Favipiravir in patients hospitalised with COVID-19 (PIONEER trial): a multicentre, open-label, phase 3, randomised controlled trial of early intervention versus standard care

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Summary

Background COVID-19 has overwhelmed health services globally. Oral antiviral therapies are licensed worldwide, but indications and efficacy rates vary. We aimed to evaluate the safety and efficacy of oral favipiravir in patients hospitalised with COVID-19.

Methods We conducted a multicentre, open-label, randomised controlled trial of oral favipiravir in adult patients who were newly admitted to hospital with proven or suspected COVID-19 across five sites in the UK (n=2), Brazil (n=2) and Mexico (n=1). Using a permuted block design, eligible and consenting participants were randomly assigned (1:1) to receive oral favipiravir (1800 mg twice daily for 1 day; 800 mg twice daily for 9 days) plus standard care, or standard care alone. All caregivers and patients were aware of allocation and those analysing data were aware of the treatment groups. The prespecified primary outcome was the time from randomisation to recovery, censored at 28 days, which was assessed using an intention-to-treat approach. Post-hoc analyses were used to assess the efficacy of favipiravir in patients aged younger than 60 years, and in patients aged 60 years and older. The trial was registered with clinicaltrials.gov, NCT04373733.

Findings Between May 5, 2020 and May 26, 2021, we assessed 503 patients for eligibility, of whom 499 were randomly assigned to favipiravir and standard care (n=251) or standard care alone (n=248). There was no significant difference between those who received favipiravir and standard care, relative to those who received standard care alone in time to recovery in the overall study population (hazard ratio [HR] 1·06 [95% CI 0·89–1·27]; n=499; p=0·52). Post-hoc analyses showed a faster rate of recovery in patients younger than 60 years who received favipiravir and standard care versus those who had standard care alone (HR 1·35 [1·06–1·72]; n=247; p=0·01). 36 serious adverse events were observed in 27 (11%) of 251 patients administered favipiravir and standard care, and 33 events were observed in 27 (11%) of 248 patients receiving standard care alone, with infectious, respiratory, and cardiovascular events being the most numerous. There was no significant between-group difference in serious adverse events per patient (p=0·87).

Interpretation Favipiravir does not improve clinical outcomes in all patients admitted to hospital with COVID-19, however, patients younger than 60 years might have a beneficial clinical response. The indiscriminate use of favipiravir globally should be cautioned, and further high-quality studies of antiviral agents, and their potential treatment combinations, are warranted in COVID-19.

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Introduction

COVID-19 is caused by SARS-CoV-2, with in excess of 6·6 million deaths reported worldwide (as of Nov 21, 2022).[1,2] Greater mortality rates in COVID-19 are associated with increased age, comorbidity, and health-care resource saturation.[1,3] Vaccination programmes have proved efficacious in mitigating the severity of COVID-19 but availability remains challenging in the global setting, while vaccine-resistant variants remain a risk.[4]

Intravenous remdesivir was the first effective antiviral agent in adults hospitalised with COVID-19.[5] Outpatient treatment with molnupiravir in at-risk adults with COVID-19 has been shown to reduce the risk of hospitalisation or death.[6] Although nirmatrelvir–ritonavir is also efficacious in non-hospitalised patients with COVID-19 who are at high risk for progression to severe disease, and who were treated within 5 days of symptom onset, there are concerns regarding the propensity of ritonavir to cause drug–drug interactions.[7] As molnupiravir and nirmatrelvir–ritonavir are novel therapeutics, issues with global access are anticipated.[6,7]

Favipiravir (Fujifilm Toyama Chemical Co, Tokyo, Japan) is an off-patent, orally ingested, pyrazinecarboxamide-derived nucleoside analogue that inhibits RNA-dependent

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See Online for appendix

Research in context

Evidence before this study

We searched MEDLINE, Scopus, Web of Science, and MedRxiv from inception to May 17, 2022, for randomised controlled trials and meta-analyses evaluating the effect of favipiravir on patients hospitalised with COVID-19 using the search terms ("COVID-19", or "SARS-CoV-2", or "2019-nCoV") and ("favipiravir" or "Avigan"). The most comprehensive meta-analysis performed to date (nine studies; 827 patients) reported a significant clinical improvement in the favipiravir group at 7 days after hospitalisation, and a non-statistically significant reduction in mortality of approximately 23%. The low sample size in each study was identified as a key limitation, with further large, clinical trials needed to evaluate efficacy and safety. At present, substantial global use of favipiravir persists, and on clinicaltrials.gov there are 109 studies evaluating the role of the medication in the treatment of COVID-19, with the majority being small in scale.

Added value of this study

PIONEER is a large, international, independent, randomised controlled trial of favipiravir in patients hospitalised with COVID-19. We found that, in comparison with standard care alone, favipiravir did not improve prespecified clinical outcomes, however, post-hoc analyses indicated an earlier time to recovery and an increased likelihood of ventilation-free survival in those younger than 60 years. No benefits were observed in patients aged 60 years and older.

Implications of all the available evidence

Favipiravir does not improve clinical outcomes in all patients admitted to hospital with COVID-19, however, patients younger than 60 years might have a beneficial clinical response. The indiscriminate use of favipiravir globally should be cautioned, and further high-quality studies of antiviral agents, and their potential treatment combinations, are warranted for the treatment of COVID-19.

RNA polymerase without exhibiting mammalian cell cytotoxicity[8] and is licensed for the treatment of novel influenza in Japan.[9] In vitro, favipiravir has shown activity against multiple RNA viruses, including SARS-CoV-2, and in-vivo animal models have shown its ability to reduce pulmonary SARS-CoV-2 viral titres and decrease transmission.[8,10,11] In a smaller study of 156 patients with COVID-19 randomly assigned (2:1) to favipiravir or placebo of favipiravir, favipiravir showed enhanced clinical outcomes, however, interpretation is confounded as patients in the control group also received favipiravir on compassionate grounds.[12] Favipiravir is widely available in Asia and has been extensively used in the treatment of COVID-19 despite little evidence of efficacy. The safety profile has not shown any significant tolerability or safety issues, based on more than 30 clinical trials across differing viral pathogens.[13] However, teratogenicity has been reported in animal studies, with drug concentrations similar to or lower than the clinical exposure.[13]

For more on the **study** see www.chelwest.nhs.uk/research/pioneer

We aimed to evaluate the efficacy and safety of oral favipiravir in patients admitted to hospital with COVID-19, in a phase 3, multicentre, multinational, open-label, randomised controlled study of favipiravir plus standard care, versus standard care alone.

Methods

Study design

The PIONEER study was an international, open-label, phase 3, randomised controlled trial, conducted across sites in the UK (n=2), Brazil (n=2) and Mexico (n=1). The trial was coordinated by the trial sponsors, the Chelsea and Westminster NHS Foundation Trust, and the NEAT ID Foundation, and performed in accordance with the principles of the International Conference on Harmonisation–Good Clinical Practice guidelines. Ethics approval was granted by the UK Medicines and Healthcare products Regulatory Agency, the national ethics committees of the participating countries, and fulfilled local regulatory requirements. The trial was overseen by an independent data and safety monitoring board (appendix p 2). The study sites collected and inputted data into an electronic clinical record form designed by Medrio. The study protocol, statistical analysis plan, and additional information are available online.

Participants

Patients older than 18 years were eligible for the trial if they were admitted to hospital for suspected or confirmed COVID-19, between May 5, 2020 and May 26, 2021, with SAR-CoV-2 infection established either by RT-PCR testing or through characteristic clinical features, comprising a fever of 37·8°C or higher or a patient-reported history of fevers, as well as the acute onset of at least one of the following respiratory symptoms: persistent cough, hoarseness, nasal discharge or congestion, shortness of breath, sore throat, wheezing or sneezing; and evidence of pulmonary infiltrates consistent with COVID-19 on chest radiograph or computed tomography scan, with alternative causes for the clinical features considered as unlikely. Exclusion criteria were pregnancy, breast feeding, enrolment in another interventional trial, inability to take medication via the oral or nasogastric route, or a known sensitivity to favipiravir (appendix p 6). Women of childbearing potential were required to have a negative serum or urine pregnancy test before enrolment. All participants were required to provide verbal consent to abstain from sexual activity for a minimum of 7 days post-completion of treatment, or to use adequate methods of

contraception. Written informed consent was obtained from all patients, or from their legal representative if they were too unwell or unable to provide consent.

Randomisation and masking

Eligible patients were randomly assigned using a permuted block design, in a 1:1 ratio, to receive open-label oral favipiravir plus standard care or standard care alone. Randomisation was conducted by an appropriately delegated member of the study team, using a centralised online portal. The study initially involved a third trial group, which was removed after instruction from the UK Medicines and Healthcare products Regulatory Agency, due to concerns regarding hydroxychloroquine and cardiac toxicity.[14] Before the cessation of the third group, those patients had been randomised 1:1:1 to receive combination treatment with hydroxychloroquine, azithromycin, and zinc sulphate. This group was subsequently excluded from the current study (appendix pp 3–5).

Procedures

Patients allocated to the favipiravir group received 1800 mg twice daily orally on day 1, followed by 800 mg twice daily from day 2 to day 10. If required, favipiravir tablets could be crushed and dispersed in water for administration in enteral tubes, or dispersed in 10–15 mL of distilled water in a syringe. Patients receiving favipiravir who were discharged from hospital before day 10, were discharged with sufficient doses to complete the medication course in the community. Medication adherence was captured on a dose-by-dose basis. Medication adherence was assessed by research team review of the in-patient medication charts, whereas post-discharge, assessment was made by pill counts and patient self-report. Over the duration of the study, standard care evolved as per local guidelines, with systemic corticosteroids, remdesivir, and tocilizumab used by the clinical teams as necessary. Before the withdrawal of the combination treatment group, patients received hydroxychloroquine 400 mg twice daily orally on day 1, followed by 200 mg twice daily orally from day 2 to day 10, azithromycin 250 mg once daily orally day 1 to day 3, and zinc sulphate 125 mL twice daily orally on day 1 to day 10.

Patients were followed up for a total of 28 days by the research team at the scheduled visits, and at study exit, with any changes in clinical status assessed on a seven-category ordinal scale: 1, not hospitalised with resumption of normal activities; 2, not hospitalised, but unable to resume normal activities; 3, hospitalised, not requiring supplemental oxygen; 4, hospitalised, requiring supplemental oxygen; 5, hospitalised, requiring nasal high-flow oxygen therapy, non-invasive mechanical ventilation, or both; 6, hospitalised, requiring extra-corporal membrane oxygenation, invasive mechanical ventilation, or both; and 7, death (appendix p 8),[15] and using the National Early Warning 2 (NEWS2) scoring system.

All non-COVID-19 associated adverse events and serious adverse events either observed by the research or clinical team, or reported to the research or clinical team, as well as all actions taken to treat the event were recorded within the participants medical notes. Data were entered into the electronic clinical record form along with the information relating to the duration and severity of the event, with the investigator's opinion of the causal relationship to the treatment (ie, unrelated, unlikely to be related, possible related, probable related, and definitively related; appendix p 9).

The trial was open-label in nature, with no blinding conducted after assignment to intervention.

Outcomes

The prespecified primary outcome was the time from randomisation to recovery of two or more points on the seven-category ordinal scale or discharge from hospital, whichever occurred first. The seven-category ordinal scale was based on previous publications, and was recommended by the WHO Research and Development Blueprint expert group.[16] Follow-up started at randomisation and was censored at day 28 or patient withdrawal. Prespecified secondary outcome measures were all-cause mortality, requirement for intensive care admission or ventilatory support, readmission rates, and change in clinical status from randomisation to 28 days after randomisation, as assessed by the time to a two-point reduction in NEWS2 score, or in the number of patients with a two-point

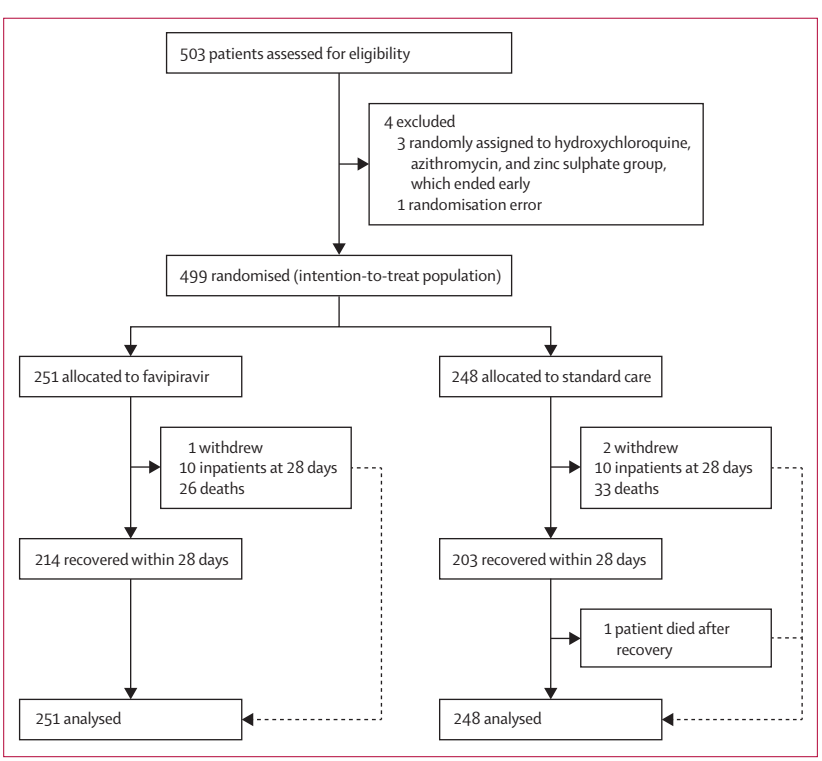

Figure 1: **Trial profile**

	All patients (n=502)*	Favipiravir group (n=251)	Standard care group (n=248)
Sex			
Female	200 (39%)	109 (43%)	88 (35%)
Male	302 (61%)	142 (57%)	160 (65%)
Age, years			
Mean (SD)	58·9 (15·3)	59·2 (16·3)	58·6 (14·2)
Median (IQR)	60 (48–69)	60 (46–72)	58 (49–68)
Range	19–98	19–98	23–96
Age <60 years	248 (49%)	120 (48%)	127 (51%)
Age ≥60 years	254 (51%)	131 (52%)	121 (49%)
SARS-CoV-2 status			
SARS-CoV-2-positive RT-PCR	446 (89%)	221 (50%)	225 (50%)
SARS-CoV-2-positive RT-PCR and aged <60 years	223 (90%)	104 (47%)	119 (53%)
SARS-CoV-2-positive RT-PCR and aged ≥60 years	223 (88%)	117 (53%)	106 (48%)
Comorbidities			
Cardiovascular	245 (49%)	114 (45%)	131 (53%)
Renal	36 (7%)	17 (7%)	19 (8%)
Hepatic	32 (6%)	18 (7%)	14 (6%)
Respiratory	86 (17%)	49 (20%)	37 (15%)
Endocrine – all	158 (32%)	68 (27%)	90 (36%)
Endocrine – non-diabetes-related	39 (8%)	16 (6%)	23 (9%)
Endocrine – diabetes-related	119 (24%)	52 (21%)	67 (27%)
Gastrointestinal	50 (10%)	30 (12%)	20 (8%)
Neurological	16 (3%)	13 (5%)	3 (1%)
Musculoskeletal	57 (11%)	36 (14%)	21 (9%)
Malignancy	17 (3%)	9 (4%)	8 (3%)
Allergies	198 (40%)	99 (39%)	99 (40%)
Country of recruitment			
Brazil	250 (50%)	118 (47%)	132 (53%)
UK	233 (46%)	122 (49%)	108 (44%)
Mexico	19 (4%)	11 (4%)	8 (3%)
Seven-category ordinal score			
WHO score	4 (4–4)	4 (4–4)	4 (4–4)
3, hospitalised, not requiring supplementary oxygen†	87 (17%)	40 (16%)	47 (19%)
4, hospitalised, requiring supplementary oxygen†	376 (75%)	190 (76%)	183 (74%)
5, hospitalised, requiring high-flow nasal cannula or non-invasive mechanical ventilation, or both†	39 (8%)	21 (8%)	18 (7%)

(Table 1 continues on next page)

reduction in NEWS2 score at 28 days. Post-hoc age-adjusted treatment analyses were performed. All outcome measures were centrally analysed on-site by members of the research team. A prespecified sensitivity analysis was performed for those patients with a positive SARS-CoV-2 RT-PCR test at hospital admission or as clinically indicated, or as part of the scheduled research visits at day 5–10 and day 14–28. Viral load data are not available for the study cohort, as an inappropriate swab storage media was utilised at one of the principle study sites. The effects of the country of recruitment, the time from onset of symptoms to the initiation of treatment, and the timing of patient recruitment, relative to the total duration of the study, which were secondary analyses of the primary outcome, are not included in this manuscript.

Statistical analysis

At design, no data were available on the effects of favipiravir or hydroxychloroquine in treating COVID-19 using the seven-category ordinal scale to inform a sample size calculation, and no advice were available on the best statistical approach for examining changes in the seven-category ordinal scale in this study to assess efficacy of antiviral medications.[16] In a trial of treatment of influenza,[15] a significant difference in the time to a two-point improvement on the same seven-category scale at day 14 was reported in 25 (63%) of 40 patients receiving combination favipiravir–oseltamivir, compared with 54 (42%) of 128 patients receiving oseltamivir only (p=0·0247). Due to the urgent need to study potential medications, it was decided to have 168 participants (as per the total number of patients in the influenza study[15]) in each of the three initial groups of the PIONEER trial. After withdrawing the hydroxychloroquine group of the study, we proceeded with the recruitment target set at 500 patients and power was enhanced for the remaining drug group.

The prespecified primary outcome was assessed with a competing-risks survival regression on the basis of a Fine–Gray's proportional subdistribution hazards model, which was prespecified and chosen because death would act as a competing event to recovery. Proportional hazard assumption was tested but no violations were found. Follow-up was calculated to the whole day, if different ordinal scores were recorded on the same day, recovery was confirmed over 24 h. Post-hoc subgroup and age-adjusted treatment effects were assessed between sexes, and in patients aged 60 years and older versus those younger than 60 years, and the cutoff for the age-related adjustment was the first selected as it produced a near median split in the number of participants, and it also met the WHO definition of risk factors associated with severe COVID-19.[17] Adherence in the favipiravir group was determined by whether or not a patient had taken 70% or more of the allocated doses within their period of study participation, which was 10 days or less (due to death, withdraw, or loss to follow-up). Patients receiving standard care only, were considered 100% adherent. Adherence was included as a covariate in the competing risks regression.

Patient demographics are reported as means (standard deviation), medians (IQR) or as percentages. Differences between treatment groups were compared by Student's *t*-test, Mann-Whitney U Test, χ^2 test, Spearman's rho or Fischer's exact test, as appropriate. Poisson regression with adjustments for the period of observation were used to compare the rates of adverse events. We did not formally test for dispersion with a likelihood ratio test.

The choice of a Poisson regression was made because some of the negative binomial models failed to converge. To assess changes in administration of standard care, a logistic regression was used to calculate the increased or decreased odds of treatment with systemic corticosteroids, antibiotics, remdesivir, and tocilizumab over the study period. Fine–Grey subdistribution hazards models were used to analyse the time to a two-point recovery in the NEWS2 score (appendix p 8) and its subcomponents, with death as a competing risk. All analyses were performed using STATA 13·1 and according to the principle of intention to treat. Data are presented as hazard ratios (HRs) with 95% CIs. All statistical tests were two-sided and a p value of less than 0·05 was considered significant. No data was imputed and missing data was assumed to occur at random.

The PIONEER study was registered with ClinicalTrials.gov, NCT04373733.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between May 5, 2020, and May 26, 2021, of the 503 patients that were assessed for eligibility, 499 patients were randomly assigned to the favipiravir group (n=251) or the standard care group (n=248). The hydroxychloroquine, azithromycin, and zinc sulphate group (n=3) of the study was terminated early. There was one randomisation failure. COVID-19 was confirmed by positive SARS-CoV-2 RT-PCR result in 446 (89%) patients, with 366 (82%) patients positive at enrolment and 80 (18%) patients positive post-enrolment during their hospital admission. Of the remaining 53 patients, 46 (87%) had influenza-like symptoms, 43 (81%) had shortness of breath, and 45 (85%) had radiographic evidence of pneumonia. The trial profile is shown in figure 1. One patient in the standard care group recovered, and was discharged from hospital, meeting the primary outcome definition of recovery, but was subsequently readmitted and died within 28 days.

A median of two comorbidities (IQR 1–3) were observed per patient, and an increasing number of comorbidities (excluding allergies) was positively correlated with increased patient age (Spearman's rho 0·38; p<0·001). There were no statistically significant differences between groups at randomisation in the proportion of patients at stages 3, 4, or 5 on the seven-category ordinal scale, who were situated in intensive care, nor any significant differences in blood inflammatory markers (table 1; appendix p 18). There were no significant between-group differences in the number of patients receiving antibiotics, corticosteroids, or remdesivir, and all four patients who received tocilizumab were in the favipiravir group (appendix p 18). The median time from the onset of symptoms as per medical history to randomisation was 8·9 days (IQR 6·2–11·1), with no significant difference between groups (table 1). Median time from hospital admission to randomisation was 0·9 days (IQR 0·7–1·3 days), with no significant difference between groups (table 1).

There was no significant difference in the primary outcome—time to recovery—between the groups in the overall study population with regard to the seven-category ordinal scale from randomisation to day 28 (HR 1·06 [95% CI 0·89–1·27]; n=499; p=0·52; figure 2A, figure 3). Post-hoc analyses showed that the time to recovery was shorter in patients younger than 60 years who received favipiravir and standard care, relative to those who received standard alone (HR 1·35 [95% CI 1·06–1·72]; n=247; p=0·01; figure 2A, figure 3). By contrast, there was no significant difference between the favipiravir group and the standard care group in patients who were aged 60 years and older (HR 0·93 [95% CI 0·70–1·22]; n=252; p=0·59; figure 2A, figure 3). The distribution of the proportions of all patients, patients younger than 60 years, and those aged 60 years and older at each stage of the seven-category ordinal scale over the 28 days are shown in the appendix (p 18). In the sensitivity analysis, the effect of favipiravir on the time to recovery in the patients with a SARS-CoV-2-positive RT-PCR test confirming the presence of COVID-19 was not significantly different from that of standard care alone (HR 1·03 [95% CI 0·85–1·25]; n=446; p=0·73; figure 3). No significant between-group differences in the seven-category ordinal scale were shown at days 7, 14, or 28 post-randomisation,

	All patients (n=502)*	Favipiravir group (n=251)	Standard care group (n=248)
(Continued from previous page)			
Serological testing			
Haemoglobin, g/dL	13·4 (12·2–14·5)	13·2 (12·1–14·4)	13·6 (12·6–14·5)
Platelets, 10^9/L	231 (175–294)	234 (180–300)	228 (169–288)
White blood count, 10^9/L	7·2 (5·2–9·7)	7·2 (4·9–9·6)	7·2 (5·3–9·8)
Neutrophil count, 10^9/L	5·7 (3·8–8·0)	5·5 (3·7–7·9)	5·7 (4·0–8·1)
Lymphocytes, 10^9/L	0·80 (0·6 – 1·2)	0·80 (0·6–1·2)	0·85 (0·6–1·2)
Fibrinogen, mg/L	5·79 (5·0 – 6·9)	5·78 (5·0–6·8)	5·89 (5·0–6·9)
C-reactive protein, mg/L	21·4 (10·9–83·9)	26·2 (11·4–81·7)	18·8 (9·1–83·9)
Urea, mmol/L	9·1 (5·7–13·6)	9·1 (5·7–12·9)	9·2 (5·9 -14·1)
Creatinine, mmol/L	86 (71–105)	85 (71–103)	88 (73–107)
Alkaline phosphatase, U/L	76 (61–97)	78 (63–100)	73 (60–95)
Alanine aminotransferase, U/L	36 (22–59)	37 (19–50)	36 (24–65)
Time to randomisation			
Time from symptom onset to randomisation, days	8·9 (6·2–11·1)	8·9 (6·2–11·0)	8·9 (6·2–11·5)
Time from admission to randomisation, days	0·91 (0·7–1·3)	0·9 (0·7–1·2)	0·9 (0·7–1·3)

Data are n (%), mean (SD), or median (IQR). *Three patients were randomly assigned to hydroxychloroquine, azithromycin, and zinc before the withdrawal of the study group; therefore, only 499 were analysed. †Proportion of those recruited in each category of the seven-category ordinal scale.

Table 1: **Characteristics at randomisation**

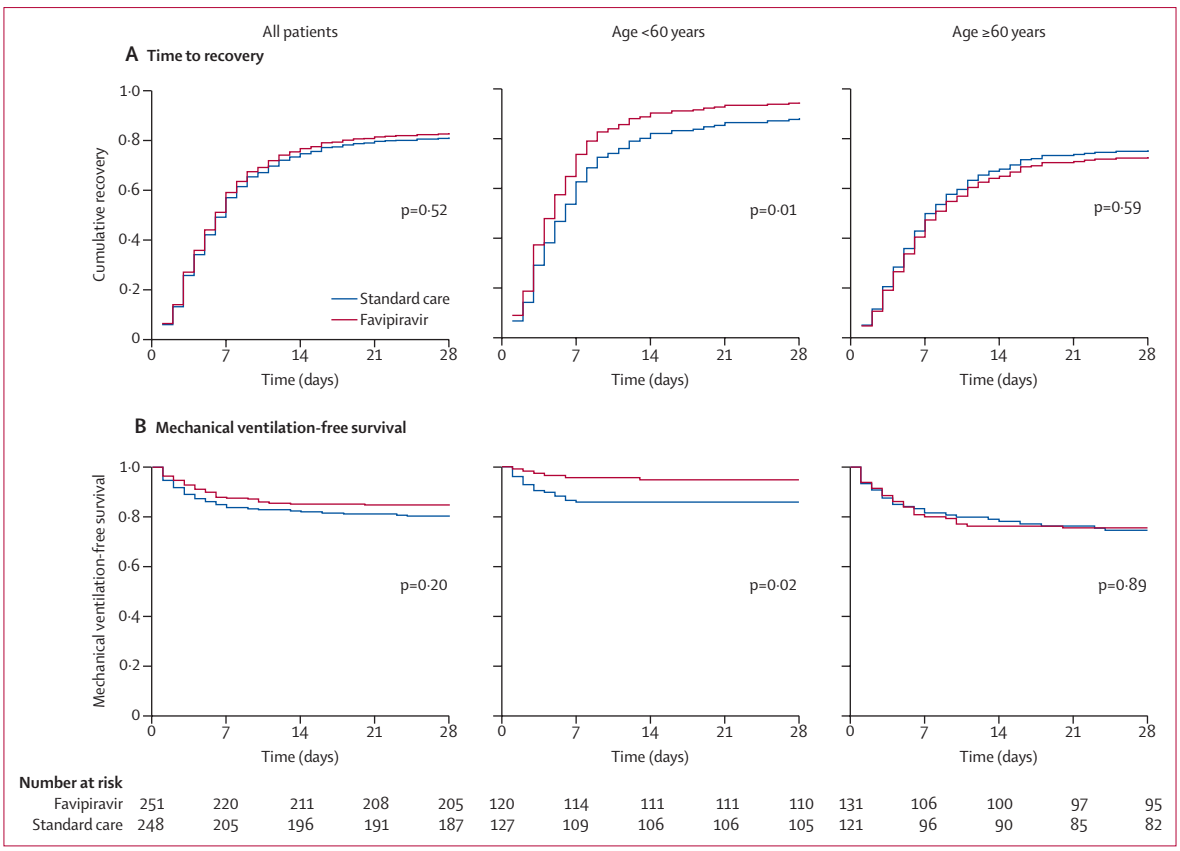

Figure 2: **Cumulative incidence of recovery in participants receiving favipiravir and standard care or standard care alone**
The p values are presented without adjustment. (A) Kaplan-Meier curve for time to recovery in patients receiving favipiravir and standard care or standard care alone, for all patients, those aged younger than 60 years, and those aged 60 years and older. (B) Kaplan-Meier curve for mechanical ventilation-free survival in patients receiving favipiravir and standard care or standard care alone, for all patients, those aged younger than 60 years, and those aged 60 years and older.

relative to baseline (appendix p 19). Forest plots and HRs are presented in figure 3 and in the appendix (p 20).

Although numerical differences in mortality at 28 days were observed between the two groups, these differences were not significant (26 [10%] of 251 patients in the favipiravir group *vs* 34 [14%] of 248 patients in the standard care group; HR 0·74 [95% CI 0·44–1·23]; n=499; p=0·24; figure 3, appendix p 15). Post-hoc analysis showed no significant between-groups differences in mortality in patients younger than 60 years (HR 0·52 [CI 95% 0·16–1·73]; n=247; p=0·29; appendix pp 15, 20) or 60 years and older (0·75 [0·42–1·32]; n=252; p=0·32; appendix pp 15, 20). No significant between-group difference in mortality rate were shown in patients with a SARS-CoV-2-positive RT-PCR test (24 [11%] of 221 patients in the favipiravir group *vs* 30 [13%] of 225 patients in the standard care group; HR 0·87 [95% CI 0·51–1·47]; n=446; p=0·60; figure 3, appendix p 21).

Post-hoc analyses showed a 66% benefit in mechanical ventilation-free survival in patients younger than 60 years (HR 0·34 [95% CI 0·13–0·85]; n=247; p=0·02; figure 3) receiving favipiravir and standard care, relative to standard care alone, whereas no significant difference between the groups was found in those aged 60 years and older (0·97 [0·59–1·59]; n=252, p=0·89; figure 3). Sensitivity analyses of patients with a positive SARS-CoV-2 RT-PCR test demonstrated that the age-adjusted treatment effects in patients receiving favipiravir and standard care were similar to that for the whole study cohort in terms of the time to recovery (aged <60 years: HR 1·33 [95% CI 1·03–1·71], n=223, p=0·03; aged ≥60 years: 0·92 [0·68–1·24], n=223, p=0·59) and in mechanical ventilation-free survival (aged <60 years: 1·35 [1·06–1·72], n=223, p=0·01; aged ≥60 years: 0·93 [0·70–1·22], n=223, p=0·59; appendix p 21).

No significant between-group differences were shown in the median time to a two-point reduction in NEWS2 score, or in the number of patients with a two-point reduction in NEWS2 score at 28 days, relative to baseline (appendix pp 8, 21).

There was a shift in clinical practice in standard care over the course of the study, and the likelihood of treatment with antibiotics decreased (OR 0·99 [95% CI 0·98–0·99]; p<0·001), whereas the chances of a patient being treated with oral corticosteroids increased (1·02 [1·01–1·02]; p<0·001). There was no trend in the use of remdesivir over time (OR 0·10 [95% CI 0·10–1·00]; p=0·27). Patient age at randomisation decreased by

0·05 years per day, relative to the age at study start date (linear regression; p<0·001), but there was no significant difference between the favipiravir group and the standard care group (appendix p 17).

One or more serious adverse events were reported in 27 (11%) patients in the favipiravir group and in 27 (11%) patients in the standard care group, with no significant difference between groups (Fisher's exact test; p=0·87; table 2). No patient became pregnant during the course of the study. A greater number of patients had one or more adverse events in the favipiravir group (97 [39%] patients) than did patients in the standard care group (75 [30%] patients; Fisher's exact test; p=0·005). Gastrointestinal and neurological adverse events were the most frequently encountered in the study, with no significant difference between groups. Notably, an increased number of patients in the favipiravir group experienced one or more renal adverse events than did patients in the standard care group (Fisher's exact test; p=0·03; table 2).

Discussion

To our knowledge, the PIONEER study is the largest randomised controlled trial of favipiravir performed in patients admitted to hospital with proven or suspected COVID-19. The study showed that treatment with favipiravir did not improve prespecified clinical outcomes. However, post-hoc analyses suggested an earlier time to recovery and an increased likelihood of ventilation-free survival with favipiravir in patients younger than 60 years. By contrast, favipiravir was not shown to be efficacious in patients 60 years and older. These age-adjusted findings were replicated when only patients with RT-PCR-confirmed COVID-19 were considered. The study population was representative of the real world, with the majority of patients possessing one or more established risk factor for severe illness in COVID-19.[18] Recruitment was completed during the first waves of the COVID-19 pandemic, with the majority of patients enrolled at a time when vaccines were not widely available. The management of COVID-19 evolved over the course of the trial, as evidence became available, with systemic corticosteroids, remdesivir, and tocilizumab incorporated into standard care, and used by the clinical teams, as needed.[19–22] Given that standard care was included in both study group allocations, the described effects of favipiravir can be considered additional, to the contemporaneously available clinical treatments.

Favipiravir did not enhance the time to recovery, the prespecified primary endpoint of the study, in patients admitted to hospital with proven or suspected COVID-19. There were numerical reductions in both mortality and ventilation-free survival but these changes were not statistically significant, and the study was likely underpowered to detect differences in survival. To elucidate potential responder groups, post-hoc analyses were performed with the 60-year age cutoff for the age-adjusted primary outcome selected as it produced a near median data split, and met the WHO definition for risk factors associated with severe COVID-19.[17] The post-hoc analyses demonstrated that the time to recovery in patients younger than 60 years was improved in those receiving favipiravir and standard care, with the cumulative incidence curves separating at around 4 days post-randomisation. When adjusting for age-related treatment effects, an improvement of 66 percentage points was observed in mechanical ventilation-free survival in patients younger than 60 years, supporting the positive age-adjusted finding relating to the primary outcome. Favipiravir was not found to be efficacious when considering any of the outcomes assessed in patients aged 60 years and older, and no evidence can be derived from this study supporting its use in this cohort.

Age-adjusted findings could potentially relate to the greater rates of comorbidity associated with increasing age

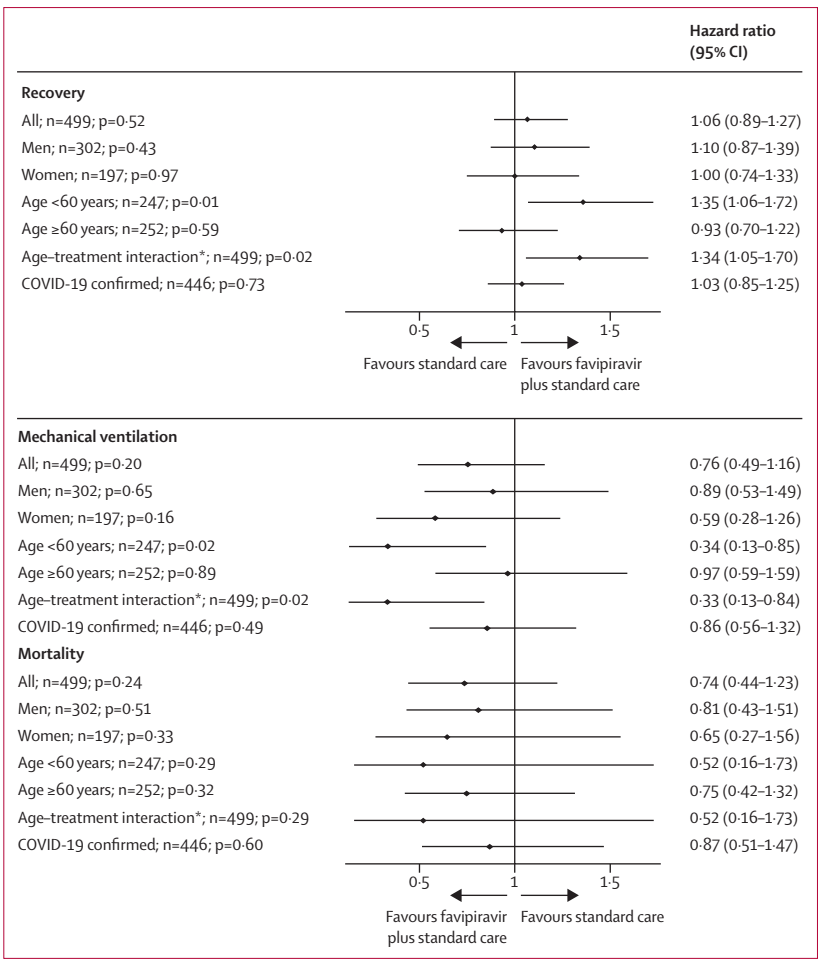

Figure 3: **Forest plots and hazard ratios for two-point improvement in ordinal score**
p values were calculated for recovery by Fine–Gray's subdistribution hazards model. Mechanical ventilation-free survival and mortality p values were calculated by Cox-proportional hazards models. *The effect of favipiravir relative to standard care after adjustment for age, and age–treatment interaction. There was no significant interaction between treatment group and gender for the three outcomes examined (p=0·53 for ordinal scale, p=0·68 for mortality; p=0·37 for death or mechanical ventilation).

	Favipiravir group (n=251)		Standard care group (n=248)		Incidence rate ratio (95% CI)	Event rate p value
	Events	Patients	Events	Patients		
Serious adverse events	36	27 (11%)	33	27 (11%)	1·04 (0·65–1·67)	0·87
Infectious	12	10 (4%)	17	17 (7%)	0·67 (0·32–1·41)	0·30
Respiratory	12	11 (4%)	5	5 (2%)	2·29 (0·81–6·50)	0·12
Cardiovascular	5	5 (2%)	1	1 (<1%)	4·77 (0·56–40·90)	0·15
Neurological	2	2 (1%)	4	4 (2%)	0·48 (0·08–2·61)	0·39
Renal	1	1 (<1%)	3	3 (1%)	0·31 (0·03–3·06)	0·32
Hepatic	3	3 (1%)	0	0	..	..
Gastrointestinal	1	1 (<1%)	2	2 (1%)	0·48 (0·04–5·27)	0·54
Electrolyte imbalance	0	0	1	1 (<1%)	..	..
Adverse events	227	97 (39%)	162	75 (30%)	1·34 (1·09–1·64)	0·005
Gastrointestinal	50	42 (17%)	49	41 (17%)	0·98 (0·66–1·45)	0·90
Neurological	35	30 (12%)	34	29 (12%)	0·98 (0·61–1·58)	0·95
Infectious	40	27 (11%)	20	18 (7%)	1·91 (1·11–3·27)	0·02
Cardiovascular	32	21 (8%)	22	20 (8%)	1·39 (0·81–2·39)	0·23
Electrolyte imbalance	19	14 (6%)	11	8 (3%)	1·65 (0·79–3·47)	0·19
Renal	10	9 (4%)	1	1 (0%)	9·56 (1·22–74·70)	0·03
Other	4	4 (2%)	5	5 (2%)	0·76 (0·21–2·84)	0·69
Hepatic	8	7 (3%)	4	2 (1%)	1·91 (0·57–6·35)	0·29
Haematological	9	7 (3%)	2	2 (1%)	4·30 (0·93–19·90)	0·06
Endocrine	6	6 (2%)	5	5 (2%)	1·15 (0·35–3·76)	0·82
Dermatological	5	5 (2%)	3	2 (1%)	1·59 (0·38–6·67)	0·52
Respiratory	4	4 (2%)	4	4 (2%)	0·96 (0·24–3·82)	0·95
Musculoskeletal	5	5 (2%)	2	2 (1%)	2·39 (0·46–12·30)	0·30

Data are n, n (%), and incidence rate ratio (95% CI) p values for the differences in the total serious adverse events and adverse event rates were calculated using Poisson regression, and p values for the differences in the number of patients reporting serious adverse events and adverse events were calculated using Fisher's exact test.

Table 2: **Serious adverse events and adverse events in patients**

in the study cohort, making recovery in patients 60 years and older more likely to be delayed through the complications of pre-existing disease. Furthermore, the recognised increased time to discharge associated with older inpatients, from secondary factors including compromised mobility and the need for social support, is likely to be relevant.[23] Alternatively, enhancements shown in clinical efficacy in patients aged younger than 60 years could relate to how favipiravir is absorbed, metabolised, and hence activated in younger patients.[24] The favipiravir dosage selected in the majority of clinical studies, including this PIONEER trial, appears to be the same that is used for the treatment of influenza, however, in-vitro data suggest that the dosage used in this study (1800 mg twice daily orally on day 1, followed by 800 mg twice daily from day 2 to day 10), might be inadequate for the treatment of COVID-19.[25] Pharmacodynamic evaluation of favipiravir and other antiviral medications, including the potential preferential response found in patients under the age of 60 years, should be a priority area for future research.

No significant difference between the favipiravir group and standard care group was noted in the total number of serious adverse events or in the number of patients that reported one or more serious adverse events. A greater total number of adverse events, a trend towards a greater number of patients with one or more adverse events, and specifically one or more renal events, were observed in the favipiravir group, relative to standard care alone. In this non-placebo controlled study, the number of non-serious adverse events that occurred in the favipiravir group might relate to a reporting bias, and further analyses in larger cohorts and blinded studies are warranted. Despite efforts to report only non-COVID related events, some of the events registered could still be considered part of the diverse pathophysiology of COVID-19, and the authors recognise this to have been a challenging determination.

Teratogenicity is a recognised limitation of many antivirals, including favipiravir and molnupiravir, with contraceptive counselling, cessation of breast feeding, and the assessment of current pregnancy status in women of childbearing potential necessitated before the initiation of treatment, and this side-effect has complicated widespread non-hospital-based usage of these antivirals.[6,13] Although nirmatrelvir–ritonavir is efficacious in reducing hospitalisation and death in patients with COVID-19 receiving community-based treatment, caution is urged given the propensity of ritonavir to cause clinically significant drug–drug interactions with commonly prescribed and over-the-counter medications.[7,26]

The PIONEER trial was initiated with a third study group incorporating hydroxychloroquine that was later removed because of the concerns associated with the agent and cardiac toxicity, which meant that three-way placebo control was not possible.[14] The substantial differences in the tablet forms of manufactured formulations of favipiravir and the combination group medications, including hydroxychloroquine, prevented use of a manufacturer's placebo, and re-capsulation was not possible due to the closure of processing facilities and the urgent need to test for new treatments. Consequentially, the open-label nature of the study was unavoidable, and despite efforts to separate clinical and research personnel, it could have led to bias in the clinical management of patients randomised to either study group. The study was designed to rapidly recruit patients admitted to hospital with COVID-19, and so patients with suspected disease, as in the real-world, were included to prevent unnecessary delays to the initiation of potential therapies. Consequentially, a number of patients were included in the trial who did not have RT-PCR-confirmed disease, however, confirmatory analyses excluding patients without proven COVID-19 showed the same prespecified and age-adjusted post-hoc findings. Another limitation of this study is that, by chance, there were more men in the standard care group and more patients with diabetes in the standard care group, with both factors associated with adverse outcomes.[27,28]

To our knowledge, the studies published thus far have not shown a clear benefit with favipiravir, although the

results have generally been dismissed by the global community, as the majority were small in cohort size, and in some cases, non-randomised. Consequently, usage of favipiravir remains widespread, with the medication included in treatment protocols for COVID-19 in Japan, Russia, Saudi Arabia, Thailand, Kenya, and in several states of India, while on clinicaltrials.gov, there are currently 109 trials evaluating the medication for the same indication.[29,30] Our findings caution the indiscriminate use of favipiravir outside of clinical trials, particularly in patients aged 60 years and older, and suggest future studies need to evaluate appropriate in-vivo dosing.

In conclusion, the PIONEER study data demonstrate that favipiravir is not efficacious in treating hospitalised adult patients with COVID-19 but that there is a suggestion that treatment might be effective in those younger than 60 years. Further high-quality studies of antivirals are needed for the treatment of COVID-19.

Contributors

PLS, CMO, PKB, MB, AP, MRJ, and MP contributed to the conception of the study and trial design. CMO, JT, AIR, FC, DJW, PLS, AT, BV, CC, CL, BM, AS, BG, BCR, BRS, SWC, and MPDR, recruited participants and acquired data. GCD. performed the statistical analysis. PLS, CMO, and GCD. wrote the first draft. All authors contributed to drafting and revising the work for intellectual content and approved the manuscript. PLS, CMO, and GCD. had access to the raw data and decision to submit the manuscript. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

The protocol, consent form, statistical analysis plan, and other relevant trial materials are available online at www.chelwest.nhs.uk/research/pioneer. The trial steering committee will facilitate the use of the trial data and approval will not be unreasonably withheld, providing the committee are satisfied that any proposed publication is of high quality, honours the commitments made to the trial patients in the consent documentation and ethics approvals, and is compliant with relevant legal and regulatory requirements (eg, relating to data protection and privacy). Deidentified participant data will be made available to bona fide researchers registered with an appropriate institution from 6 months to 36 months after publication. However, the steering committee will have the right to review and comment on any draft manuscripts before publication. Those wishing to request access should contact chelwest.research@nhs.net.

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