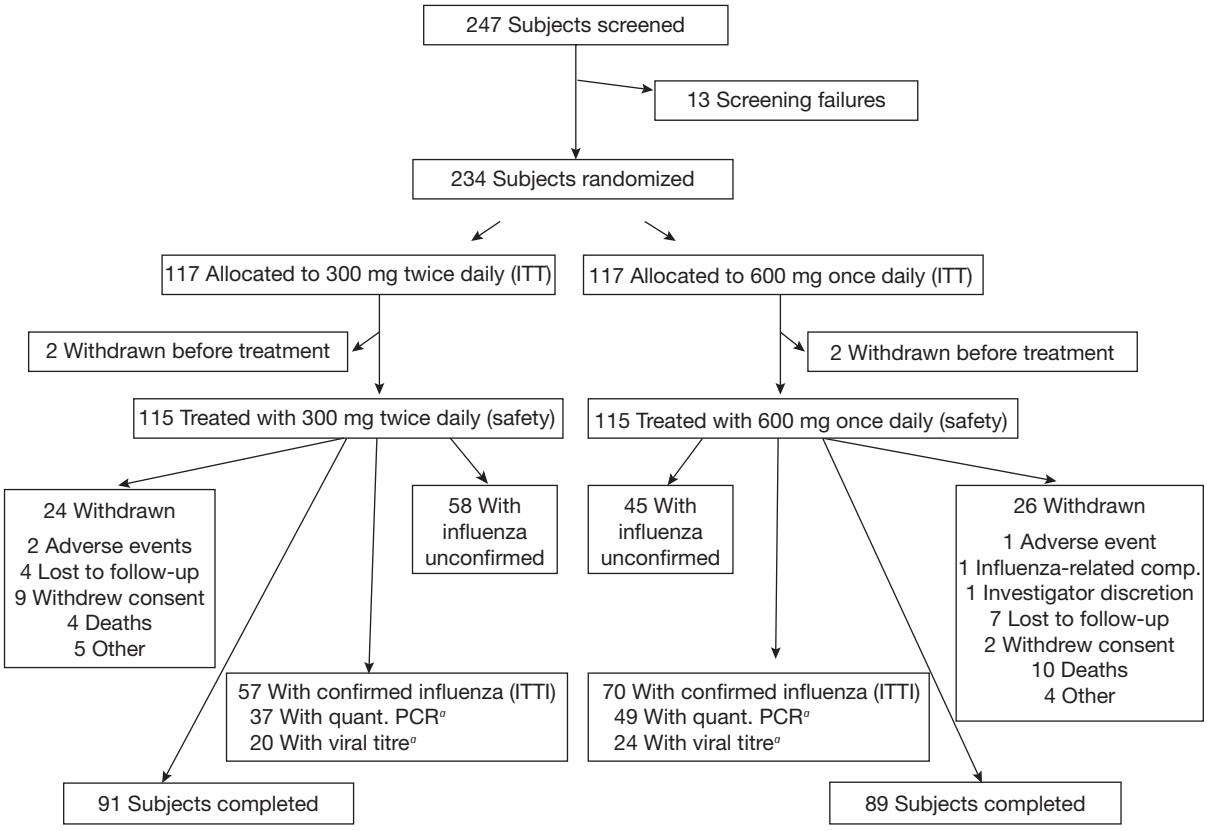
Subject disposition and baseline characteristics

Of the 230 randomized subjects who received ≥1 dose of peramivir (Figure 1), 127 subjects had influenza confirmed by one or more tests (Table 2) comprising the ITTI population. Thirty-three of the randomized patients received a reduced dose of peramivir based on reduced baseline creatinine clearance. The age range in the ITTI population was 14–92 years (Table 2). Many of the ITTI subjects were obese (BMI≥30 kg/m^2) and few (33%) were vaccinated for influenza (38 seasonal, 9 pandemic and 2 unknown type). Of those with confirmed influenza, most had influenza A 2009 (H1N1). The majority of subjects presented with severe illness at study entry: 19% were intubated and admitted to an ICU, 69% required supplemental oxygen, 29% had an abnormal chest X-ray, 43% had at least 1 grade 3 or 4 laboratory toxicity, 8% presented with moderate renal impairment (CrCl 30–49 ml/min), 79% had received a prior antiviral treatment and 52% were receiving corticosteroids at baseline, primarily for underlying respiratory conditions. Of those patients who had received prior antiviral therapy, most had received oseltamivir for a median of 2 days. The 600 mg once daily group had more subjects with severe disease (that is, baseline need for supplemental oxygen or ICU admission and higher APACHE score) and other risk factors (no vaccination, corticosteroids) than the 300 mg twice daily group. No differences were noted in demographics or baseline factors describing illness severity between those subjects with confirmed influenza infection (the ITTI population) and the total study population (Table 2).

Virology

At baseline, 44 subjects had detectable virus by culture (Figure 2A) and 86 subjects had detectable virus by PCR (Figure 2B); pre-enrolment exposure to antivirals may have contributed to the low detection of influenza at enrolment. The overall time-weighted change in virus titre from baseline to 48 h measured by culture, the primary end point, was -1.51 ±0.98 $TCID_{50}$/ml (300 mg twice daily =-1.66, 600 mg once daily =-1.47, P=0.65; Table 3). The median change from baseline in groups with a short (<48 h) and long (≥48 h) prior duration of illness was -1.98 and -1.11 $TCID_{50}$/ml, respectively. The baseline predictors for greater reductions in viral titres were high baseline $TCID_{50}$ (P<0.001), high screening lymphocyte values (P=0.001) and prior influenza vaccination (P=0.008). The percentages of total baseline positive subjects who remained culture positive at 48, 72 and 96 h were 14%, 3% and 0%, respectively (Figure 3A). For viral shedding measured by RT-PCR, no treatment group differences were detected in the change from baseline to

Figure 1. Subject disposition



[a]Positive at baseline and post-baseline. Comp., complications; ITT, intention-to-treat; ITTI, intent-to-treat infected; quant., quantitative.

48 h (P=0.77). The percentages of subjects with positive RT-PCR viral RNA titres at 48, 72 and 96 h were 67%, 54% and 40%, respectively, with 18% positive at day 10 (216 h; Figure 3B). There was a correlation between change in viral titre measured by culture and molecular techniques (r^2=0.563, P<0.001).

Influenza A 2009 H1N1 viruses isolated at baseline from the ITTI population were more susceptible to peramivir than the other approved NAIs (Additional file 1), as was true in the one subject with an influenza A indeterminate baseline isolate tested. There were no meaningful decreases in susceptibility of isolates during treatment except for one subject. Isolates from this individual (peramivir 300 mg twice daily), who was previously treated with oseltamivir, demonstrated an increase from peramivir baseline 50% inhibitory concentration (IC_{50}; 0.01 nM) to post-treatment (31.02 nM), and this was the only subject whose isolate showed an IC_{50} increase of >2 SD after exposure to peramivir. Post-treatment (but not pre-treatment) isolates from this subject contained an H275Y substitution in the NA gene; deep sequencing was not performed.

Clinical assessments

The overall median time from randomization to clinical resolution (see parameters in Table 1) was 92 h (Table 4). TTCR was strongly correlated with time to resolution of oxygen desaturation (r^2=0.751, P<0.0001). After adjusting for baseline predictors, TTCR was very similar in both treatment groups. Overall, 35% of subjects qualified for protocol-specified extension of peramivir treatment through days 6–10 because of continued clinical instability. Two subjects receiving extended treatment died on day 6 and 9, respectively. A third subject who met criteria for extended treatment was discharged at day 5 and was alive at day 28.

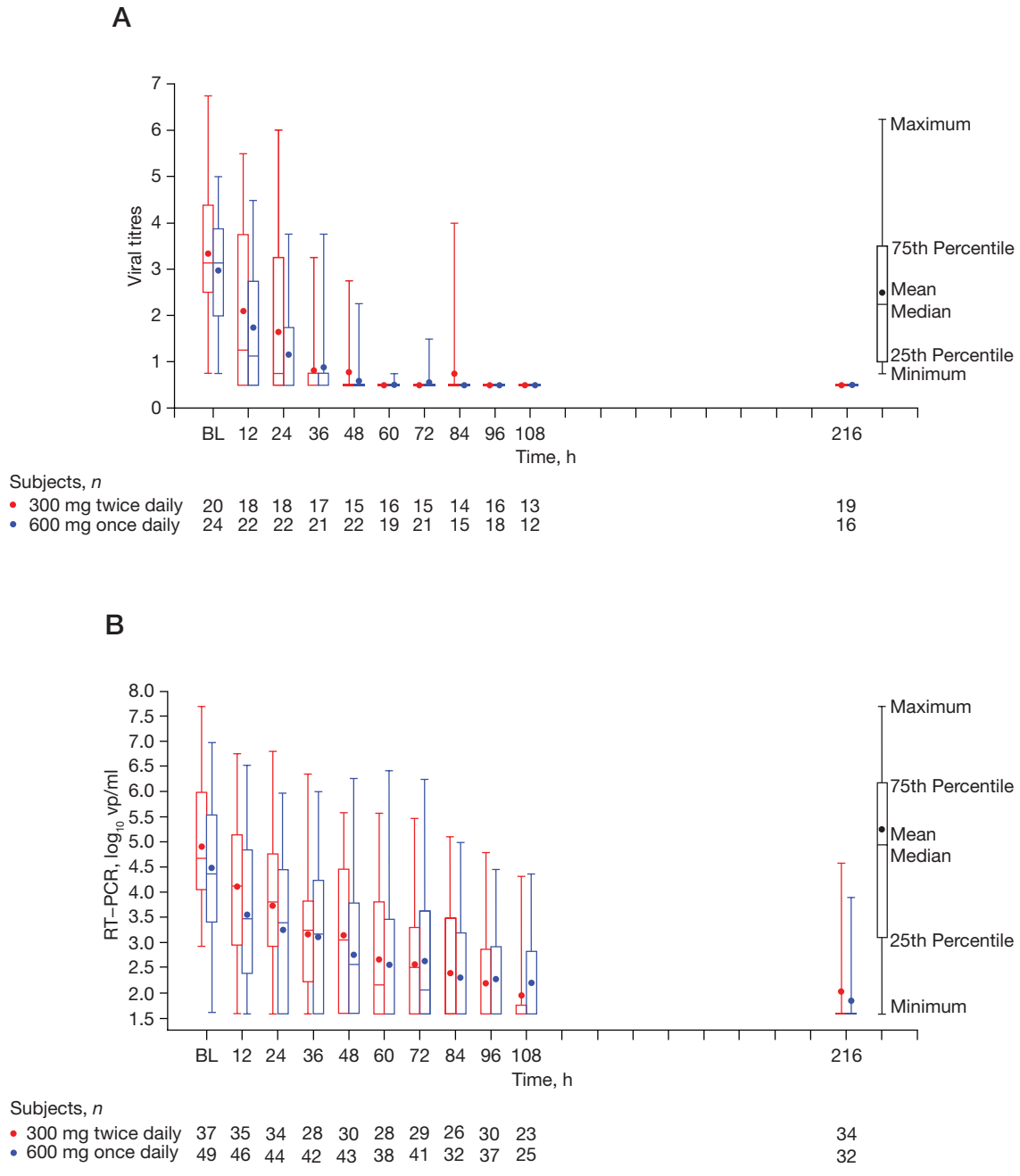
Survival at day 14 and day 28 was 95% and 90%, respectively. When baseline predictors of survival (ICU admission, supplemental oxygen use) were controlled, there were no significant treatment group differences. The subject-rated end points, time to alleviation of symptoms (median, 145 h) and time to resumption of usual activity (median 27 days), were not correlated with the objective end point, time to clinical resolution, or its individual components. Due to the small

Table 2. Demographics and baseline characteristics

	ITTI population			Total for ITT population (*n*=234)
	300 mg twice daily (*n*=57)	600 mg once daily (*n*=70)	Total (*n*=127)	
Median age, years (min, max)	45.4 (14, 92)	46.3 (19, 88)	45.8 (14, 92)	49.3 (14, 92)
Age categories				
Children 6–11 years, *n* (%)	0	0	0	0
Adolescents 12–17 years, *n* (%)	1 (2)	0	1 (2)	4 (2)
Adults (≥18 years), *n* (%)	56 (98)	70 (100)	125 (99)	230 (98)
Gender				
Male, *n* (%)	21 (37)	39 (56)	60 (47)	95 (41)
Female, *n* (%)	36 (63)	31 (44)	67 (53)	139 (59)
Race				
White, *n* (%)	35 (61)	43 (61)	78 (61)	162 (69)
Black, *n* (%)	8 (14)	9 (13)	20 (16)	29 (12)
Other, *n* (%)	14 (25)	18 (26)	29 (23)	43 (19)
Ethnicity				
Hispanic, *n* (%)	11 (19)	18 (26)	29 (23)	45 (19)
Non-Hispanic, *n* (%)	46 (81)	52 (74)	98 (77)	189 (81)
Median BMI, kg/m^2 (min, max)	30.1 (17, 70)	29.5 (18, 56)	29.7 (17, 70)	29.4 (16.8, 70.1)
Obese (BMI≥30 kg/m^2), *n* (%)	27 (47)	33 (47)	60 (47)	103 (44)
Influenza vaccination, *n* (%)	22 (39)	20 (29)	42 (33)	77 (33)
Confirmed influenza by subtype[a]				
Influenza A – 2009 H1N1, *n* (%)	43 (75)	51 (73)	94 (74)	95 (41)
Influenza A – indeterminate, *n* (%)	10 (18)	16 (23)	26 (20)	26 (11)
Influenza B, *n* (%)	2 (4)	1 (1)	3 (2)	3 (<1)
Influenza A + B, *n* (%)	1 (2)	1 (1)	2 (2)	2 (<1)
Influenza indeterminate subtype, *n* (%)	1 (2)	1 (1)	2 (2)	2 (<1)
Influenza A – seasonal H1N1, *n* (%)	0	0	0	0
Influenza A – H3N2, *n* (%)	0	0	0	0
Hemisphere				
Northern, *n* (%)	50 (88)	63 (90)	113 (89)	215 (92)
Southern, *n* (%)	7 (12)	7 (10)	14 (11)	19 (8)
ICU admission at baseline, *n* (%)	9 (16)	15 (21)	24 (19)	39 (17)
Median APACHE II score (min, max)	12 (4, 28)	16 (9, 28)	13 (4, 28)	15 (4, 28)
Abnormal chest X-ray at baseline, *n* (%)	20 (35)	17 (24)	37 (29)	59 (25)
Duration of illness at baseline				
≤48 h, *n* (%)	10 (18)	12 (17)	22 (17)	34 (15)
>48 h, *n* (%)	47 (82)	58 (83)	105 (83)	200 (85)
Median duration of hospitalization at baseline, days (min, max)	1 (0, 5)	1 (-1, 28)	1 (-1, 28)	2 (1, 7)
Moderate renal impairment (30–49 ml/min), *n* (%)	6 (11)	4 (6)	10 (8)	21 (9)
Any grade 3/4 laboratory toxicity[b], *n* (%)	20 (35)	35 (50)	55 (43)	98 (42)
Grade 3/4 screening albumin, *n* (%)	2 (4)	7 (10)	9 (7)	14 (6)
Grade 3/4 screening lymphocytes, *n* (%)	6 (11)	15 (21)	21 (17)	37 (16)
Grade 3/4 screening neutrophils, *n* (%)	0	3 (4)	3 (2)	3 (1)
Supplemental oxygen required, *n* (%)	35 (61)	52 (74)	87 (69)	158 (68)
Subjects receiving antivirals at baseline, *n* (%)	47 (82)	53 (76)	100 (79)	170 (73)
Median duration of antiviral treatment, days (min, max)	1 (1, 7)	2 (1, 7)	1.5 (1, 7)	2 (1, 7)
Subjects receiving corticosteroids at baseline, *n* (%)	25 (44)	41 (59)	66 (52)	120 (51)

[a]Of the 128 subjects with laboratory-confirmed influenza, 102 subjects were documented by central laboratory testing of study specimens by PCR, viral culture or by an increase in convalescent antibody titre. Twenty-six subjects had a documented laboratory diagnosis from a local laboratory prior to study entry. One of the 128 patients did not receive a dose of study drug. [b]Clinical and laboratory toxicities were graded according to the Division of AIDS Table for Grading the Severity of Adult and Paediatric Adverse Events. APACHE, acute physiology and chronic health evaluation; ITT, intent-to-treat; ITTI, intent-to-treat infected.

Figure 2. Boxplots of viral titres by study visit



(A) Boxplots of viral titres by tissue culture infective dose $(TCID)_{50}$. **(B)** Boxplots of viral titres by quantitative real-time PCR. Negative viral titre by culture is a $\log_{10}$ $TCID_{50}$/ml=0.5. BL, baseline; VP, virus particles.

number of subjects with detectable virus at baseline in the ITTI, it was not possible to correlate virological and clinical outcomes.

A multivariate analysis of the time to clinical resolution was conducted to determine factors important in determining outcome. The final multiple regression model suggested that subjects increased duration of hospitalization prior to treatment, admission in the ICU, presence of grade 3 or 4 albumin at screening, use of supplemental oxygen at baseline and prior vaccination tended to have longer time to clinical resolution.

Table 3. Viral shedding in subjects with positive baseline and post-baseline viral titre[a]

	300 mg twice daily	600 mg once daily
Titres measured by viral culture		
Median at baseline, log_{10} $TCID_{50}$/ml (range)	3.13 (0.75–6.75)[b]	3.13 (0.75–5.00)[c]
Median change to 48 h, log_{10} $TCID_{50}$/ml (95% CI)	-1.66 (-2.32, -0.61)[b]	-1.47 (-1.89, -0.75)[c]
Median change to 108 h, log_{10} $TCID_{50}$/ml (95% CI)	-2.02 (-3.38, -1.08)[b]	-2.01 (-2.66, -1.36)[c]
Median change to 216 h, log_{10} $TCID_{50}$/ml (95% CI)	-2.29 (-3.55, -1.67)[b]	-2.09 (-2.85, -1.44)[c]
Titres measured by RT-PCR		
Median at baseline, log_{10} virus particles/ml (range)	4.67 (2.92–7.69)[d]	4.36 (1.60–6.97)[e]
Median change to 48 h, log_{10} virus particles/ml (95% CI)	-1.00 (-1.52, -0.77)[d]	-1.07 (-1.24, -0.67)[e]
Median change to 108 h, log_{10} virus particles/ml (95% CI)	-1.65 (-1.99, -1.45)[d]	-1.59 (-1.86, -1.24)[e]
Median change to 216 h, log_{10} virus particles/ml (95% CI)	-2.15 (-2.38, -1.96)[d]	-1.79 (-2.11, -1.35)[e]

[a]Intent-to-treat infected population. [b]n=20. [c]n=24. [d]n=37. [e]n=49. RT, real-time; TCID, tissue culture infective dose.

Pharmacokinetics

All subjects were assessed for pre-dose and post-dose (30 min) peramivir concentration on day 5 of treatment. Overall exposure was similar in both groups. The pre-dose (trough) mean (SD) concentrations were 1,074 (2,462) ng/ml and 377 (717) ng/ml and the post-dose (peak) mean (SD) concentrations were 21,887 (13,876) ng/ml and 31,007 (36,682) ng/ml in the 300 mg twice daily and 600 mg once daily groups, respectively. The full pharmacokinetic profile from a subset of 11 patients who had detailed PK samples drawn is shown in Additional file 1.

Safety

The proportion of subjects who reported adverse events during the study was similar between treatment groups (Table 5). Among those with adverse events, 61% reported mild or moderate events, and 20% each reported severe or life-threatening events. The subjects who remained clinically unstable on day 5 and therefore received >5 days of treatment with peramivir were more likely (86%) to report adverse events than those receiving treatment ≤5 days (56%). Approximately half of the serious adverse events reported were respiratory (for example, ARDS, respiratory failure and chronic obstructive pulmonary disease), followed by infections (for example, septic shock, sepsis and pneumonia), renal failure and cardiovascular disorders.

Clinical laboratory toxicities were reported by 91% of all subjects, with 38% of those toxicities being grade 3 or 4. Overall, few subjects in either treatment group experienced shifts to grade 3 or 4 for any laboratory parameter during the study, and the incidence was similar between treatment groups. Clinically significant laboratory abnormalities were reported as adverse events (Table 5). Episodes of renal failure were generally not deemed to be associated with therapy by the investigators and resolved in surviving patients.

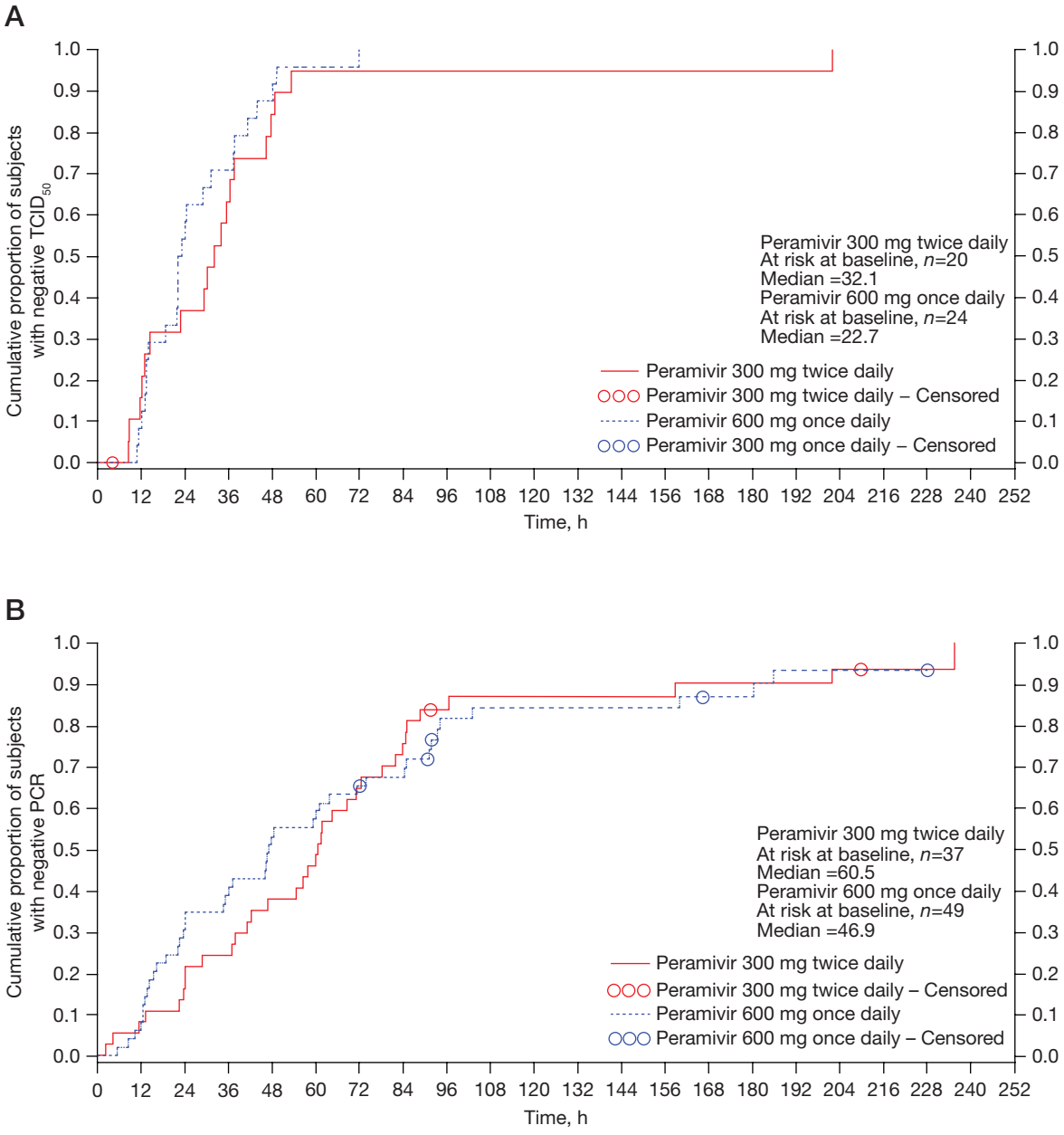
Discussion

This open-label study is one of the largest prospective studies of an influenza antiviral performed in the hospital setting. The virology results demonstrate substantial reductions in nasopharyngeal viral titres with intravenous peramivir but no differences between treatment with peramivir 300 mg twice daily and 600 mg once daily. Furthermore, no clinically relevant differences in safety outcomes were noted between the two dosing regimens. Further, the paper provides valuable information about the virological kinetics and clinical response to antiviral therapy in a population with severe illness due to influenza.

It was designed and initiated early in the 2009 pandemic to assess the safety and effectiveness of two regimens of intravenous peramivir in seriously ill subjects hospitalized with 2009 influenza A (H1N1) virus. It was specifically designed to be open-label because patients could access intravenous peramivir via the EUA mechanism, which did not permit the prospective collection of clinical or virological data. The enrolment criteria were broad and there was no exclusion on the grounds of previous antiviral treatment or length of illness prior to randomization. Most subjects had received antivirals prior to enrolment, and most had been ill for >48 h. Based on prognostic indicators and demographics at entry, the study population appears representative of the hospitalized patient population in the US during the 2009–2010 pandemic [4,25–27].

Approximately twice as many subjects had confirmed influenza by RT-PCR than by primary culture, confirming that RT-PCR is a more sensitive assay in a prospective clinical trial setting [28,29]. All influenza isolates were susceptible to NAIs at baseline and thereafter, with the exception of those from one subject, previously treated with oseltamivir who developed an H275Y mutation while receiving peramivir. In this

Figure 3. Time to negative culture or PCR



(A) Time to first negative culture (tissue culture infective dose $[TCID]_{50}$ ≤0.5; *n*=44). **(B)** Time to first negative quantitative PCR (≤1.58 $\log_{10}$ virus particles/ml for influenza A and ≤1.49 $\log_{10}$ virus particles/ml for influenza B; *n*=86).

study, conducted in the setting of hospitalized subjects with pandemic influenza, viral clearance appeared to be slower (96 h) with intravenous peramivir than in a previous study of peramivir (48 h) in the setting of hospitalized subjects recently diagnosed with seasonal influenza treated with lower doses of intravenous peramivir (200 or 400 mg once daily for 5 days) [14]. These results are consistent with those reported by other investigators who prospectively evaluated patients with severe 2009 H1N1 pneumonia [7,30,31].

In addition to the differences in viral strain and lack of immunity increasing clinical severity compared to seasonal influenza, the subjects in the current study were likely more seriously ill because of broader inclusion criteria that allowed enrolment of study participants who were recently treated with other antivirals

Table 4. Clinical end points[a]

	300 mg twice daily (*n*=57)	600 mg once daily (*n*=70)	Total (*n*=127)
Median TTCR[b], h (95% CI)			
Overall ITTI population[c]	45 (41, 118)	166 (84, 273)	92 (46, 166)
Population requiring supplemental O_2 at baseline	166 (66, NA)	177 (116, 283)	177 (116, 278)
Population not requiring supplemental O_2 at baseline	29 (19, 42)	20 (12, 173)	27 (16, 41)
Population admitted to ICU at baseline	NA	283 (115, 283)	NA (283, NA)
Population not admitted to ICU at baseline	43 (29, 66)	116 (46, 190)	–
Median time to hospital discharge, days (95% CI)	6.0 (5.0, 8.0)	6.0 (6.0, 11.0)	6 (6, 8)
Incidence of complications			
Otitis, *n* (%)	1 (2)	0	1 (1)
Sinusitis, *n* (%)	4 (7)	3 (4)	7 (6)
Bronchitis, *n* (%)	11 (19)	11 (16)	22 (17)
Pneumonia, *n* (%)	35 (61)	46 (66)	81 (64)
Incidence of post-baseline ICU admission, *n* (%)	2 (4)	6 (9)	8 (6)
Median duration of post-baseline ICU admission, days (95% CI)	7 (2, 11)	7 (4, 9)	7 (2, 11)
14-day survival[b], %	98	93	95
28-day survival[b,d]			
Overall ITTI population, %	94	86	90
Population requiring supplemental O_2 at baseline, %	91	83	86
Population not requiring supplemental O_2 at baseline, %	100	100	100
Population admitted to ICU at baseline, %	89	73	79
Population not admitted to ICU at baseline, %	96	91	93
Proportion with ≥5 days treatment, *n* (%)	16 (28)	28 (40)	44 (35)
Median time to fever resolution, h (95% CI)	27 (13, 37)	24 (13, 54)	25 (14, 36)
Median time to resolution of O_2 saturation, h (95% CI)	22 (11, 42)	46 (15, 166)	26 (18, 92)
Median time to alleviation of symptoms[b], h (95% CI)	135 (89, 184)	158 (103, 306)	145 (117, 187)
Median time to resumption of usual activities[b], days (95% CI)	28 (18, NA)	25 (14, 29)	27 (18, 32)

[a]Intent-to-treat infected (ITTI) population. [b]Estimated using the method of Kaplan–Meier. [c]Baseline predictors of time to clinical resolution (TTCR) in multivariable logistic regression: supplemental O_2 (HR=0.349, 95% CI 0.204, 0.594), ICU admission (HR=0.233, 95% CI 0.089, 0.609) and longer pre-treatment hospitalization (HR=1.171, 95% CI 1.027, 1.337). [d]Baseline predictors of survival in χ^2 analysis: supplemental O_2 (*P*=0.014), ICU admission (*P*=0.034). NA, not estimated.

and who had a longer duration of illness. Of the subjects with confirmed influenza, at baseline 43% had grade 3/4 laboratory abnormalities, 69% required supplemental oxygen, 19% required intubation and immediate ICU admission, and 83% had been ill for ≥48 h compared with 0%, 0%, 0% and 27% respectively, in the previous study [14]. The similarly-defined median TTCR was 37 h in the peramivir 400 mg once daily group [14] compared with 92 h in the current study, again indicating a more severely ill population in the current study. Furthermore, the component of TTCR that correlated with the total end point in the seasonal influenza study of less severe subjects was fever; in our study the main driver of TTCR was oxygen saturation. The severity of illness of subjects enrolled in this study was also demonstrated by the median time to resumption of usual activities (median 27 days), which was notably longer than the same subject-reported outcome previously reported from hospitalized subjects with seasonal influenza treated with intravenous peramivir (median 9 days) [14].

Safety results in the current study demonstrated that peramivir at either 600 mg once daily or 300 mg twice daily appeared generally safe and well tolerated in this seriously ill hospitalized population, although this study did not include oseltamivir-treated or non-treated comparator groups. No clinically relevant differences in safety outcomes were noted between the two dosing regimens. An apparent imbalance in the incidence of acute renal failure between the two treatment groups was accounted for by an imbalance in prognostic factors at randomization, with proportionally more subjects in the 600 mg once daily group requiring ICU admission (21% versus 16%) and supplemental oxygen (74% versus 61%) compared with the 300 mg twice group. All cases of acute renal failure were assessed by investigators as unrelated or unlikely related to peramivir. Further, the incidence of adverse events were similar to an earlier study with lower dose peramivir in a population with lower overall severity of illness [14]. When peramivir 600 mg once daily was administered to US

Table 5. Treatment-emergent adverse events[a]

Adverse event	300 mg twice daily (*n*=114)	600 mg once daily (*n*=116)	Total (*n*=230)
Any adverse event, *n* (%)	90 (79)	85 (73)	175 (76)
Drug-related adverse event, *n* (%)	22 (19)	19 (16)	41 (18)
Serious adverse event, *n* (%)	21 (18)	26 (22)	47 (20)
Deaths, *n* (%)	8 (7)	14 (12)	22 (10)
Adverse events leading to withdrawal, *n* (%)	4 (4)	8 (7)	12 (5)
Adverse events in ≥5% of subjects in either group			
Constipation, *n* (%)	19 (17)	11 (9)	30 (13)
Diarrhoea, *n* (%)	13 (11)	16 (14)	29 (13)
Hypokalaemia, *n* (%)	8 (7)	14 (12)	22 (10)
Nausea, *n* (%)	10 (9)	8 (7)	18 (8)
Peripheral oedema, *n* (%)	10 (9)	8 (7)	18 (8)
Hypotension, *n* (%)	7 (6)	11 (9)	18 (8)
Anaemia, *n* (%)	5 (4)	13 (11)	18 (8)
Insomnia, *n* (%)	13 (11)	4 (3)	17 (7)
Hyperglycaemia, *n* (%)	7 (6)	7 (6)	14 (6)
Hypertension, *n* (%)	5 (4)	9 (8)	14 (6)
Headache, *n* (%)	7 (6)	5 (4)	12 (5)
Oedema, *n* (%)	2 (2)	6 (5)	8 (3)
Agitation, *n* (%)	2 (2)	6 (5)	8 (3)
Acute renal failure[b], *n* (%)	1 (1)	7 (6)	8 (3)

[a]Safety population. [b]Episodes of renal failure were generally not deemed to be associated with therapy by the investigators and resolved in surviving patients.

hospitalized patients treated for suspected 2009 influenza A (H1N1) under the EUA, all-cause mortality was 211/1,371 (15%) compared with 10% at 28 days in the current study [32]. This compares well with other reports [3,26,27]. Mortality was substantially lower than in a recently reported uncontrolled retrospective study of intravenous peramivir from California [33]. 27% of the EUA patients reported serious or selected adverse events using MedWatch compared with 20% in the current study, and the FDA concluded that it was unlikely that intravenous peramivir adversely affected outcome [32]. In patients treated for seasonal influenza, intravenous peramivir has also been well tolerated in adults [11–14] and children [34].

The results in the current study provided a peramivir pharmacokinetic profile similar to that previously reported from emergency investigational new drug peramivir-treated patients [17,23,35] and human volunteers [36,37]. After dosing on day 5, trough peramivir concentrations were more than two orders of magnitude greater than the IC_{50} for 2009 H1N1 neuraminidase inhibition (0.03–0.5 nM) [20].

There were several limitations to the current study. First, this was an open-label study with no control arm, although end points such as virology were objective. Due to the study's broad eligibility criteria and despite randomization, there were unexpected differences in baseline severity between treatment groups, leading to apparently different outcomes; these differences were accounted for after corrections for the baseline imbalance. These broad entry criteria, coupled with the properties of the pandemic virus, contributed to a low number of subjects with confirmed influenza at baseline, particularly with positive viral culture. Finally, there are currently no well-validated clinical end points for assessing antiviral efficacy in hospitalized patients. Further analysis of this database may provide insight into optimizing the design and analysis of such studies. Another major limitation was the relatively small proportion of patients with proven influenza. Many of the patients with negative testing likely had previously influenza infection since they generally had similar characteristics and risk for influenza as those with documented influenza. Lastly, the subjects generally had specimens collected from the upper airway; previous data has clearly demonstrated that viral replication can persist for a longer period of time in the lower airway than in the upper airway [30]. As such, some of the individuals with negative studies for influenza could have been infected in the lower airway without evidence of infection by upper airway sampling.

It is important to note that the study also clearly demonstrates the difficulty of conducting clinical trials of novel antivirals active against influenza in hospitalized patients. The heterogeneous nature of the patients at baseline and severity of illness make establishing a single clinical end point for all enrolled

patients challenging. Specifically, disease pathogenesis, clinical course and prognosis are affected by the age and immunological status of the patient, presence of comorbidities, reasons for admission, time to presentation for care and the specific characteristics of the infecting virus. Furthermore, placebo-controlled studies are generally not acceptable to subjects or their guardians when they are severely ill. As such, comparator arms may be difficult to select and may not lend themselves to demonstrating superiority of the agent under investigation [29].

In conclusion, intravenous peramivir 600 mg/day once daily or in divided doses twice daily, administered to hospitalized subjects in this large open-label trial was associated with decreases in viral shedding and clinical improvement of most patients with similar results between treatment groups. Peramivir was generally safe and well tolerated in this study, and could be an important novel antiviral with which to treat persons hospitalized with influenza, either alone or in combination with other drugs. A randomized controlled study of intravenous peramivir added to standard-of-care versus standard-of-care alone was recently terminated following a determination by the study's Data Monitoring Committee at a planned interim analysis that the difference between the peramivir and control groups for the primary end point was small and a recalculated sample size was greater than a predefined futility boundary. A Phase III study comparing oseltamivir to intravenous zanamivir in hospitalized patients is also in progress. Full results from these studies will be key in assessing the role of intravenous NAIs in hospitalized patients.

Acknowledgements

This work was supported primarily by HHS/BARDA (Advanced development contract HHS0100200700032C) and secondarily by BioCryst Pharmaceuticals, the manufacturer of peramivir.

Study management was provided by Julie Daves and Amy McCullough, BioCryst Pharmaceuticals, Inc. Study monitoring and data management were performed by Quintiles, Inc. (Durham, NC, USA), pharmacokinetic analysis was performed by Sharon Baughman of ProPharma Services, LLC (Ventura, CA, USA) and statistical analysis was performed by Jenna Elder of PharPoint Research, Inc. (Wilmington, NC, USA), all of which were funded by BioCryst. In the preparation of the manuscript, authors were assisted by a professional medical writer, Elizabeth Field, Field Advantage Medical Communication, LLC (Durham, NC, USA), who was funded by BioCryst. A full list of individuals whom the authors would like to acknowledge can be found in Additional file 2.

Disclosure statement

JEH, PC and WPS are current or former employees of BioCryst Pharmaceuticals, the manufacturer of peramivir, and hold equity and stock options. All other authors have received research funding from BioCryst. JE provides consultant services to BioCryst as an employee of Pharpoint Research. MGI has received research funding from BioCryst, Roche, Cellex, Chimerix and Adamas, and has been a consultant for BioCryst, Biota, Cellex, Chimerix, GSK, MP Bioscience, NexBio, Roche, T2 Diagnostics, Toyama and Vertex (unpaid), and for Elan, Astellas and Abbott Molecular (paid). BO reports receiving study grant support from Neuren Pharmaceuticals and Brainscope and Heartscape Technologies. He is also on the speakers' board for Sanofi-Aventis, GSK and BMS. WO is an employee of and an independent contractor to eStudy Site. eStudy Site received a grant from BioCryst for WO to be the principal investigator for this study at eStudy Site's La Mesa, California research site. All other authors declare no competing interests.

Additional files

Additional file 1: Supplemental information showing dosing for renal insufficiency, *in vitro* susceptibility results and pharmacokinetic results of the study can be found at http://www.intmedpress.com/uploads/documents/2892_Ison_Additional_file_1.pdf

Additional file 2: A full list of study investigators, their personnel and participating patients can be found at http://www.intmedpress.com/uploads/documents/2892_Ison_Additional_file_2.pdf

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Accepted 29 July 2013; published online 28 August 2013