The Assessment of the Efficacy and Safety of Favipiravir for Patients with SARS-CoV-2 Infection: A Multicenter Non-randomized, Uncontrolled Single-arm Prospective Study

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Abstract:
Objective Among treatment options for coronavirus infectious disease 2019 (COVID-19), well-studied oral medications are limited. We conducted a multicenter non-randomized, uncontrolled single-arm prospective study to assess the efficacy and safety of favipiravir for patients with COVID-19.

Methods One hundred participants were sequentially recruited to 2 cohorts: cohort 1 (Day 1: 1,600 mg/day, Day 2 to 14: 600 mg/day, n=50) and cohort 2 (Day 1: 1,800 mg/day, Day 2 to 14: 800 mg/day, n=50). The efficacy endpoint was the negative conversion rate of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the odds ratio (OR) of cohort 2 to cohort 1 for negative conversion on Day 10 was calculated. Characteristics of all participants and profiles of adverse events (AEs) were collected and analyzed.

Results The mean age of participants was 62.8±17.6 years old. Thirty-four patients (34.0%) experienced worsening pneumonia, 7 (7.0%) were intubated, and 4 (4.0%) died during the observation period. Cohort 2 showed a higher negative conversion rate than cohort 1 [adjusted OR 3.32 (95% confidence interval (CI), 1.17 to 9.38), p=0.024], and this association was maintained after adjusting for the age, sex, body mass index, and baseline C-reactive protein level. Regarding adverse events, hyperuricemia was most frequently observed followed by an elevation of the liver enzyme levels (all-grade: 49.0%, Grade ≥3: 12.0%), and cohort 2 tended to have a higher incidence than cohort 1. However, no remarkable association of adverse events was observed between patients <65 and ≥65 years old.

Conclusion The antiviral efficacy of favipiravir was difficult to interpret due to the limitation of the study design. However, no remarkable issues with safety or tolerability associated with favipiravir were observed, even in elderly patients with COVID-19.

Key words: COVID-19, favipiravir, safety, efficacy

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Introduction

The new coronavirus [severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)] and its infectious disease, coronavirus infectious disease 2019 (COVID-19), has become widespread globally, and severe pneumonia from COVID-19 has caused many deaths (1). Administration of
steroids and the provision of intensive care, such as invasive ventilation and extracorporeal membranous oxygenation, are essential for ensuring the survival of patients with severe COVID-19. In contrast with the use of these therapeutic tools, there has been a delay in the development of effective anti-viral drugs. When COVID-19 becomes widespread among the elderly population, particularly those living at home or in nursing homes, more simple and effective oral medications will be needed (2). Vaccination and the early administration of SARS-CoV-2-neutralizing antibody are both effective measures for preventing COVID-19; however, oral anti-viral agents play a role in treating breakthrough infection in these patients.

Favipiravir is an RNA-dependent RNA polymerase inhibitor that has been approved in Japan for use against novel or re-emerging pandemic influenza virus infections (3). A trial evaluating the efficacy of favipiravir in patients with severe fever with thrombocytopenia syndrome (SFTS) has also been conducted in Japan (4). Favipiravir has received increasing attention and been the subject of several clinical trials worldwide during the current COVID-19 pandemic. In Japan, Doi et al. reported the clinical efficacy of favipiravir in an open-label, cross-over prospective study (5). However, they failed to show a sufficient clinical benefit of early administration of favipiravir for viral clearance with statistical significance. In addition, Shinkai et al. conducted a phase III clinical trial in COVID-19 patients who did not receive oxygen therapy and reported the efficacy and safety of favipiravir (6). Despite the relevance of these data, favipiravir has not been approved in Japan or in Western countries for the treatment of COVID-19.

In this study, we evaluated the efficacy and safety of favipiravir in a multicenter, open-label single-arm study conducted in Japan in patients with COVID-19.

Materials and Methods

Study design

This was a prospective, multicenter, open-label, single-arm trial to assess the efficacy and safety of oral favipiravir in mild-to-moderate symptomatic COVID-19 patients. The study was centrally approved by the certified review board of Gunma University Hospital [IRB#2019-087 (1784)] and registered in the Japan Registry of Clinical Trials (jRCTs 031190226). We prepared documentation describing the potential side effects of favipiravir, such as hypersensitivity syndrome, liver dysfunction, diarrhea, cytopenia and hyperuricemia. Written informed consent was then obtained from all study participants.

Participants

Patients were recruited at five hospitals in Gunma and Saitama Prefectures in Japan. The recruitment period was between March 14, 2020, to May 11, 2021, and follow-up was completed by May 25, 2021. The inclusion criteria were as follows: 1) age ≥20 years old; 2) a diagnosis of COVID-19 based on a positive finding of quantitative reverse transcription-polymerase chain reaction (RT-PCR); 3) pulmonary lesions confirmed by chest imaging or a fever ≥37.5 °C, regardless of SpO2 or severity of pneumonia; 4) inpatient status; and 5) written consent for participation. Two RT-PCR methods were used in this study: the primary method in Japan reported by Shirato et al. (7) and the BD MAX™ SARS-CoV-2 assay [detailed methods reported by Asai et al. (8)].

The following exclusion criteria were applied: 1) breastfeeding, 2) pregnancy, and 3) not agreeing to use effective contraceptive methods (for women and for men with female partners). Use of other medications with antiviral activity, including lopinavir/ritonavir, remdesivir, and interferon, was prohibited during the study period.

Procedures

Favipiravir was dosed in two arms, and the first day of favipiravir administration was defined as Day 1, regardless of the onset day. We initiated this study with cohort 1, in which favipiravir was dosed at 1,600 mg orally twice on the first day followed by 800 mg orally twice per day for a total of 5 days (up to 14 days if the improvement of symptoms was insufficient) (dose 1). We began the study with a relatively low dose based on the value approved for the treatment of patients with influenza in Japan (9) out of an abundance of caution.

After enrolling 50 patients using dose 1, as originally planned, we then initiated enrollment of an additional cohort (cohort 2) from November 20, 2020, in which the study protocol was changed to include a higher dose of favipiravir. In cohort 2, the favipiravir dose was 1,800 mg orally twice on the first day, followed by 800 mg orally twice per day, for a total of 5 days (up to 14 days if the improvement of symptoms was insufficient) (dose 2) (Figure). We used this dose because it had been adopted in a single-arm trial that assessed the efficacy and safety of favipiravir for patients with SFTS (4) and in a phase III clinical trial for COVID-19 patients with moderate pneumonia in Japan, based on the results of basic and clinical research (6).

We mainly aimed to evaluate the efficacy and safety of favipiravir at previously approved or attempted doses, as described above.

Outcomes

The efficacy endpoint was the negative conversion rate of SARS-CoV-2 at Day 10 (counted from the initiation of favipiravir), which was defined as the number of patients negative for any SARS-CoV-2 test at Day 10/number of enrolled patients. The SARS-Cov-2 tests were all performed by RT-PCR. The change in serum C-reactive protein (CRP) from baseline (Day 0±2 days) to Day 10 (±2 days), which was calculated as the numerical difference in the CRP value between baseline and Day 10, was also evaluated.

Adverse events (AEs) were documented as the safety end-
Patient enrollment. One hundred participants were sequentially recruited to 2 cohorts; 50 patients were initially enrolled in cohort 1, and another 50 were sequentially enrolled in cohort 2 after enrolling cohort 1. All enrolled participants received at least 1 dose of favipiravir (100 patients in the safety population). In cohort 1, favipiravir was dosed at 1,600 mg orally twice on the first day followed by 600 mg orally twice per day, for a total of up to 14 days. In cohort 2, 1,800 mg orally on the first day, followed by 800 mg orally per day, for a total of up to 14 days. PPS: per-protocol set

Statistical analyses

The analysis of the negative conversion rate of SARS-CoV-2 was performed in the per protocol set (PPS), defined as subjects with the data required for analyses. The change in the CRP level was also analyzed in the PPS population. The safety population for assessing AEs was defined as all subjects who received at least one dose of favipiravir (Figure).

Continuous variables are presented as the mean±standard deviation (SD) or median [interquartile range (IQR)], and categorical variables are presented as percentages. Regarding the comparison of patient demographics between the cohorts, for continuous variables, we used Student’s t-test and the Mann-Whitney U test for normally and non-normally distributed data, respectively. A χ² test method was used for categorical variables.

Multivariable logistic regression was used to estimate the odds ratio (OR) of cohort 2 to cohort 1 for negative conversion of SARS-CoV-2. Model 1 was adjusted for the age, sex, and body mass index (BMI); and model 2 was adjusted for the covariates in model 1 plus the baseline CRP level. In the subgroup analysis, the cut-off for the baseline CRP level was set as the median value (2.78 mg/dL). The change in CRP (Day 10 CRP - baseline CRP), which was normally distributed, was presented as the adjusted mean [95% confidence interval (CI)] calculated using the margins command in STATA and adjusted for the baseline CRP level, age, sex, and BMI.

All statistical analyses were performed using the Stata 14.0 software program (Stata Corp., College Station, USA) with two-sided p values <0.05 considered significant.

Results

Baseline characteristics

A total of 100 patients (50 each in cohorts 1 and 2) were consecutively enrolled in this study. All patients received at least one dose of favipiravir. Patients who had no data for the Day 10 SARS-Cov-2 test were excluded from the PPS analyses (Figure). The safety population included all patients.

Table 1 lists the patients’ characteristics at baseline, stratified by cohort. The mean age was 62.8±17.6 years old, and the proportion of women was 43.0%. There were no significant differences between the cohorts except for in the CRP
Table 1. Baseline Characteristics.

|                      | Total (n=100) | Cohort 1 (n=50) | Cohort 2 (n=50) | p value |
|----------------------|--------------|-----------------|-----------------|---------|
| Age, years           | 62.8 (17.6)  | 65.1 (17.1)     | 60.4 (17.8)     | 0.18    |
| Women, n             | 43 (43.0%)   | 23 (46.0%)      | 20 (40.0%)      | 0.54    |
| BMI, kg/m²            | 26.0 (5.3)   | 25.0 (4.9)      | 27.0 (5.6)      | 0.068   |
| CRP*, mg/dL          | 2.77 (0.98, 6.02) | 4.18 (0.99, 7.51) | 1.96 (0.72, 5.00) | 0.021   |
| BT, °C               | 37.6 (0.9)   | 37.6 (1.0)      | 37.7 (0.8)      | 0.045   |
| WBC, ×10³/μL         | 5.8 (2.6)    | 6.0 (3.0)       | 5.6 (2.0)       | 0.43    |
| Hb, g/dL             | 13.8 (2.0)   | 13.7 (2.0)      | 14.0 (2.1)      | 0.47    |
| AST*, U/L            | 33.0 (26.0, 54.0) | 32.0 (25.0, 62.0) | 35.0 (27.0, 51.0) | 0.91    |
| ALT*, U/L            | 31.0 (17.0, 50.0) | 29.0 (17.0, 56.0) | 34.0 (17.0, 50.0) | 0.81    |
| SBP, mmHg            | 129.1 (20.3) | 130.5 (20.9)    | 127.7 (19.8)    | 0.49    |
| Use of steroids, n   | 40 (40.0%)   | 18 (36.0%)      | 22 (44.0%)      | 0.41    |
| Duration of favipiravil*, days | 11 (6.5, 14) | 11 (6.1, 14)   | 11 (6.1, 14)   | 0.47    |

BMI: body mass index, CRP: C-reactive protein, BT: body temperature, WBC: white blood cell, Hb: hemoglobin, AST: aspartate aminotransferase, ALT: alanine transaminase, SBP: systolic blood pressure. Data are presented as the mean (SD) or *median (IQR).

Table 2. Overall Outcomes of Study Participants.

|                      | Total (n=100) | Cohort 1 (n=50) | Cohort 2 (n=50) | p value |
|----------------------|--------------|-----------------|-----------------|---------|
| Death                | 4 (4.0%)     | 3 (6.0%)        | 1 (2.0%)        | 0.307   |
| Intubated            | 7 (7.0%)     | 3 (6.0%)        | 4 (8.0%)        | 0.695   |
| Worse of pneumonia   | 34 (34.0%)   | 15 (30.0%)      | 19 (38.0%)      | 0.398   |

Table 3. Odds Ratio for SARS-Cov-2 Testing in the PPS Population.

|                      | Cohort 1 n=47 | Cohort 2 n=39 | p      |
|----------------------|---------------|---------------|--------|
| SARS-Cov-2 test negative, n (%) | 10 (21.3%)    | 20 (51.3%)    | 0.004  |
| Odds ratio           |               |               |        |
| Unadjusted           | 1.0 (ref)     | 3.89 (1.52 to 9.96) | 0.005  |
| Model 1              | 1.0 (ref)     | 3.79 (1.45 to 9.95) | 0.007  |
| Model 2              | 1.0 (ref)     | 3.32 (1.17 to 9.38) | 0.024  |

Model 1: adjusted for age, sex, and BMI. Model 2: adjusted as for Model 1+baseline CRP.

Overall outcomes

Table 2 shows the outcomes of participants. Among the 100 total patients, 4 (4.0%) died, 7 (7.0%) were intubated, and 34 (34.0%) suffered worsening of pneumonia. The trigger of intubation and definition of worsening were both left to the clinical decision of each physician. No significant differences were observed between cohorts 1 and 2 in the incidences of these clinical events.

Negative conversion rate of SARS-CoV-2

There was negative conversion of SARS-CoV-2 in 30/86 patients (34.9%). The negative conversion rate of SARS-CoV-2 was higher in cohort 2 than in cohort 1 (cohort 1, 21.3%; cohort 2, 51.3%; p=0.004) (Table 3). The odds ratio of cohort 2 for negative conversion was 3.89 (95% CI, 1.52 to 9.96; p=0.005) compared with cohort 1. The statistical significance of this association was maintained in the multivariable analysis after adjusting for the age, sex, BMI (Model 1), and baseline CRP level (Model 2) (Table 3). Other variables, including the age, sex, BMI, and baseline CRP level, were not associated with negative conversion in the multivariable logistic regression model.

The results of a subgroup analysis of the OR for negative conversion of SARS-CoV-2 are shown in Table 4. There was significant interaction between the cohort and steroid use for negative conversion of SARS-CoV-2; among patients without steroid use, cohort 2 patients had a higher OR than cohort 1. Although there was no interaction between the cohort and other sub-groups for negative conversion of SARS-CoV-2, there was a trend in cohort 2 toward greater efficacy of favipiravir in the groups with a low BMI, low baseline CRP level, and no steroid use.
### Table 4. Subgroup Analysis of OR for SARS Cov-2 Test Negative.

|                      | Cohort 1 (n=47) | Cohort 2 (n=39) | OR (95%CI) | p value for interaction |
|----------------------|-----------------|-----------------|-----------|------------------------|
| Overall              | 10/47 (21.3%)   | 20/39 (51.3%)   | 3.89 (1.52 to 9.96)* | 0.96                   |
| Age                  |                 |                 |           |                        |
| <65 (n=42)           | 6/23 (26.1%)    | 11/19 (57.9%)   | 3.89 (1.06 to 14.32)* |                        |
| ≥65 (n=44)           | 4/24 (16.7%)    | 9/20 (45.0%)    | 4.09 (1.02 to 16.40)* |                        |
| Sex                  |                 |                 |           | 0.793                  |
| Men (n=48)           | 5/25 (20.0%)    | 12/23 (52.2%)   | 4.36 (1.22 to 15.64)* |                        |
| Women (n=38)         | 5/22 (22.7%)    | 8/16 (50.0%)    | 3.40 (0.84 to 13.76)  |                        |
| BMI                  |                 |                 |           | 0.506                  |
| <25 (n=43)           | 4/25 (16.0%)    | 9/18 (50.0%)    | 5.25 (1.28 to 21.57)* |                        |
| ≥25 (n=42)           | 6/21 (28.6%)    | 11/21 (52.4%)   | 2.75 (0.77 to 9.86)   |                        |
| Baseline CRP         |                 |                 |           | 0.282                  |
| <2.78 (n=42)         | 4/20 (20.0%)    | 13/22 (59.1%)   | 5.78 (1.44 to 23.12)* |                        |
| ≥2.78 (n=41)         | 6/27 (22.2%)    | 5/14 (35.7%)    | 1.94 (0.47 to 8.05)   |                        |
| Steroid use          |                 |                 |           | 0.033                  |
| No (n=50)            | 7/30 (23.3%)    | 16/20 (80.0%)   | 13.14 (3.29 to 52.46)* |                        |
| Yes (n=36)           | 3/17 (17.7%)    | 4/19 (21.1%)    | 1.24 (0.24 to 6.58)   |                        |

*p<0.05

### Table 5. Adverse Events Associated with Favipiravir Use.

#### a. all

|                      | Total (n=100) | Cohort 1 (n=50) | Cohort 2 (n=50) |
|----------------------|--------------|-----------------|-----------------|
| Hyperuricemia        | 49 (49.0%)   | 13 (26.0%)      | 36 (72.0%)*     |
| ALT increased        | 25 (25.0%)   | 16 (32.0%)      | 9 (18.0%)       |
| AST increased        | 20 (20.0%)   | 13 (26.0%)      | 7 (14.0%)       |
| Allergic reaction    | 5 (5.0%)     | 3 (6.0%)        | 2 (4.0%)        |
| Creatinine increased | 2 (2.0%)     | 2 (4.0%)        | 0 (0%)          |
| Diarrhea             | 1 (1.0%)     | 1 (2.0%)        | 0 (0%)          |
| Anorexia             | 1 (1.0%)     | 0 (0%)          | 1 (2.0%)        |

#### b. More than Grade 3

|                      | Total (n=100) | Cohort 1 (n=50) | Cohort 2 (n=50) |
|----------------------|--------------|-----------------|-----------------|
| Hyperuricemia        | 12 (12.0%)   | 4 (8.0%)        | 8 (16.0%)       |
| ALT increased        | 4 (4.0%)     | 4 (8.0%)        | 0 (0%)          |
| AST increased        | 4 (4.0%)     | 4 (8.0%)        | 0 (0%)          |

AST: aspartate aminotransferase, ALT: alanine transaminase. Allergic reactions included skin rash, hives, and itching. *p<0.001 compared to cohort 1

### Change in the CRP level

The changes in the CRP level between cohort 1 and 2 are shown in Supplementary material 2. There was no marked difference in the adjusted mean change in the CRP level between cohorts 1 and 2 [adjusted mean (95% CI) for cohort 1, -1.98 (-3.47 to -0.50) mg/dL; cohort 2, -2.30 (-3.86 to -0.75) mg/dL; p=0.772].

### AEs

AEs associated with the use of favipiravir are shown in Table 5. A total of 103 AEs were reported among the 100 patients in the safety population. The most common AE was hyperuricemia (defined as ≥7.0 mg/dL), which occurred in 49/100 (49.0%) and was more frequent in cohort 2 than in cohort 1 (cohort 1: 13/50, 26.0%; cohort 2: 36/50, 72.0%; p<0.001). Other reported AEs included elevated ALT [25/100 (25%)] and AST levels [20/100 (20%)]. Grade ≥3 AEs were also noted for hyperuricemia (12/100, 12.0%), elevated ALT levels (4/100, 4.0%), and elevated AST levels (4/100, 4.0%). There was no marked difference in the rate of AEs between the two cohorts except for in hyperuricemia (Grade ≥1).

Table 6 shows AEs stratified by age (<65 and ≥65 years old). There were no significant differences in AEs between these age groups except that ALT elevation was less frequent in the older group than in the younger group. None of the severe AEs (Grade 4 and 5), including the four deaths due to COVID-19, were associated with favipiravir. Therefore, favipiravir seemed to be safe, even in elderly patients ≥65 years old, causing only mild to moderate hyperuricemia and increases in ALT and AST levels.
Table 6. AEs Stratified by Age.

|                  | All (n=100) | Cohort 1 (n=50) | Cohort 2 (n=50) |
|------------------|-------------|-----------------|-----------------|
|                  | <65 y (n=53) | ≥65 y (n=47)    | <65 y (n=24)    | ≥65 y (n=26)    | <65 y (n=29)    | ≥65 y (n=21) |
| Hyperuricemia    | 26 (49.1%)  | 23 (48.9%)      | 5 (20.8%)       | 8 (30.8%)       | 21 (72.4%)      | 15 (71.4%)   |
| ALT increased    | 19 (35.8%)  | 6 (12.8%)*      | 10 (41.7%)      | 6 (23.1%)       | 9 (31.0%)       | 0 (0%)*      |
| AST increased    | 13 (24.5%)  | 7 (14.9%)       | 7 (29.1%)       | 6 (23.1%)       | 6 (20.7%)       | 1 (4.8%)     |
| Allergic reaction| 3 (5.7%)    | 2 (4.3%)        | 3 (12.3%)       | 0 (0%)          | 0 (0%)          | 2 (9.5%)     |
| Creatinine increased | 1 (1.9%)  | 1 (2.1%)        | 1 (4.2%)        | 1 (3.8%)        | 0 (0%)          | 0 (0%)       |
| Diarrhea         | 1 (1.9%)    | 0 (0%)          | 1 (4.2%)        | 0 (0%)          | 0 (0%)          | 0 (0%)       |
| Anorexia         | 1 (1.9%)    | 0 (0%)          | 0 (0%)          | 0 (0%)          | 1 (3.4%)        | 0 (0%)       |

AST: aspartate aminotransferase, ALT: alanine transaminase. Allergic reactions included skin rash, hives, and itching. *p<0.05

Discussion

A major problem in the treatment of COVID-19 has been the absence of an effective, safe and orally administrable anti-viral drug. In this study, we administered favipiravir to patients with COVID-19 using the same doses used to treat influenza and SFTS in cohorts 1 and 2 (3, 4). Only 21.3% of patients in cohort 1 and 51.3% in cohort 2 achieved negative conversion of SARS-CoV-2. These rates are relatively low compared with those reported previously in Japan (5). Although the present observation period was short (15 days), favipiravir appears to have a limited effect for achieving rapid viral clearance. This trend is consistent with the results of a recent meta-analysis (10).

We used two models to analyze differences in negative conversion rates of SARS-CoV-2 between cohorts 1 and 2, including the age, sex, BMI, and baseline CRP level. The results showed that negative conversion was more frequent in cohort 2 than in cohort 1 (Table 3). A sub-analysis between cohorts 1 and 2 that included the impact of steroid use (timing of addition is shown in Supplementary material 3) in addition to these variables revealed a higher OR of negative conversion in cohort 2 than in cohort 1 in both those <65 years old (3.89; 95% CI 1.06-14.32) and ≥65 years old (4.09; 95% CI 1.02-16.40), those with a BMI <25 (5.25; 95% CI 1.28-21.57), those with a CRP level below the median (5.78; 95% CI 1.44-23.12), and in those without steroid use (13.1; 95% CI 3.29-52.46) (Table 4). These results suggest that a higher dose of favipiravir may be a viable treatment option, even in elderly or obese patients whose COVID-19 is not severe without the need for steroids.

Regarding the profiles of AEs, there was a trend toward a higher prevalence of hyperuricemia in cohort 2 than in cohort 1, but no serious AEs occurred in either cohort (Table 5). A notable point of our study is that we reported the results of actual treatment of COVID-19 by oral medication among older patients (mean age, 62.8 years old) than those in recent reports. The frequencies of AEs, such as hyperuricemia and elevated liver enzyme levels, were within the expected ranges, and there were no serious AEs due to treatment with favipiravir. Furthermore, on comparing participants <65 and ≥65 years old, there was no remarkable association of AEs with elderly age in either cohort (Table 6). These data strongly support the safety of favipiravir, especially in elderly people.

The results of a single-blind phase III study conducted in Japan showed that patients receiving favipiravir achieved a significant difference in clinical improvement about three days earlier than those receiving a placebo (6). However, they did not show any improvement in survival as observed in patients administered dexamethasone who required oxygen (11). It is possible that these clinical trials of favipiravir recruited patients mainly with non-severe COVID-19 who were able to take the drug orally and thus in whom the disease was less likely to be fatal than in others. The variety of clinical manifestations of COVID-19, which range from mild to severe, increase the difficulty of proving the effect of one drug for improving the survival of patients. For this reason, no clear effect has been shown for individual anti-viral drugs, such as lopinavir/ritonavir, except for remdesivir (12-15).

Rival drugs to favipiravir include intravenous monoclonal antibody cocktails (16-18) and molnupiravir as an orally administrable anti-viral (19). However, in terms of monoclonal antibodies, drug shipping and storage via a cold chain system are both complex processes, especially for patients living in their own home or in a nursing home. Importantly in this regard, oral medication that can be stored without a cold chain system is available, even in elderly or obese patients whose COVID-19 is not severe without the need for steroids.
been vaccinated or have neutralizing antibodies against SARS-CoV-2 is changing the clinical manifestation of COVID-19. In this clinical setting as well, favipiravir may have advantages over alternatives because of its safety in elderly patients, oral administration route, and lack of requirement for storage in a cold chain system.

Several limitations associated with the present study warrant mention. Because the study design did not include a control group and was non-randomized, it was difficult to confirm the anti-viral effect of favipiravir precisely. The non-blinded design may also have affected the AE rate. Furthermore, we cannot deny that viral clearance may have depended on host immunity rather than the efficacy of favipiravir. We did not record information regarding underlying disease, such as diabetes mellitus, cardiovascular or malignant diseases, or immunocompromised conditions, which critically affect the severity, response to the treatment, and clinical outcome of COVID-19. Therefore, our data were not adjusted by the underlying disease condition of participants. In addition, recruitment of participants in cohorts 1 and 2 was sequentially performed in different phases of the pandemic, corresponding in the “1st to 2nd wave” and “3rd to 4th wave” in Japan, respectively. Therefore, different strains of SARS-CoV-2 (Wuhan or alpha) may have been included in each cohort. We should therefore bear in mind that the outcomes may have been affected by the virulence of each strain. However, the typing data of SARS-CoV-2 was not available in this study. Of further note, the differences in management procedures, including the diagnostic methods, time to hospitalization, and use of steroids, may have been confounding factors influencing the outcomes. In the earlier phase of this study, the time from onset to participation tended to be prolonged (5.5 days in cohort 1 and 4.0 days in cohort 2, summarized in supplemental Table 4) due to the limited diagnostic resources in the early stage of the pandemic. This delay in intervention may be one reason why the patients in cohort 1 had a higher CRP level at baseline than those in cohort 2 (Table 1). We should also bear in mind that the efficacy of dexamethasone was described in a publication on July 17, 2020 (11), so later-phase participants (cohort 2, approved June 24, 2020) requiring oxygen may have been given steroids based on this evidence.

In conclusion, this prospective, open-labeled, single-arm study was unable to demonstrate the clinical efficacy of favipiravir, and its virological efficacy was difficult to interpret due to the limitation of the study design. However, no remarkable issues with the safety or tolerability of favipiravir were observed, even in elderly patients with COVID-19. Further investigations are needed to confirm the clinical and virological efficacy of favipiravir for COVID-19.

The authors state that they have no Conflict of Interest (COI).

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