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Favipiravir for COVID-19 in adults in the community in PRINCIPLE, an open-label, randomised, controlled, adaptive platform trial of short- and longer-term outcomes

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SUMMARY

Background: Evidence for the effect of favipiravir treatment of acute COVID-19 on recovery, hospital admissions and longer-term outcomes in community settings is limited.
Methods: In this multicentre. open-label, multi-arm, adaptive platform randomised controlled trial participants aged ≥18 years in the community with a positive test for SARS-CoV-2 and symptoms lasting ≤14 days were randomised to: usual care; usual care plus favipiravir tablets (loading dose of 3600 mg in divided doses on day one, then 800 mg twice a day for four days); or, usual care plus other interventions. Co-primary endpoints were time to first self-reported recovery and hospitalisation/death related to COVID-19, within 28 days, analysed using Bayesian models. Recovery at six months was the primary longer-term outcome. Trial registration: ISRCTN86534580.
Findings: The primary analysis model included 8811 SARS-CoV-2 positive mostly COVID vaccinated participants, randomised to favipiravir (n = 1829), usual care (n = 3256), and other treatments (n = 3726). Time to self-reported recovery was shorter in the favipiravir group than usual care (estimated hazard ratio 1·23 [95% credible interval 1·14 to 1·33]), a reduction of 2·98 days [1·99 to 3·94] from 16 days in median time to self-reported recovery for favipiravir versus usual care alone. COVID-19 related hospitalisations/deaths were similar (estimated odds ratio 0·99 [0·61 to 1·61]; estimated difference 0% [−0·9% to 0·6%]). 14 serious adverse events occurred in the favipiravir group and 4 in usual care.

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By six months, the proportion feeling fully recovered was 74·9% for favipiravir versus 71·3% for usual care (RR = 1·05, [1·02 to 1·08]).
Interpretation: In this open-label trial in a largely vaccinated population with COVID-19 in the community, favipiravir did not reduce hospital admissions, but shortened time to recovery and had a marginal positive impact on long term outcomes.

Research in context

Evidence before this study

A search of PubMed on 4th October 2023, using the following search terms (randomised OR trial) AND (favipiravir) AND (COVID* OR SARS-CoV-2 OR SARS-CoV) AND (SYSTEMATIC REVIEW), with search results limited to reviews published in 2021 onwards, identified fifteen relevant systematic reviews, some with meta-analyses. The majority of trials included in the reviews were conducted in hospital settings, had small sample sizes, and were judged to be at moderate-high risk of bias. The dose of favipiravir used varied between the included studies, as well as the comparator, making meta-analysis difficult.

One of the more comprehensive reviews with searches conducted up to 2 March, 2022, included 157 studies, of which 24 were randomised clinical trials. When compared with standard care, favipiravir increased viral clearance at day 5, reduced the mean time to clinical improvement and fever abatement, and shortened the time to improvement in radiological imaging, but did not improve mortality and led to more cases of hyperuricaemia. A recent systematic review and meta-analysis with searches conducted up to February 2023 included nine trials comparing favipiravir with placebo/usual care among outpatients with COVID-19. There was no evidence of a benefit in proportions with clinical recovery, hospitalisation, or viral clearance. We are not aware of any outpatient trials of favipiravir that have reported outcomes beyond 28 days.

Added value of this study

Favipiravir is already approved as an anti-influenza drug in Japan. As favipiravir targets RNA-dependent RNA-polymerase, a relatively conserved protein in RNA viruses, there is potential for it to have broad spectrum anti-viral activity. Trials of favipiravir in COVID-19 patients to date have largely been conducted in secondary care settings, with mixed findings. Findings from the pragmatic PRINCIPLE trial in the UK fill an evidence gap by providing estimate effects for favipiravir treatment on time taken for recovery (reduced by three days from a median of 16 days), and on hospital admissions (no evidence of a difference) and longer term symptomatic and functional outcomes (a clinically meaningful effect is unlikely) among COVID-19 outpatients.

Implications of all the available evidence

There has been conflicting evidence of a beneficial impact of favipiravir on certain outcomes in hospitalised COVID-19 patients from trials of variable quality, while generally smaller trials conducted in COVID-19 patients in the community have not found convincing evidence of a benefit of favipiravir on viral load nor time to symptom resolution, and there are no trials reporting outcomes beyond 28 days. Taken together with our findings in this open-label trial of a modest reduction in time to feeling recovered, no benefit on reducing hospitalisations, and limited longer-term benefits on recovery and function, favipiravir at the dose and duration used in the present trial (3600 mg loading dose on day 1 followed by 800 mg twice a day for four days) should mainly be used if there is an imperative to moderately reduce the time taken for recovery from COVID-19.

Introduction

There is an ongoing need to identify effective and scalable treatments for COVID-19, as cases and short- and long-term morbidity from COVID-19 remain prevalent. A number of re-purposed drugs have been trialled as COVID-19 treatments, with some success.[1,2] Favipiravir is an antiviral drug that is licensed in Japan for the treatment of influenza.[3] Favipiravir enters host cells and through a process of phosphoribosylation becomes its active form, favipiravir ribofuranosyl-5′-triphosphate (favipiravir RTP).[4] Favipiravir RTP, a purine nucleotide analogue, inhibits viral RNA dependent RNA polymerase (RdRp).[4] Given that RdRp is highly conserved across a number of RNA viruses,[5] favipiravir has potential for broad spectrum activity against RNA viruses, including SARS-CoV-2.

Favipiravir has been evaluated in COVID-19 clinical trials, with mixed evidence of benefit. A large systematic review and meta-analysis identified 24 randomized control trials comparing favipiravir with placebo, usual care or other antiviral agents. In meta-analyses, there was some evidence of a benefit with favipiravir in day five viral clearance (but not at other timepoints), fever resolution, and time to clinical improvement, but no difference in length of hospitalisation and mortality. However, all trials were small (n < 250), only three were assessed as being at low risk of bias, and the majority were conducted in secondary care.

A recent systematic review and meta-analysis identified nine trials of favipiravir versus placebo/usual care in outpatients, and found no evidence of a benefit in the proportions with clinical recovery, hospitalisation, or viral clearance by 28 days.[6] There are no trials assessing the impact of favipiravir on longer-term outcomes beyond 28 days, reflecting a broader lack of trials of interventions to prevent and treat long COVID-19.[7] Therefore, we aimed to determine whether favipiravir treatment of people with acute COVID-19 in the community and at higher risk of an adverse outcome: speeds recovery; reduces COVID-19 related hospital admission or death; and, improves long-term outcomes beyond 28 days.

Methods

Trial design

We assessed the effectiveness of favipiravir in the UK national, multi-centre, primary care, open-label, multi-arm, prospective adaptive Platform Randomised trial of Treatments in the Community for Pandemic and Epidemic Illnesses (PRINCIPLE), which opened on 2nd April 2020, and closed to recruitment on 1st July 2022, although

long-term follow-up of participants continues. The protocol is available in the appendix (pp 6–102) and at the trial website, www.principletrial.org. A "platform trial" allows multiple treatments for the same disease to be tested simultaneously. A master protocol defines prospective decision criteria for dropping interventions from the platform for futility or superiority, or adding new interventions.[8] This allows interventions with little evidence of meaningful benefit to be rapidly removed from the platform and potentially replaced by new interventions, thereby directing resources towards identifying community-based treatments for COVID-19. Interventions evaluated in PRINCIPLE include hydroxychloroquine, azithromycin,[9] doxycycline,[10] inhaled budesonide,[2] colchicine,[11] ivermectin,[12] and, reported here, favipiravir.

The UK Medicines and Healthcare products Regulatory Agency and the South Central-Berkshire Research Ethics Committee (Ref20:/SC/0158) approved the trial protocol. Online consent was obtained from all participants. The authors vouch for the accuracy and completeness of the data and for fidelity to the protocol. An independent Trial Steering Committee and Data Monitoring and Safety Committee provided trial oversight.

Participants

From the beginning of the trial, people in the community were eligible if they were aged ≥65 years, or 50–65 years with comorbidities (appendix pp16–17), and had ongoing symptoms from polymerase chain reaction (PCR) confirmed or suspected COVID-19 (in accordance with the UK National Health Service definition at the time of high temperature and/or new, continuous cough and/or change in sense of smell/taste),[13,14] which had started within the previous 14 days. When the favipiravir arm opened to recruitment, eligibility criteria had been expanded to allow enrolment of participants aged 18 years and above. Initially, participants aged 18–64 years needed to additionally either have a comorbidity and/or report breathlessness. However, from 29th July 2022, all patients aged 18 years or over with a positive SARS-CoV-2 test (lateral flow or PCR) and who were within 14 days of the onset of ongoing symptoms consistent with COVID-19 were eligible for inclusion.

Exclusion criteria were: allergy to favipiravir; currently taking favipiravir; gout; severe liver disease; known or suspected pregnancy; breastfeeding; and, women of childbearing potential or men with a partner of childbearing potential not willing to use highly effective contraception for the 28-day duration of the trial.

Initially, eligible people were recruited, screened and enrolled through participating general medical practices, but from May 17, 2020, people across the UK could also enrol online or telephonically. After patients completed a baseline and screening questionnaire, a clinician or trained research nurse confirmed eligibility using the patient's primary care medical record or summary care record, accessed remotely where necessary, before randomisation. Multiple, purposely developed UK-wide inclusion and diversity community outreach strategies were implemented[15] with the aim of increasing recruitment of people from ethnically diverse communities and socioeconomically deprived backgrounds, who have been disproportionally affected by COVID-19.[16]

Randomisation and masking

Eligible, consenting participants were randomised using a secure, in-house, web-based randomisation system (Sortition version 2.3). Randomisation was stratified by age (< 65 years /≥ 65 years), and presence of comorbidity (yes/no), and probabilities were determined using response adaptive randomisation via regular interim analyses, which allowed allocation of more participants to interventions with better observed time to recovery outcomes (appendix p29). The allocation probability for the usual care arm remained fixed at $1/Z$ throughout the trial, where Z is the number of active interventions studied in the platform. The trial team was blinded to randomisation probabilities.

Trial procedures

Participants were followed up through an online, daily symptom diary for 28 days after randomisation, supplemented with telephone calls to non-responders on days 7, 14 and 28. The diary included questions about illness recovery (ascertained by answering the question, "Do you feel fully recovered today? (i.e. symptoms associated with illness are no longer a problem) Yes/No"), overall illness severity (a rating of how well they are feeling on a scale of 1–10 [1 being the worst and 10 being the best]), individual symptom severity on a four-point scale (0 = no problem to 3 = major problem), healthcare service utilisation, use of medications (over the counter, antibiotics or inhaled corticosteroids), WHO-5 questionnaire, and vaccinations. Participants could nominate a trial partner to help provide follow-up data. We obtained consent to ascertain healthcare use outcome data from general practice and hospital records.

Trial interventions

Participants received usual care plus favipiravir with a loading dose of 3600 mg in two divided doses on day one, followed by 800 mg twice daily for four days. Initially, participants received 200 mg tablets and were advised to take nine tablets (1800 mg) twice a day on day one, followed by four tablets (800 mg) twice daily for four days (50 tablets in total). Due to supply issues, from 11th April 2022, participants received 400 mg tablets and were instead advised to take five tablets (2000 mg) in the morning and four tablets (1600 mg) in the evening, followed by two tablets (800 mg) twice daily for four days (25 tablets in total). Medication and study packs were delivered to the participant by urgent courier. Usual care in the UK National Health Service for suspected COVID-19 in the community was largely conservative and focused on managing symptoms with antipyretics.[17] From 16th December 2021, a minority of extremely clinically vulnerable patients, could also access antiviral treatment or a monoclonal antibody infusion.[18]

Primary outcomes

The trial commenced with the primary outcome of COVID-19 related hospitalisation or death within 28 days. However, hospitalisation rates in the UK[19] were lower than initially expected.[20] Therefore, the Trial Management Group and Trial Steering Committee recommended amending the primary outcome to also include illness duration, which is an important outcome for patients and has substantial economic and social impacts. This received ethical approval on September 16, 2020, and was implemented before performing any interim analyses. Thus, the trial has two co-primary endpoints measured within 28 days of randomisation: 1) time to first reported recovery defined as the first instance that a participant reports feeling recovered; and 2) hospitalisation or death related to COVID-19. Decisions about COVID-19 relatedness were made after independent review of available data by two clinicians blinded to treatment allocation and study identifiers.

Secondary outcomes

Secondary outcomes (defined in section 3.3. of the Master Statistical Analysis Plan, appendix pp 126–133) included a binary outcome of early sustained recovery (recovered by day 14 and remains recovered until day 28), time to sustained recovery (date participant first reports recovery and subsequently remains well to 28 days), daily rating from 1–10 of how well participants felt, time to

initial alleviation of symptoms (date symptoms first reported as minor or none), time to sustained alleviation of symptoms (date symptoms first reported as minor or none and subsequently remain minor or none to 28 days), time to initial reduction of severity of symptoms (among people with symptoms at baseline, date symptom severity reported at least one scale lower), worsening of symptoms (worsening symptom by one grade from mild to moderate/severe, or from moderate to severe, and excluding individuals reporting symptom severity as major at baseline), contacts with healthcare services, hospital assessment without admission, duration of hospital admission, oxygen administration, Intensive Care Unit admission, mechanical ventilation, WHO ordinal scale of clinical progression, adherence to study treatment (ascertained from daily diaries which participant recorded their medication use or phone calls if diaries not completed), WHO-5 Well-Being Index,[21] serious adverse events, all cause death or non/elective or urgent hospitalisation, and reports of new household infections.

All time to event analyses used date of randomisation as baseline. We included secondary outcomes that capture sustained recovery due to the often recurrent and relapsing nature of COVID-19 symptoms.

Long term follow-up outcomes

All participants were contacted via email or phone call at three, six and 12 months after randomisation, accepting responses up to 3 months after each date (3 months [range:2·7–5·7]; 6 months [range:5·9–9·3]; 12 months [range: 12–17]) and requested to complete a questionnaire.

The primary outcome for the effect of favipiravir treatment of acute COVID-19 on longer-term outcomes was participant-report of feeling fully recovered at 6 months. Secondary outcomes collected at 3, 6 and 12 months included: number of unwell days in the preceding two weeks if the participant reported partial or no recovery from their original COVID-19 illness (range from 0 to 14 days); wellness rating on the day of questionnaire completion (scale of 1–10); WHO-5 Well-Being Index[21]; persistence of pre-specified COVID-19 symptoms (feverish, cough, shortness of breath, chest pain, loss of smell, loss of taste, nausea/vomiting, diarrhoea, headache, muscle ache, generally unwell, fatigue); impact of COVID-19 on work/studies; contacts with healthcare services from 28 days after randomisation up until the timepoint of questionnaire completion; and, feeling fully recovered at 12 months.

Statistical analysis

Sample size calculation and statistical analyses are detailed in the Adaptive Design Report (appendix 4, pp158–329) and the Master Statistical Analysis Plan (appendix 3, pp103–157). In the Adaptive Design Report we justify sample sizes by simulating the operating characteristics of the adaptive design in multiple scenarios, which explicitly account for response adaptive randomisation, possible early stopping for futility/success and multiple interventions. In brief, for the primary outcome analyses, assuming a hazard ratio of 1.3 (median time to recovery of nine days in the usual care group and seven for favipiravir), approximately 400 participants per group would provide 90% power to detect a 2-day difference in median recovery time. Assuming 5% hospitalisation in the usual care group at the time of designing the study, approximately 1500 participants per group would provide 90% power to detect a 50% reduction in the relative risk of hospitalisation/death for favipiravir versus usual care.

The first co-primary outcome - time to first self-reported recovery - was analysed using a Bayesian piecewise exponential model with pieces specified as 1-week intervals (0–7, 7–14, 14–21, 21–28 days). This piecewise exponential model was pre-specified when the time to recovery distribution was uncertain, as it allowed the usual care hazard rate for recovery to be flexible and vary across the 28-day follow-up period. The second co-primary outcome - hospitalisation/death - was analysed using a Bayesian logistic regression model. Both models were regressed on treatment group and stratification covariates (age < 65 years/≥ 65 years and comorbidity yes/no), and vaccination status. These primary outcomes were evaluated using a "gatekeeping" strategy to preserve the overall Type I error without additional adjustments for multiple hypotheses. The hypothesis for the time-to-first-recovery endpoint was evaluated first, and if the null hypothesis was rejected, the hypothesis for the second co-primary endpoint of hospitalisation/death was evaluated. In the context of multiple interim analyses, the master protocol specifies that each null hypothesis is rejected if the Bayesian posterior probability of superiority exceeded 0·99 for the time to recovery endpoint and 0·975 (via gate-keeping) for the hospitalisation/death endpoint. For the purposes of defining futility rules, we pre-specified a clinically meaningful hazard ratio for time to first reported recovery as 1·2 or larger (equating to approximately 1·5 days difference in median time to recovery, assuming 9 days recovery in the usual care arm), and a clinically meaningful odds ratio as 0·80 or smaller for hospitalisations/deaths (equating to approximately a 1% decrease in the hospitalisation rate, assuming a rate of 5% in the usual care arm). However, due to the larger sample size as the trial continued, while the trial team remained blinded to accumulating data, the team determined that the futility rule for hospitalisation/death might be too conservative. With the approval of the Trial Steering Committee, the futility rule was made more aggressive by increasing the futility threshold for the probability of meaningful benefit on hospitalisation from 1% to 25%, a change dated 1st June 2022, and described in detail in Appendix A to Adaptive Design Report version 5·0 (appendix 4, pp330).

If there was insufficient evidence of a clinically meaningful benefit in time to recovery, futility was declared and randomisation to that intervention stopped, meaning other interventions could be evaluated more rapidly. For each primary outcome endpoint (time to recovery and hospitalisation/death), a pre-specified model-based estimate of absolute benefit (days and percent, respectively) was obtained by applying the model-based estimate of treatment benefit (hazard ratio or odds ratio, respectively) to a bootstrap sample of the concurrent and eligible usual care population.

At the beginning of the trial, due to initial difficulties with community SARS-CoV-2 PCR testing in the UK, participants with suspected COVID-19 were included in the primary analysis population irrespective of confirmatory testing. When testing became more accessible, the Trial Steering Committee recommended restricting the primary analysis population to those with confirmed COVID-19 (this change was included in protocol version 7·1, February 22, 2021, approved March 15, 2021, before the favipiravir arm had opened). Therefore, the pre-specified primary analysis population included all eligible SARS-CoV-2 positive participants randomised to favipiravir, usual care, and other interventions, from the start of the platform trial until the favipiravir arm was closed on July 1, 2022. This population included participants randomised to usual care before the favipiravir group opened. The primary analysis models included parameters to adjust for temporal drift in the trial population, by estimating the primary endpoint in the usual care group across time via Bayesian hierarchical modelling.[22]

We also conducted a key pre-specified sensitivity analysis of the primary outcomes using the concurrent randomised population; defined as all SARS-CoV-2 positive participants randomised during the time period when the favipiravir arm was active. To determine the applicability of our results to situations where PCR testing may not be readily available, we also conducted secondary analyses of time to recovery and COVID-19 related hospitalisation/death among the overall study population, irrespective of SARS-CoV-2 status.

Analyses of all secondary outcomes and pre-specified sub-group analyses were conducted using SARS-CoV-2 positive participants eligible for favipiravir and concurrently randomised to favipiravir or usual care; the concurrently randomised and eligible SARS-CoV-2 positive population. Secondary time-to-event outcomes were analysed using Cox proportional hazard models, and binary outcomes were analysed using logistic regression, adjusting for comorbidity, age, duration of illness and vaccination status. Due to the high proportion contributing to the analyses of primary outcomes (5413/5638 = 96%), we did not explore the potential impact of missing data.

Analyses of long-term follow-up outcomes were conducted using SARS-CoV-2 positive participants eligible for favipiravir, and concurrently randomised to favipiravir or usual care and contributing to the primary analyses of the day 1–28 outcomes. A sensitivity analysis of the primary outcome included all SARS-CoV-2 positive participants eligible for favipiravir who were concurrently randomised to favipiravir or usual care, regardless of whether they contributed to the day 1–28 primary analyses. Generalised linear models were fitted adjusting for the same covariates as in the main analyses (appendix 5, page 343).

All model assumptions were evaluated. Analyses were conducted using R (version 4·0·3) and Stata (version 16·1 and 18·0).

Role of the funding source

The funder had no role in the study design, data collection, analyses, interpretation, writing of the paper, nor the decision to submit for publication. All authors had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the analyses.

Results

Population

The first participant was randomised into PRINCIPLE on April 2, 2020. Enrolment into the favipiravir group started on April 8, 2021. On July 1, 2022, the Trial Steering Committee advised the Trial Management Group to stop randomisation to favipiravir because the pre-specified futility criterion had been met on hospitalisation/death. Enrolled participants taking favipiravir were asked to stop taking treatment as futility had been reached, but were followed up for 12 months. During this period of the study between 8th April 2021 and 1st July 2022, the period when participants were randomised to favipiravir or usual care, COVID-19 the Omicron variant was prevalent in the UK.

Of 11768 participants who had been randomised, 1950 were allocated to favipiravir, 4461 to usual care alone, and 4837 to other treatments (Fig. 1). The Bayesian primary analysis model included data from 8811 of 9577 (92·0%) SARS-CoV-2 positive participants who provided follow-up data and were randomised to favipiravir (n = 1829), usual care alone (n = 3256), and other treatment groups (n = 3726). The average age (range) of participants was 54·1 (18 – 100) years, 4970 (94%) were white and 3745 (70·9%) had comorbidities. At randomisation, the median time from symptom onset was 5 (interquartile range 3 to 7) days. Baseline characteristics were similar between groups (for concurrent and eligible population) (Table 1 and S1). Data regarding inhaled corticosteroid was not consistently recorded early in the trial, but in the concurrent randomisation analysis population, 345/1897 (18·2%) of the favipiravir arm and 319/1725 (18·5%) of the usual care arm reported taking inhaled corticosteroids at randomisation or during follow-up [331/

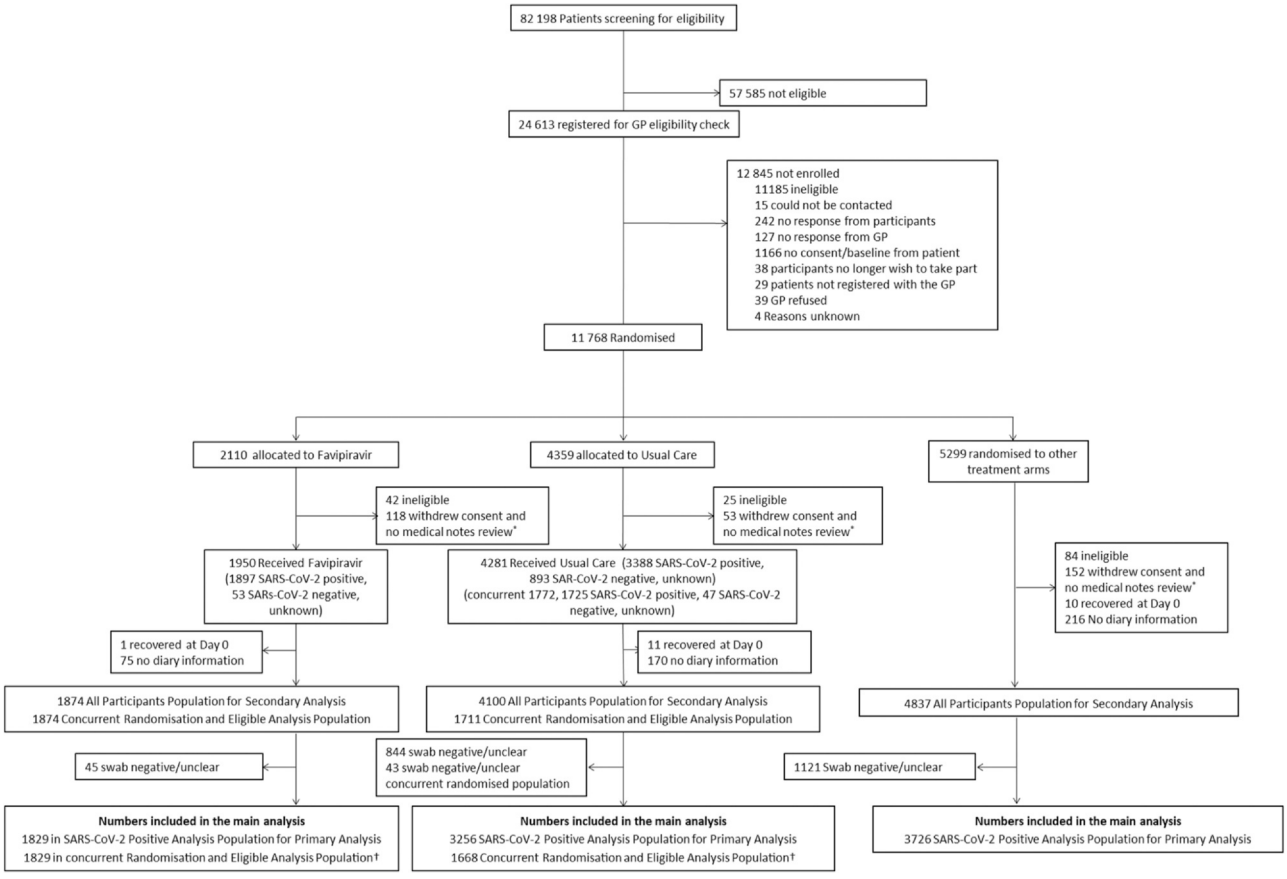


Fig. 1. Participant flow diagram.

Table 1
Baseline characteristics of SARS-CoV-2 positive participants by treatment group.

	Primary analysis population		Concurrent and eligible analysis population	
	Favipiravir (N = 1897)	Usual Care (N = 3388)	Favipiravir (N = 1897)	Usual Care (N = 1725)
Age, year				
mean(SD)	51.5 (13.0)	55.6 (12.9)	51.5 (13.0)	52.0 (12.8)
18–49	739 (39%)	912 (27%)	739 (39%)	650 (38%)
50–64	850 (45%)	1460 (43%)	850 (45%)	790 (46%)
65 and over	308 (16%)	1016 (30%)	308 (16%)	285 (17%)
Sex, n(%)				
Female	1169 (62%)	1972 (58%)	1169 (62%)	1079 (63%)
Male	725 (38%)	1412 (42%)	725 (38%)	642 (37%)
Other	1 (< 1%)	3 (< 1%)	1 (< 1%)	3 (0%)
Missing, n(%)	2 (< 1%)	1 (< 1%)	2 (< 1%)	1 (0%)
Ethnicity, n(%)[a]				
White	1779 (94%)	3191 (94%)	1779 (94%)	1651 (96%)
Mixed background	39 (2%)	35 (1%)	39 (2%)	22 (1%)
South Asian	35 (2%)	110 (3%)	35 (2%)	26 (2%)
Black	8 (< 1%)	13 (< 1%)	8 (< 1%)	8 (0%)
Other	36 (2%)	38 (1%)	36 (2%)	18 (1%)
Missing, n(%)	0	1 (< 1%)	0	0
IMD quintile, n(%)				
(Most deprived) 1	226 (12%)	460 (14%)	226 (12%)	202 (12%)
2	294 (15%)	528 (16%)	294 (15%)	266 (15%)
3	360 (19%)	646 (19%)	360 (19%)	314 (18%)
4	446 (24%)	779 (23%)	446 (24%)	396 (23%)
(Least deprived) 5	571 (30%)	975 (29%)	571 (30%)	547 (32%)
Duration of illness prior to randomisation, median(IQR)	4.0 (3.0–7.0)	5.0 (3.0–8.0)	4.0 (3.0–7.0)	4.0 (3.0–7.0)
Smoking status, n(%)				
Current smoker	130 (7%)	223 (7%)	130 (7%)	127 (7%)
Former smoker	551 (29%)	1199 (35%)	551 (29%)	569 (33%)
Never smoker	1195 (63%)	1931 (57%)	1195 (63%)	1011 (59%)
Missing, n(%)	21 (1%)	35 (1%)	21 (1%)	18 (1%)
Received SARS-CoV−2 vaccination, n(%)	1804 (95%)	2227 (66%)	1804 (95%)	1642 (95%)
Vaccine doses received, n(%)				
0	93 (5%)	1161 (34%)	93 (5%)	83 (5%)
1	71 (4%)	215 (6%)	71 (4%)	68 (4%)
2	1044 (55%)	1189 (35%)	1044 (55%)	938 (54%)
3	642 (34%)	759 (22%)	642 (34%)	581 (34%)
4	46 (2%)	59 (2%)	46 (2%)	50 (3%)
5	1 (< 1%)	5 (< 1%)	1 (< 1%)	5 (0%)
Comorbidity, n(%)	1278 (67%)	2467 (73%)	1278 (67%)	1175 (68%)
Asthma, COPD or lung disease, n(%)	433 (23%)	692 (20%)	433 (23%)	394 (23%)
Diabetes, n(%)	149 (8%)	402 (12%)	149 (8%)	121 (7%)
Heart problems[b]**, n(%)**	137 (7%)	338 (10%)	137 (7%)	135 (8%)
High blood pressure for which you are taking medications, n(%)	381 (20%)	894 (26%)	381 (20%)	316 (18%)
Liver disease, n(%)	7 (< 1%)	36 (1%)	7 (< 1%)	10 (0%)
Stroke or other neurological problem, n(%)	66 (3%)	137 (4%)	66 (3%)	60 (3%)
Weakened immune system due to a serious illness or medication (e.g., chemotherapy), n(%)	117 (6%)	220 (6%)	117 (6%)	105 (6%)
Missing, n(%)	0	10 (< 1%)	0	0
Body mass index (BMI) at or above 35 kg/m2, n(%)	368 (19%)	748 (22%)	368 (19%)	328 (19%)
Missing, n(%)	0 (< 1%)	28 (1%)		
Use of medications at baseline				
Taking angiotensin-converting enzyme inhibitor, n(%)[c]**, n(%)**	195 (10%)	431 (13%)	195 (10%)	159 (9%)
Missing, n(%)	5 (< 1%)	8 (< 1%)	5 (< 1%)	1 (< 1%)
Baseline symptoms				
Fever, n(%)				
No problem	699 (37%)	1343 (40%)	699 (37%)	612 (35%)
Mild problem	767 (40%)	1301 (38%)	767 (40%)	727 (42%)
Moderate problem	376 (20%)	656 (19%)	376 (20%)	345 (20%)
Major problem	55 (3%)	88 (3%)	55 (3%)	41 (2%)
Cough, n(%)				
No problem	192 (10%)	416 (12%)	192 (10%)	173 (10%)
Mild problem	882 (46%)	1569 (46%)	882 (46%)	806 (47%)
Moderate problem	703 (37%)	1188 (35%)	703 (37%)	641 (37%)
Major problem	120 (6%)	215 (6%)	120 (6%)	105 (6%)
Shortness of breath, n(%)				
No problem	892 (47%)	1509 (45%)	892 (47%)	766 (44%)
Mild problem	662 (35%)	1260 (37%)	662 (35%)	630 (37%)
Moderate problem	304 (16%)	547 (16%)	304 (16%)	293 (17%)
Major problem	39 (2%)	72 (2%)	39 (2%)	36 (2%)
Muscle ache, n(%)				
No problem	378 (20%)	717 (21%)	378 (20%)	341 (20%)
Mild problem	758 (40%)	1325 (39%)	758 (40%)	701 (41%)
Moderate problem	602 (32%)	1024 (30%)	602 (32%)	520 (30%)

(*continued on next page*)

Table 1 (*continued*)

	Primary analysis population		Concurrent and eligible analysis population	
	Favipiravir (N = 1897)	Usual Care (N = 3388)	Favipiravir (N = 1897)	Usual Care (N = 1725)
Major problem	159 (8%)	322 (10%)	159 (8%)	163 (9%)
Nausea, n(%)				
No problem	1403 (74%)	2455 (72%)	1403 (74%)	1286 (75%)
Mild problem	383 (20%)	691 (20%)	383 (20%)	342 (20%)
Moderate problem	98 (5%)	195 (6%)	98 (5%)	84 (5%)
Major problem	13 (1%)	47 (1%)	13 (1%)	13 (1%)
Feeling generally unwell, n(%)				
No problem	22 (1%)	73 (2%)	22 (1%)	16 (1%)
Mild problem	588 (31%)	1103 (33%)	588 (31%)	562 (33%)
Moderate problem	1007 (53%)	1695 (50%)	1007 (53%)	891 (52%)
Major problem	280 (15%)	507 (15%)	280 (15%)	256 (15%)
Missing, n(%)	0	10 (< 1%)	0	0
Diarrhea, n(%)				
No problem	1490 (79%)	2581 (76%)	1490 (79%)	1328 (77%)
Mild problem	298 (16%)	576 (17%)	298 (16%)	296 (17%)
Moderate problem	81 (4%)	178 (5%)	81 (4%)	87 (5%)
Major problem	28 (1%)	43 (1%)	28 (1%)	14 (1%)
Missing, n(%)	0	10 (< 1%)	0	0
Loss of sense of smell/taste, n(%)				
No problem	1017 (54%)	1210 (36%)	1017 (54%)	916 (53%)
Mild problem	409 (22%)	511 (15%)	409 (22%)	393 (23%)
Moderate problem	223 (12%)	274 (8%)	223 (12%)	193 (11%)
Major problem	248 (13%)	318 (9%)	248 (13%)	223 (13%)
Missing, n(%)	0	1075 (32%)	0	0
Headache, n(%)				
No problem	323 (17%)	423 (12%)	323 (17%)	314 (18%)
Mild problem	764 (40%)	938 (28%)	764 (40%)	705 (41%)
Moderate problem	620 (33%)	704 (21%)	620 (33%)	514 (30%)
Major problem	190 (10%)	248 (7%)	190 (10%)	192 (11%)
Missing, n(%)	0	1075 (32%)		
Abdominal pain, n(%)				
No problem	1439 (76%)	1726 (51%)	1439 (76%)	1270 (74%)
Mild problem	336 (18%)	412 (12%)	336 (18%)	318 (18%)
Moderate problem	105 (6%)	151 (4%)	105 (6%)	119 (7%)
Major problem	17 (1%)	24 (1%)	17 (1%)	18 (1%)
Missing, n(%)	0	1075 (32%)		
Have you taken antibiotics since your illness started, n(%)	82 (4%)	186 (5%)	82 (4%)	79 (5%)
Missing, n(%)	0 (< 1%)	2 (< 1%)	0	0
Use of healthcare services at baseline				
GP, n(%)	293 (15%)	630 (19%)	293 (15%)	246 (14%)
Other primary care services, n(%)	51 (3%)	163 (5%)	51 (3%)	43 (2%)
NHS 111, n(%)	123 (6%)	258 (8%)	123 (6%)	94 (5%)
A&E, n(%)	19 (1%)	45 (1%)	19 (1%)	19 (1%)
Other healthcare services, n(%)	50 (3%)	79 (2%)	50 (3%)	35 (2%)
Baseline wellbeing score, mean(SD)	4.9 (1.4)	4.9 (1.4)	4.9 (1.4)	4.9 (1.5)
Missing, n(%)	0	1075 (32%)	0	0
Day 1 wellbeing score, mean(SD) [min,max]	5.1 (1.4) [1.0 to 9.0]	5.2 (1.5) [1.0 to 10.0]	5.1 (1.4) [1.0 to 9.0]	5.2 (1.4) [1.0 to 9.0]
Missing, n(%)	128 (7%)	370 (11%)	128 (7%)	116 (7%)
Well-being (WHO5 Questionnaire), mean(SD)[d]	55.9 (23.5)	52.8 (24.8)	55.9 (23.5)	55.7 (23.7)
Missing, n(%)	0	2 (< 1%)	0	0

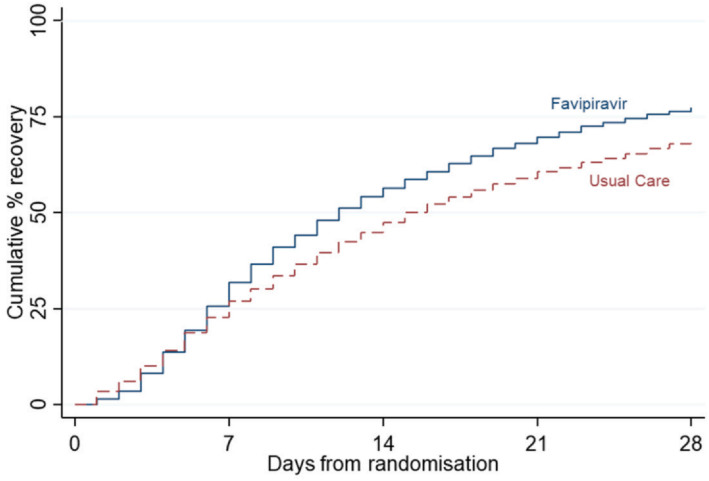
[a] Data on ethnicity were collected retrospectively via notes review before July 2020.
[b] E.g. angina, heart attack, heart failure, atrial fibrillation, valve problems.
[c] Such as Ramipril, Lisinopril, Perindopril, Captopril or Enalapril.
[d] Well-being is measured using the WHO well-being index which includes 5 items relating to well-being measured on a five-point scale. A total score is computed by summing the scores to the five individual questions to give a raw score ranging from 0 to 25 which is then multiplied by 4 to give the final score from 0 representing the worst imaginable well-being to 100 representing the best imaginable well-being.

1829 (18·1%) and 310/1668 (18·6%) respectively of those with measured primary outcome].

Of 1854 participants randomised to favipiravir who provided medication use information, 1659 (89·5%) reported initiating favipiravir and 1613 (87·0%) reported taking it on all five days.

Primary Outcomes

In the SARS-CoV-2 positive primary analysis population, the observed median time to first recovery was 12 days in the favipiravir group compared to 14 in the usual care group (Fig. 2). In the concurrent randomisation analysis population (excluding participants randomised to usual care before the favipiravir arm opened and excluding those with unknown outcomes), the observed median time to first recovery was 12 in the favipiravir group and 16 in the usual care group (Table 2). Based on the Bayesian primary analysis model which adjusted for temporal drift, there was evidence of a benefit in time to first self-report of recovery in the favipiravir group versus usual care (hazard ratio 1·23, 95% Bayesian credible interval [1·14 to 1·33]. Based on a bootstrap estimated median time to recovery of 16 days in the concurrent and eligible usual care SARS-CoV-2 positive population, the model-based estimated hazards ratio corresponded to an estimated 2·98 (1·99 to 3·94) fewer days in median time to first reported recovery for favipiravir relative to usual care. The probability that self-reported time to recovery was shorter in the favipiravir group versus usual care (i.e. probability of



Favipiravir						
	Not yet recovered	1829	1332	807	548	404
	Censored	0	36	53	71	72
	Recovered	0	461	969	1210	1353
Usual Care						
	Not yet recovered	3256	2468	1729	1260	973
	Censored	0	57	96	128	143
	Recovered	0	731	1431	1868	2140

Fig. 2. Time to first reported recovery (Primary Population Analysis - SARS-CoV-2 positive analysis population).

superiority) was >0·999, which met the pre-specified superiority threshold of 0·99. The probability of meaningful effect (pre-specified as a hazard ratio ≥1·2 for the purpose of evaluating futility) was 0·86 (Table 2). This treatment effect was consistent in the concurrent randomisation and overall study population (Table 2).

In the SARS-CoV-2 positive primary analysis population, there were 28/1829 (1·5%) COVID-19 related hospitalisations/deaths in the favipiravir group (28 hospitalisations, 0 deaths), and 144/3256 (4·4%) in the usual care group (143 hospitalisations, of whom 11 died, and 1 death without hospitalisation). The higher levels of hospitalisations/deaths in the usual care group in the primary analysis population were driven by the high event rate before the favipiravir arm opened. In the usual care group in concurrent randomisation analysis population, which excluded participants randomised to usual care before the favipiravir arm opened, there were 23/1668 (1·4%) COVID-19 related hospitalisations/deaths in the usual care group (22 hospitalisations of whom 2 died, and 1 death without hospitalisation). In the Bayesian primary analysis model, which takes into account the temporal change in event rates, COVID-19 related hospitalisations/deaths in the favipiravir group compared to usual care were similar, with an estimated odds ratio of 0.99 (95% credible interval 0·61 to 1·61). Based on a bootstrap estimated hospitalization rate of 1·4% in the concurrent and eligible usual care population, the model-based estimated odds ratio corresponds to an estimated difference in the hospitalisation rate of 0 (95% credible interval −0·9% to 0·6%) (Table 2). The probability that COVID-19 related hospitalisations/deaths were lower in the favipiravir arm versus usual care (i.e. probability of superiority) was 0·508. The probability that there was a meaningful reduction in COVID-19 related hospitalisations/deaths (predefined as an odds ratio of 0·80 or smaller) was 0.194.

Secondary outcomes

Analyses of secondary outcomes, using the concurrent randomisation and eligible SARS-CoV-2 positive population, are presented in Table 2, Figs. S1, and S3 – S6. There was evidence of a benefit of favipiravir on early recovery and time to alleviation of some symptoms (Table 2). There was no evidence of differences in new household infections, antibiotic prescribing, hospital admissions, use of oxygen or mechanical ventilation and any healthcare utilisation outcomes between favipiravir and usual care.

In the pre-specified subgroup analyses, there was no strong statistical evidence that symptom duration prior to randomisation, baseline illness severity score, inhaled corticosteroid use, age or comorbidity modified the effect of favipiravir on time to first reported recovery (Fig. S2a) and hospitalisation/death (Fig. S2b), although numbers were small. There were 14 hospitalisations unrelated to COVID-19 in the favipiravir group and 4 in usual care.

Long term follow-up outcomes

Baseline characteristics were comparable for individuals included in the long-term follow-up analyses (Table S1, appendix pp356). Primary and secondary analyses are presented in Table 3. At six months, 1125/1503 (74·9%) and 956/1340 (71·3%) reported feeling fully recovered from the original COVID-19 illness in the favipiravir group versus usual care, respectively (RR 1·05, 95% CI [1·02 to 1·08] p = 0·0019). The results were consistent in the sensitivity analysis. Favipiravir had a favourable effect on participant wellness rating, WHO-5 Well-Being Index, persistence of pre-specified COVID-19 symptoms and impact on work/studies, compared with usual care. There was no difference in the number of days that unrecovered participants felt unwell in the preceding two weeks, healthcare use, nor time off work between groups at the 12-month follow-up. All other long-term outcomes are reported in the appendix (pp359 – 394).

Discussion

Summary

This analysis from a pragmatic, open-label, platform, randomised controlled trial of community treatments for COVID-19 found that favipiravir reduced the time taken to recovery by about three days from the median of 16 days in the usual care group (Hazard ratio 1·2, 95% CI 1·1–1·3). The proportion of illness duration reduced (rather

Table 2
Primary and Secondary Outcomes.

	Favipiravir	Usual Care	Estimated difference median TTR or hospitalisation/death rate (95% BCI)	Hazard Ratio/Odds Ratio (95% BCI)	Pr (Superiority)	Pr (Meaningful)
Primary outcomes (Primary analysis: SARS-CoV−2 positive population)	(N = 1829)	(N = 3256)				
Time – first reported recovery, days	12 (6–26)[a]	14 (6 – not reached)[a]	2·98 (1·99 – 3·94)[b]	1·23 (1·14 – 1·33)[b]	> 0·999[b]	0·860[b]
Hospitalisation/death at 28 days	28/1829 (1%)[a]	144/3256 (4%)[a]	0% (−0·9% – 0·6%)[c]	0·99 (0·61 – 1·61)	0·508[c]	0·194[c]
Primary outcomes (Secondary analysis: all participants population)	(N = 1874)	(N = 4100)				
Time – first reported recovery, days	12 (6–26)[a]	14 (6 – not reached)[a]	2·73 (1·74 – 3·69)[b]	1·21 (1·12 – 1·3)[b]	> 0·999[b]	0·722[b]
Hospitalisation/death at 28 days	28/1874 (1%)[a]	162/4100 (4%)[a]	0% (−0·8% – 0·6%)[c]	0·99 (0·61 – 1·61)	0·514[c]	0·195[c]
Primary outcomes (Sensitivity analysis: concurrent randomisation population)	(N = 1829)	(N = 1668)				
Time – first reported recovery, days	12 (6–26)[a]	16 (8 – not reached)[a]	3·03 (1·98 – 4·03)[b]	1·24 (1·14 – 1·34)[b]	> 0·999[b]	0·868[b]
Hospitalisation/death at 28 days	28/1829 (1%)[a]	23/1668 (1%)[a]	−0·2% (−1·4% – 0·5%)[c]	1·13 (0·65 – 1·95)[c]	0·338[c]	0·11[c]
Secondary outcomes[d]	**Favipiravir**	**Usual Care**	**Estimated treatment effect (95% CI)**		**P-value**	
Early sustained recovery, n/N (%)[a]	453/1828 (24·8%)	273/1666 (16·4%)	1·52 (1·33 – 1·73)		< 0·0001	
Sustained recovery, n/N (%)	1116/1829 (61·0%)	869/1668 (52·1%)				
Time – sustained recovery (days), median (IQR)	25 (13 – not reached)	27 (18 – not reached)	1·33 (1·21 – 1·45)[e]		< 0·0001	
Alleviation of all symptoms, n/N (%)	1428/1562 (91·4%)	1252/1407 (89·0%)				
Time – alleviations of all symptoms (days), median (IQR)	4 (2–9)	5(2–10)	1·14 (1·06 – 1·23)[e]		0·0009	
Sustained alleviation of all symptoms, n/N (%)	1266/1562 (81·0%)	1054/1407 (74·9%)				
Time – sustained alleviation of all symptoms (days), median (IQR)	11 (4–25)	16 (6–27)	1·26 (1·16 – 1·37)[e]		< 0·0001	
Initial reduction of severity of symptoms, n/N (%)	1594/1828 (87·2%)	1330/1667 (79·8%)				
Time – initial reduction of severity of symptoms (days), median (IQR)	7(4–15)	9 (5–19)	1·30 (1·21 – 1·39)[e]		< 0·0001	
Rating of how well participant feels (1 worst, 10 best), mean (SD) [n]						
Day 7	7·2 (1·6) [1730]	6·8 (1·7) [1591]	0·42 (0·31 – 0·53)[f]		< 0·0001	
Day 14	7·9 (1·5) [1690]	7·5 (1·7) [1544]	0·39 (0·27 – 0·51)[f]		< 0·0001	
Day 21	8·2 (1·6) [1622]	7·9 (1·7) [1454]	0·35 (0·21 – 0·48)[f]		< 0·0001	
Day 28	8·4 (1·5) [1685]	8·1 (1·7) [1501]	0·30 (0·14 – 0·45)[f]		0·0002	
Well-being (WHO5 Questionnaire), mean (SD)[n]						
Day 14	47·3 (22·2) [1725]	44·4 (22·6) [1561]	3·18 (1·86 – 4·51)[f]		< 0·0001	
Day 28	59·1 (21·9) [1710]	55·9 (23·0) [1528]	3·38 (2·05 – 4·71)[f]		< 0·0001	
Self-reported contact with ≥1 healthcare service, n/N (%)	819/1828 (44·8%)	798/1665 (47·9%)	0·88 (0·77 – 1·01)[d]		0·071	
GP reported contact with ≥1 healthcare service, n/N (%)	660/1625 (40·6%)	559/1467 (38·1%)	1·11 (0·96 – 1·29)[d]		0·15	
New infections in household, n/N (%)	525/1825 (28·8%)	484/1661 (29·1%)	0·98 (0·85 – 1·14)[d]		0·82	
Prescription of antibiotics, n/N (%)	84/1564 (5·4%)	81/1428 (5·7%)	0·94 (0·68 – 1·31)[d]		0·75	
Hospital assessment without admission, n/N (%)	32/1829 (1·7%)	29/1668 (1·7%)	1·01 (0·59 – 1·73)[g]		> 0·99	
Oxygen Administration, n/N (%)	13/1824 (0·7%)	9/1664 (0·5%)	1·32 (0·52 – 3·51)[g]		0·67	

(*continued on next page*)

Table 2 (*continued*)

	Favipiravir	Usual Care	Estimated difference median TTR or hospitalisation/death rate (95% BCI)	Hazard Ratio/Odds Ratio (95% BCI)	Pr (Superiority)	Pr (Meaningful)
Mechanical ventilation, n/N (%)	0/1825 (0·0%)	0/1664 (0·0%)	N/A		N/A	
ICU admission, n/N (%)	1/1825 (0·1%)	0/1663 (0·0%)	N/A		N/A	
All-cause mortality and hospitalisation within 28 days of randomisation	35/1829 (1·9%)	31/1668 (1·9%)	1·041 [0·636 – 1·705][f]		0·87	
Serious adverse events	14	4				
Number of participants with at least one serious adverse event	12 (0.7%)	4 (0.2%)				

BCI – Bayesian credible interval.

[a] Observed median (interquartile range) time to recovery or observed number (%) hospitalisation/death. These values have not been adjusted for the temporal drift. The usual care group in the primary and secondary analysis populations included participant randomised before the favipiravir arm opened and therefore direct comparisons may reflect temporal differences in the underlying outcome rather than a treatment effect.

[b] Estimated difference (favipiravir -usual care) in median time to recovery derived from a Bayesian piecewise exponential model adjusted for age, comorbidity and vaccination status at baseline, with 95% BCI. A positive value in estimated median time to recovery (or HR < 1) corresponds to an increase in time to recovery in days in favipiravir compared to Usual Care. Pr(Superiority) is the probability of superiority and treatment superiority is declared if Pr (superiority) ≥0.99 versus usual care. Pr(Meaningful) is probability that the hazards ratio for favipiravir versus usual care is 2·0 or larger.

[c] Estimated absolute percentage difference (favipiravir -usual care) in hospitalisation/death derived from a Bayesian logistic regression model adjusted for age, comorbidity and vaccination status at baseline, with 95% Bayesian credible interval. A positive value in the estimated difference percentage (or OR < 1) favours favipiravir. Pr(Superiority) is the probability of superiority and treatment superiority is declared if Pr(superiority) ≥0·975 versus usual care. Pr (Meaningful) is the probability that the odds ratio for favipiravir versus usual care is 0·80 or smaller.

[d] All secondary outcome analyses were conducted on the concurrent randomisation SARS-CoV-2 positive population, but restricted to those who are in the favipiravir and usual care group only.

[e] Relative risks adjusted for age, comorbidity at baseline, duration of illness, and vaccination status at baseline.

[f] Estimated hazard ratio derived from a Cox proportional hazard model adjusted for age, comorbidity at baseline, duration of illness, and vaccination status at baseline, with 95% confidence interval.

[g] Mixed effect model adjusting age, comorbidity, duration of illness, vaccination status at baseline, and time. Participant was fitted as a random effect. WHO well-being score was also adjusted for the score at baseline.

[h] Unadjusted relative risks due to low event rate.

than the absolute number of days with illness saved) is the more meaningful assessment of benefit; given that mean illness duration varies over time with COVID-19, our blind prior was that a benefit with an HR of less than 1·2 would not be considered clinically meaningful.

There was no evidence that favipiravir reduced the need for hospital admission and any other measures of hospital utilisation. Favipiravir treatment improved secondary measures of wellbeing, sustained recovery, and symptom alleviation. There were small differences in those feeling fully recovered at six months, favouring treatment with favipiravir (RR = 1·05, [1·02 to 1·08]).

The findings were similar in the primary analysis, which included all SARS-CoV-2 positive participants, and in the sensitivity analyses that include only those contemporaneous controls randomised during the time that favipiravir was in the trial. For most patients, these findings do not support the routine use of favipiravir as treatment for COVID-19 in the community among a largely vaccinated population at the dose and duration we used. It is possible that the improvement in recovery time could be an efficient use of resources for some groups such as key workers.

Comparison with current evidence

Five double-blind, outpatient randomised trials of favipiravir for COVID-19 have been conducted,[23–27] with between 116 to 1187 participants. All used a dosing regimen similar to PRINCIPLE, of 1800 mg twice daily on day one, followed by 1600 mg daily in divided doses, but most trials had a longer duration of seven,[23] ten[24,26] or fourteen[27] days. Where reported, the median or mean age of participants was around ten or more years lower than PRINCIPLE, at 40 years or less, and unlike PRINCIPLE most trials had a majority of unvaccinated participants.

One trial (n = 1187) assessed the primary outcome of time to sustained recovery within 28 days,[26] and found no evidence of benefit with favipiravir. There was also no difference in a combined secondary outcome of emergency department visit or hospitalisation or death, and no effect on time to undetectable SARS-CoV-2 viral load. The four other smaller trials assessed a virological primary outcome, with no clear effect on viral load or time to viral clearance.[23–28] A systematic review and meta-analysis including all the above trials, and four other smaller or open label trials of outpatient favipiravir, also found no evidence of an effect on recovery, or virological outcomes.[6]

No trials have assessed the effect of acute favipiravir treatment on longer-term outcomes beyond 28 days. Our results therefore add to those of the placebo-controlled trials described above, providing an estimate of the effects of favipiravir in an older, largely vaccinated population. Whilst we found that favipiravir modestly reduced the time to feeling fully recovered, it did not have an effect on hospitalisations/mortality compared with usual care and is unlikely to provide a clinically meaningful long-term benefit.

Our evaluation of[12] for COVID-19 from the PRINCIPLE trial found evidence of modest benefit in time to first report of recovery (hazard ratio 1·145, 95% Bayesian credible interval [1·066 to 1·231], which corresponds to an estimated 2·055 (0·999 to 3·06) fewer days in median time to first reported recovery for[12] relative to usual care. However, the estimated hazard ratio was less than the pre-specified meaningful effect of 1·2. A small benefit of ivermectin was similarly observed in terms of the proportion of participants feeling fully recovered at 3, 6 and 12 months, on a range of measures of recovery and time to recovery, and on ratings of wellbeing.[12]

Strengths and limitations

PRINCIPLE is the first UK randomised trial to evaluate the effect of early favipiravir treatment on time to recovery and hospital

Table 3
Long term follow-up: Primary and Secondary Outcomes.

	Favipiravir (N = 1829)	Usual Care (N = 1668)	Adjusted treatment effect [95% CI][a]	P-value[b]
Primary outcome[c]:				
Feeling fully recovered[a], n/N(%)				
3 months	1089/1507 (72·3)	911/1370 (66·5)	1·07 [1·03 – 1·11]	0·0001
6 months[c]	1125/1503 (74·9)	956/1340 (71·3)	1·05 [1·02 – 1·08]	0·0019
12 months	1232/1582 (77·9)	1034/1412 (73·2)	1·05 [1·02 – 1·08]	0·0011
Primary outcome: sensitivity analysis	(N = 1897)	(N = 1725)		
Feeling fully recovered[a], n/N(%)				
3 months	1089/1507 (72·3)	915/1375 (66·5)	1·07 [1·03 – 1·10]	0·0001
6 months[c]	1126/1507 (74·7)	961/1346 (71·4)	1·05 [1·01 – 1·08]	0·0033
12 months	1235/1586 (77·9)	1040/1418 (73·3)	1·05 [1·02 – 1·08]	0·0017
Secondary outcomes:				
Number of unwell days in the past two weeks[b], mean (SD) [n]				
3 months	10·2 (4·57) [418]	10·1 (4·64) [459]	0·28 [−0·33 – 0·89]	0·37
6 months	9·7 (4·67) [378]	10·2 (4·62) [384]	−0·50 [−1·14 – 0·15]	0·13
12 months	9·3 (4·97) [350]	9·4 (4·87) [378]	−0·25 [−0·91 – 0·41]	0·46
Rating of how well participant feels (1 worst, 10 best)[b], mean (SD) [n]				
3 months	8·2 (1·62) [1506]	8·1 (1·68) [1370]	0·15 [0·02 – 0·27]	0·0196
6 months	8·0 (1·70) [1503]	7·8 (1·79) [1340]	0·17 [0·05 – 0·29]	0·0066
12 months	7·8 (1·75) [1582]	7·7 (1·79) [1411]	0·14 [0·02 – 0·26]	0·0206
Well-being (WHO−5)[b], mean (SD) [n]				
3 months	61·2 (22·22) [1506]	59·7 (22·30) [1368]	1·69 [0·31 – 3·06]	0·0162
6 months	61·7 (21·90) [1503]	59·1 (22·80) [1340]	2·66 [1·28 – 4·04]	0·0002
12 months	60·8 (22·43) [1582]	59·0 (22·52) [1411]	1·90 [0·54 – 3·26]	0·0060
Ongoing persistent COVID−19 symptoms at 3, 6 and 12 months[d], n/N (%)	76/1643 (4·6)	97/1502 (6·5)	0·71 [0·53 – 0·95]	0·0205
Impact of COVID−19 on work/occupation/studies, n/N (%) and median (IQR) [n]				
Stopping work/studies[d]	93/1690 (5·5)	125/1543 (8·1)	0·68 [0·52 – 0·87]	0·0029
Having time off work/studying[d]	290/1690 (17·1)	260/1543 (16·9)	1·01 [0·87 – 1·17]	0·93
Total time off work/studying (days)[e]	14·0 (7·0 to 37·0) [290]	16·0 (7·0 to 37·0) [259]	−2·47 [−6·87 – 1·94]	0·27
Change job/occupation/studies	78/1690 (4·6)	82/1543 (5·3)	0·86 [0·64 – 1·16]	0·33
Healthcare service utilisation, n/N (%) and median (IQR) [n]				
Any contact[d]	350/1690 (20·7)	348/1543 (22·6)	0·92 [0·80 – 1·04]	0·18
Number of contacts	3·0 (2·0 to 7·0) [350]	4·0 (2·0 to 8·0) [348]	NA	NA

Favipiravir versus concurrent usual care.

[a] Relative risks, derived from mixed effect logistic regression model, adjusted for assessment time point, age, presence of comorbidity, duration of illness at randomisation, vaccination status, and an interaction between randomised group and assessment time point as fixed effects, and participant as a random effect.

[b] Linear mixed model adjusted for randomised group, assessment time point, age, presence of comorbidity, duration of illness at randomisation, vaccination status, baseline score (if applicable), and an interaction between randomised group and assessment time point as fixed effects, and participant as a random effect.

[c] Primary outcome. A sensitivity analysis of the primary outcome includes all SARS-CoV-2 positive participants eligible for favipiravir who were concurrently randomised to favipiravir or usual care, regardless of whether they contributed to the day 1-28 primary analyses.

[d] Pre-specified long COVID-19 symptoms (feverish, cough, shortness of breath, chest pain, loss of smell, loss of taste, nausea/vomiting, diarrhoea, headache, muscle ache, generally unwell and fatigue); Relative risks, derived from mixed effect logistic regression model, adjusted for randomised group, age, presence of comorbidity, duration of illness at randomisation, and vaccination status.

[e] Quintile regression adjusted for randomised group, age, presence of comorbidity, duration of illness at randomisation, and vaccination status.

admission for mostly vaccinated people with COVID-19 in the community. The pragmatic design of the PRINCIPLE trial allowed for efficient evaluation of the effectiveness of favipiravir as it might be used in the community. We focused on patients at increased risk of complications and used routine electronic health records to confirm hospitalisation/death, and obtained primary outcome data on over 91·5% of participants. Participants were able to participate in the trial without leaving their homes through use of novel central recruitment processes. These processes have facilitated recruitment of over 11,700 participants to the trial platform, including people living in areas without research-active general practices, and who are typically under-represented in primary care research studies. Our trial has been actively promoted to people from diverse communities. Under the leadership of our Pharmacy, and Inclusion and Diversity Lead, we have targeted ethnic minority communities and people in areas of socio-economic deprivation through numerous outreach activities, including collaboration with religious organisations, universities, and healthcare and pharmacy networks. Despite this, the proportion of participants of minority ethnic origin in this analysis is lower than in the UK general population.

The response adaptive randomisation analyses were performed by an unblinded team and updated probabilities were not shared with the trial team or any other blinded team members. The use of response adaptive randomisation in the PRINCIPLE trial platform has allowed randomisation probabilities to be adjusted, in light of emerging data from interim analyses, allowing a higher proportion of participants to be allocated to better performing arms.(This increases the chance of participants receiving an intervention that may be beneficial, and increases the efficiency with which interventions are declared successful or futile. Further, the Bayesian primary analysis model leverages previous enrolments in the usual care arm, whilst taking into account changes in the control population over time (temporal drift). The ability to harness data from historical, non-contemporaneously recruited controls may increase the precision of estimates, allowing stoping recruitment to the favipiravir arm as soon as pre-specified futility criteria had been met.

We used a pragmatic and open-label, trial design. In contrasts to efficacy trials, an open label trial is suited to answering a pragmatic question of the effectiveness of a treatment in the course of routine clinical care compared to care without the addition of that treatment.Placebos are not used as part of routine care.[29–31] The control condition therefore reflects best current care without the drug in question, reflecting what would happen under usual circumstances.[30] The trial therefore assessed whether there is value to adding in a new drug over and above usual care. An open label design does not allow estimation of the contribution of either placebo

or nocebo effects to any observed differences between randomized groups.[31,32] This is important, as favipiravir was found not to improve the rate of viral clearance.[33] However, favipiravir may mediate inflammation[34,35] which could impact on a sense of feeling recovered.

Knowing whether one is taking a treatment with proven efficacy or not can impact upon help seeking behaviour. Patient reported outcome measures such as symptom scores and rating of well-being are at potential risk from reporting bias due to the open-label trial design. However, whilst for many conditions there can be substantial placebo effects, for acute respiratory infections, even where beliefs in medication are high, the estimates from open label trials with self-report outcomes, for example sore throat,[36] acute bronchitis[37] and otitis, suggest either no placebo effects or minimal effects when compared with placebo controlled trials in Cochrane reviews. PRINCIPLE has already found for other potential COVID therapeutic of evidence of no meaningful effect for doxycycline,[10] azithromycin,[9] and ivermectin,[12] a trend for harm from colchicine,[11] and of benefit from inhaled budesonide.[2] Effect sizes in open trials are generally similar to those of placebo controlled trials.[38,39] Small, absolute differences may be statistically significant different but not necessary clinically meaningful.[40]

We used time to feeling fully recovered as our primary outcome as it was of greatest interest to our patient and public contributors. This outcome is best ascertained by direct patient report, rather than by the use of surrogate measures.

Our co-primary endpoint of hospitalisations/deaths is a more objective endpoint, and has been used as the sole, primary endpoint in an analogous trial.[41] However, when the prevalence of these outcomes are low - in the context of a largely, multiply vaccinated population - large trial sample sizes are incurred, and assessment of outcomes related to participant recovery/well-being are highly relevant. In addition, in our study, highly relevant secondary outcomes such as antibiotic prescribing or GP reported healthcare utilisation showed no differences between randomised groups.

Whilst our findings do not suggest that favipiravir has a strong beneficial effect when used in the community at the dose and duration used in this study, it is possible that the effects of favipiravir might have been enhanced had a higher dose of the drug been used.[23] However, this needs to be balanced with an increased risk of adverse events. In our trial, there were 14 SAEs in the favipiravir group and four in the usual care alone group (number needed to harm =160). A increase in hyperuricaemia was noted in phase 2 evaluations following favipiravir administration.(Favipiravir has also been found to be teratogenic in animal studies, and has not been trialled in pregnant or breastfeeding women. If favipiravir were to be deployed as a COVID-19 therapeutic in the community, a cautious approach would need to be adopted in people of reproductive age. In the present trial, we excluded: women with known or suspected pregnancy; women who were breastfeeding; and, women of childbearing potential or men with a partner of childbearing potential who were not willing to use highly effective contraception for the 28-day duration of the trial.

Participants were eligible if they were within 14 days of symptom onset, and participants started favipiravir a median of 5 days after symptom onset. Given the mechanism of action of favipiravir – viral RdRp inhibition – it is possible that treatment with favipiravir sooner after symptom onset may have led to a more beneficial impact on outcomes; future trials of favipiravir could investigate this further through subgroup analysis. However, we found no evidence of difference between the effect of favipiravir in participants receiving the study drug within seven days of symptom onset and greater than seven days of symptom onset.

In light of the prevalence of cases and morbidity from COVID-19, and the emergence of new variants from COVID-19, it remains imperative that new agents to treat the disease are evaluated in their intend use populations.[42] The PANORAMIC trial is investigating the effects of the novel antivirals molnupiravir (52) and nirmatrelvir/ritonavir on short and longer-term outcomes of COVID-19 infection, incorporating health economic assessments[43] and virology substudies.[44]

Conclusion

Results from this open-label randomised controlled trial with long-term follow-up suggest that for the duration and at the dose used in the PRINCIPLE trial evaluation, favipiravir could be used in the community in a largely vaccinated population only if there is an imperative to moderately reduce time taken to recovery.

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Author contributions

CCB and FRDH have full access to all of the data in the study, take responsibility for the integrity of the data and the accuracy of the data analysis., and decided to publish the paper. BS, NSB, L-MY, CCB, FDRH, GH, MS, OVH, OAG, JD, DR contributed to trial design. SdeL, PHE, NT and MPG and PL helped plan the trial and ongoing recruitment, and study supervision. EO, NT, SdeL, were responsible for acquisition of data. JG was responsible for all aspects of trial data management. OAG, CCB, MS, L-MY, JD, VH, and FDRH, drafted the manuscript. BS, NSB, L-MY, MAD, MF, CTS, VH, MS, FRDH, CCB and PL contributed to statistical analysis and/or interpretation. All members of the PRINCIPLE writing group critically revised the manuscript. The members of the PRINCIPLE Collaborative Group and their roles in the conduct of the trial are listed in the appendix.

Data availability

Data can be shared with qualifying researchers who submit a proposal with a valuable research question as assessed by a committee formed from the TMG including senior statistical and clinical representation. A contract should be signed.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Drs. Saville, Berry, Detry, Fitzgerald and Saunders report grants from The University of Oxford, for the Sponsor's grant from the UK NIHR, for statistical design and analyses for the PRINCIPLE trial during the conduct of the study. Prof de Lusignan is Director of the Oxford-RCGP Research and Surveillance Centre and reports that through his University he has had grants outside the submitted work from AstraZeneca, GSK, Sanofi, Seqirus and Takeda for vaccine

related research, and membership of advisory boards for AstraZeneca, Sanofi and Seqirus. Profs Hobbs and Butler reports grants from UKRI, during the conduct of the study. All other authors have no competing interests to declare.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2024.106248.

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