Favipiravir in patients with early mild-to-moderate COVID-19: a randomized controlled trial

Yoav Golan, MD, MS, FIDSA, Tufts Medical Center, Appili Therapeutics, Boston, MA, USA

Jesus Abraham Simon Campos, MD, Kohler & Milstein Research S.A. de C.V., Merida, Mexico

Rob Woolson, MS, Rho, Inc., Durham, NC, USA

Donald Cilla, Pharm.D., MBA, Appili Therapeutics, Waterford, VA, USA

Rodolfo Hanabergh, MD, Quality Professional Healthcare, Miami, FL, USA

Yaneicy Gonzales-Rojas, MD, Verus Clinical Research, Corp., Coconut Grove, FL, USA

Reynaldo Lopez, MD, Bioresearch Institute LLC, Hollywood, Florida, USA

Robert Finberg, M.D. (deceased), UMass Memorial Hospital, Worcester, MA, USA

Armand Balboni, MD, PhD, Appili Therapeutics, Inc., Waterford, VA, USA

CORRESPONDING AUTHOR

Yoav Golan MD, MS, FIDSA

Tufts Medical Center

Address: 800 Washington St, Boston, MA, USA 02111

e-mail: ygolan@appilitherapeutics.com

RUNNING TITLE: Favipiravir in COVID-19

ABSTRACT

Background: Despite vaccination, many remain vulnerable to COVID-19 and its complications. Oral antivirals to prevent COVID-19 progression are vital. Based upon perceived potency and clinical efficacy, favipiravir is widely used to treat COVID-19. Evidence from large randomized controlled trials (RCT) is lacking.

Methods: In this multicenter double-blinded placebo-controlled RCT, adults with early mild-to-moderate COVID-19 were 1:1 randomized to favipiravir or placebo. The study evaluated time to sustained clinical recovery (TT-SCR), COVID-19 progression, and cessation of viral shedding.

Results: Of 1187 analyzed patients across 40 centers, 83.3% were Hispanic, 89.0% unvaccinated, 70.3% SARS-CoV-2 seronegative, and 77.8% had risk factors for COVID-19 progression. The median time from symptom presentation and from positive test to randomization was three and two days, respectively. There was no difference in TT-SCR (median of 7 days for both groups; p=0.80), COVID-19 progression [11 patients each (1.9% vs. 1.8%); p=0.96], time to undetectable virus [median=6 days, 95% CI (6-8) vs. 7 days, 95% CI (6-9)], or in undetectable virus by end of therapy (73.4% vs. 72.3%; p=0.94). Outcomes were consistent across the analyzed sub-groups. Adverse events were observed in 13.8% and 14.8% of favipiravir-treated and placebo-treated subjects, respectively. Uric acid elevation was more frequent among favipiravir-treated subjects (19.9% vs. 2.8%).

Conclusions: Favipiravir was well tolerated but lacked efficacy in TT-SCR, progression to severe COVID-19, or cessation of viral shedding and should not be used to treat patients with COVID-19. (Supported by Appili Therapeutics

KEYWORDS: COVID-19, treatment, progression, antiviral, favipiravir

Clinical Trials Registration: NCT04600895

INTRODUCTION

Prevention remains the mainstay of COVID-19 management, but it is not perfect.[1-2] Many around the world have limited access to vaccination, do not qualify, or refuse it, resulting in vast unvaccinated populations.[3-6] In addition, the emergence of novel viral variants which are less affected by vaccines and monoclonal antibodies, combined with the relatively short period of protection and lack of protective immunity among many recipients, results in ongoing transmission, disease and deaths.[7-12] The availability of effective, safe, and tolerable antivirals to treat early COVID-19 and prevent its progression is therefore of critical importance.

Favipiravir, an RNA-dependent RNA polymerase inhibitor, has been shown to have broad in vitro activity against RNA viruses, including a variety of Coronaviruses and specifically SARS-CoV-2, the causative agent of COVID-19.[13-15] Favipiravir was evaluated in multiple studies with results that are widely interpreted as supporting its use in the treatment of patients with COVID-19.[16-21] This led to its authorization or endorsement in some countries and widespread use outside of the United States.[21-25] However, some trials failed to show a favorable effect or retracted and data from adequately designed double-blinded RCTs is lacking.[26-31] We present the results of a phase 3 multicenter trial evaluating the efficacy and safety of favipiravir in the treatment of COVID-19.

METHODS

Trial Design and Oversight

The PRESECO (PREvent SEvere COvid-19) study was a randomized, multicenter, double-blinded, placebo-controlled, superiority trial evaluating the safety and efficacy of favipiravir as an outpatient treatment in patients with mild to moderate early COVID-19. This was a 28-day study conducted at 27 sites in the US, 7 in Brazil, and 6 in Mexico. The study design and choice of endpoints followed the US Food and Drug Administration's (FDA) guidance to industry.[32-34] The study followed Good Clinical Practice principles (ICH Harmonized Tripartite Guideline).[35] The authors accept responsibility for the accuracy and completeness of the data, the analyses, and adherence to the trial protocol. The study's protocol and statistical analysis plan (SAP) evolved throughout the study to accommodate relevant emerging information on COVID-19 and its management, changing FDA guidance to industry, and updated guidelines from the Centers for Disease Control and Prevention (CDC). Study protocols, SAPs, and description of study amendments are available at NEJM.org.

Trial Participants

Enrollment eligibility included age 18 years or older, mild-to-moderate COVID-19, first positive RT-PCR or Rapid Antigen assay within three days of enrollment, first symptoms within five days of enrollment, having at least two moderate or severe COVID-19 symptoms, and signing an informed consent.[33,36] COVID-19-related symptoms included runny nose, sore throat, shortness of breath, cough, tiredness, body aches, headache, chills, feeling feverish, nausea, diarrhea, and vomiting. Early in the trial, taste or smell changes were included in the entry criteria; however, later, based upon an evolving understanding of COVID-19 symptom time course, taste and smell were excluded. Subjects enrolled based solely upon taste and smell

changes were not analyzed. Exclusion criteria included bacterial or viral infection other than SARS-CoV-2, treatment with high dose steroids, receipt of remdesivir or SARS-CoV-2 monoclonal antibodies. A complete list of inclusion and exclusion criteria is provided in the Appendix.

Efficacy

The primary endpoint of this study was Time to Sustained Clinical Recovery, calculated as the number of days from start of study medication to sustained symptom alleviation, defined by: Oxygen saturation ≥94% at rest, and Oral temperature <38.0 ºC, and all COVID-19-associated symptoms reaching a score of mild or none for four consecutive days.[32] Patients who died, required hospitalization, or withdrew from the study with an unknown outcome, were considered not reaching the primary endpoint. A key secondary endpoint was proportion of patients with COVID-19 progression, defined as requiring an emergency department visit or hospitalization for COVID-19 worsening or shortness of breath, or death ('narrow definition').[32] An additional definition of progression included the narrow definition criteria, as well as symptomatic worsening, defined as two or more additional moderate or severe COVID-19 symptoms, or new fever, or new desaturation ('broad definition').

Virologic Outcome

An additional pre-specified secondary endpoint was time (in days) to undetectable SARS-CoV-2 load in saliva assays. Patients in the viral shedding sub-study collected a saliva specimen daily on study Days 1 through 10. Patients who had detectable virus at baseline (study Days 1, 2, or 3) were included in the analysis.

Trial Procedures

At enrollment, patients were randomized 1:1 to oral favipiravir 1800 mg twice daily on Day 1, followed by 800 mg twice daily on Days 2-10, or matching placebo for 10 days (Supplement Figure 1). Participants received the current standard of care. Randomization was performed via an Interactive Web Randomization System and maintained by a third party. Most study interactions were performed by telehealth. To assess COVID-19 manifestations, we followed guidance by the Office of New Drugs at the FDA, which were based upon CDC's recommendations as of August 28, 2020.[33] Subjects recorded their symptoms, temperature, and O_2 saturation, as well as protocol adherence daily, in an electronic patient-reported outcome (ePRO) instrument that was programmed with reminders to complete data entry to reduce missing data. To minimize enrollment bias related to electronic illiteracy, we allowed the use of paper-based PRO as an alternative.[32] The unblinding code was not broken for any subject throughout the study.

Analysis populations

The modified-intent-to-treat (mITT) population, which included all randomized patients who received study medication, was the primary analysis population. Additional analysis populations included the Per Protocol (PP) population, which included patients who took at least 80% of study medication and had no protocol violations that would affect the primary efficacy endpoint; and the mITT2 population, which included patients who received study medication and reported (in ePRO) sufficient protocol mandated COVID-19 symptoms (two or more COVID-19 symptoms worse than mild) on enrollment. The PP and mITT2 populations were used in sensitivity analyses of the primary and key secondary endpoints (Supplement Table 1). Pre-specified subgroup analyses of the primary and secondary endpoints were performed to assess

whether treatment efficacy varied according to serostatus, age, time from positive SARS-CoV-2 test to enrollment, and risk status for COVID-19 progression (defined in the appendix). Additional post-hoc analyses included geographical region, race, and uric acid elevation.

Safety

Safety was assessed by documenting adverse events (AEs) and serious AEs (SAEs), according to the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term (version 23.1) and obtaining laboratory tests.

Statistical Analysis

We planned to enroll 1250 patients to attain 815 clinical recoveries ensuring power of 85%. The definitive sample size calculation was based on group sequential design with a possibility to stop for efficacy or futility at interim. The viral shedding sub-study was powered at 80% with a planned sample size of 500 patients to attain 112 events of viral shedding cessation.

We utilized survival analysis to analyze the time-to-event variables. Failure curves were constructed for time to positive event using Kaplan-Meier estimates. Time to sustained clinical recovery and virologic outcomes were compared using a two-sided Gehan-Wilcoxon test. Differences between treatments in proportions of COVID-19 progression were evaluated using a two-sided Chi-square test or Fisher's exact test, as applicable. The corresponding confidence interval for the difference in proportions were calculated. Adjustment for multiple testing was performed to control the overall type 1 error to ≤5% for the interim and final analysis on the primary efficacy endpoint. A hierarchical approach was also used to control the overall type 1 error to ≤5% for the primary and key secondary endpoints. The order of testing was: (1) Sustained clinical recovery, (2) COVID-19 progression (broad definition), and (3) COVID-19 progression (narrow definition). Statistical significance would not be claimed if the parameter

preceding the parameter being tested did not reach statistical significance. Additional information, including handling of missing data, is in the Supplementary Appendix.

RESULTS

Patients

Between November 2020 and October 2021, 1231 patients were randomized; 1187 were included in the mITT population (USA: 963, Mexico: 160, Brazil: 65), 599 received favipiravir, and 588 received placebo (Figure 1). Baseline characteristics were generally similar across treatment groups (Table 1). Most participants were of Hispanic ethnicity (83.3%), unvaccinated (89%), seronegative for COVID-19 nucleocapsid antibodies (70.3%) at enrollment and had risk factors for COVID-19 progression (77.8%). The median number of days from onset of COVID-19 symptoms and from first positive COVID-19 test to randomization was three and two days, respectively.

Efficacy

The median time to sustained clinical recovery in the favipiravir and placebo groups, was 7 days (95% CI 7-8 days) and 7 days (95% CI 6-8), respectively. By study Day 28, sustained clinical recovery was reached by 87.8% of favipiravir-treated and 87.3% placebo-treated subjects (p=0.80) (Figure 2B). Because the primary analysis showed no statistical significance, the hierarchical analyses approach mandated that all secondary efficacy analyses are considered as not having reached statistical significance. Regardless, analyses of the key secondary endpoints were performed and failed to reach statistical significance. In each the favipiravir and placebo groups, 11 patients (1.9% vs 1.8%) experienced COVID-19 progression (narrow definition), (p=0.96) (Figure 2A). Similarly, there was no difference in COVID-19 progression using the

broad definition for progression between favipiravir-treated and placebo-treated patients (Supplement Table 2). Outcomes were consistent across all analysis populations and a lack of efficacy of favipiravir in relation to the primary and key secondary endpoints was seen in the additional analysis populations (Supplement Figure 2). A lack of efficacy was also observed across all treatment groups in the analyzed subgroups for the primary and secondary endpoints.

Virologic Outcome

Of the 482 patients in the mITT viral shedding sub-study, 272 (favipiravir 140, placebo 132) had detectable viral load at baseline (Study Day 1, 2, or 3) and were included in the analysis. Approximately 50% of patients had converted to undetectable SARS-CoV-2 viral load by Day 6 (95% CI [6-8 days]) in the favipiravir group and by Day 7 (95% CI [6-8 days]) in the placebo group; 73.4% of patients in the favipiravir treatment group reached undetectable SARS-CoV-2 Viral load by Day 10, compared with 72.3% in the placebo group. There was no difference in time to cessation of viral shedding between the treatment groups (p=0.94) (Figure 3). Outcomes were consistent across analysis populations (Supplement Figure 3).

Safety

Adverse events occurred in 84 patients (13.8%) in the favipiravir group and 89 patients (14.8%) in the placebo group. Of these, 14 (2.3%) in the favipiravir group and 20 (3.3%) in the placebo group were considered possibly, probably, or definitely related to study drug (Table 2 and Supplement Table 3). Treatment discontinuations due to AEs occurred in 9 patients (1.5%) and 7 patients (1.2%) in the favipiravir and placebo groups, respectively. The most common AEs included nausea (favipiravir: 8 patients, 1.3% vs. placebo: 5 patients, 0.8%), cough (7 patients, 1.1% vs. 5 patients, 0.8%), and dizziness (5 patients, 0.8% vs. 10 patients,1.7%) (Table 2). Serious AEs occurred in 12 (2.0%) and 14 (2.3%) patients in the favipiravir and placebo groups,

respectively (Table 2 and Supplement Table 4). The most common SAEs included COVID-19 pneumonia in 5 (0.8%) patients in each group, pneumonia (favipiravir: 3 patients, 0.5% vs. placebo: 1 patient, 0.2%), COVID-19 worsening (2 patients, 0.3% vs. 3 patients, 0.5%), and dyspnea (1 patient, 0.2% vs. 2 patients, 0.3%). Study investigators determined all SAEs in the favipiravir group unrelated to study treatment. One death occurred during the study in a patient receiving placebo. The death was attributed to complications of COVID-19 pneumonia (Table2). Abnormally elevated uric acid levels at treatment end were seen in 105 favipiravir-treated patients (19.9%, 95% CI [16.5%-23.3%]) vs. 15 placebo-treated (2.8%, 95% CI [1.4%-4.3%]), and the mean uric acid change in favipiravir-treated patients was 30.1% (SD 51.6) vs. 6.6% (SD 21.2) in placebo-treated patients (Table 2). Abnormally elevated alanine aminotransferase at treatment end was seen in 68 favipiravir-treated [12.9%, 95% CI (10.1%-15.8%)] vs. 44 placebo-treated [8.3%, 95% CI (6.0%-10.7%)] patients (Supplement Table 5).

DISCUSSION

In this multicenter, double-blind RCT, we evaluated the efficacy and safety of favipiravir in patients with mild to moderate early COVID-19. Favipiravir treatment was associated with uric acid elevation but no documented episodes of gout. Otherwise, favipiravir was safe and well tolerated. Favipiravir lacked a mitigating effect on COVID-19 symptoms, measured as time to sustained clinical recovery, and did not decrease the progression of COVID-19, measured as the development of new moderate or severe symptoms or the need for emergency room visits and hospitalizations. In addition, the pace to cessation of viral shedding was not affected by

favipiravir treatment. This lack of favipiravir effect was observed across analysis populations and patient subgroups.

Several factors may explain favipiravir's lack of efficacy. Insufficient potency is a leading concern. Favipiravir was not systematically studied in vitro against most SARS-CoV-2 variants. The amount of information for variants that have been studied is limited and demonstrates a high ED50, suggesting that higher drug concentrations than may be achievable with the studied dose are required for efficacy.[14-15] COVID-19 animal studies, as well as pharmacologic modelling to fully understand the pharmacokinetic-pharmacodynamic profile of favipiravir, inform dosing decisions, and mitigate subtherapeutic exposures, are not available. In addition, it is not clear whether favipiravir exposure may vary across populations of patients with COVID-19, requiring better understanding of dosing considerations among patients who are non-Asian, young, or overweight. Although the patients' self-documented medication adherence was high, undocumented lack of medication adherence related to high pill burden could have contributed to inconsistent exposure. Lastly, some patients may have been further into their COVID-19 course; therefore, out of the essential viral-replication window for antivirals to exert a beneficial effect.

Results of studies evaluating favipiravir's efficacy, published and unpublished, are mixed and possibly misleading by supporting a favorable effect.[16-20,26-31] Such studies can be divided into anecdotal case series and quasi-experimental studies, all of which were open-label and mostly small in sample size.[16-20] Only a few controlled double-blind studies have been performed; however, they were underpowered, and some were terminated early for futility.[26-31] A telling trend emerges when reviewing the results. Many of the open-label quasi-experimental studies demonstrated efficacy of favipiravir in mitigating COVID-19 symptoms or improving outcomes.[16-20] However, of the six RCTs conducted, only one was double-blind, none

demonstrated proven clinical efficacy, and none demonstrated effective viral cessation. [26-31] Positive sentiments emerging from open-label quasi-experimental studies have been the basis for the widespread endorsement, even regulatory authorization in some countries, of using favipiravir for the management of COVID-19.[22-25]

The PRESECO study was limited in several ways. A major challenge in performing trials early in the pandemic is the rapidly evolving understanding of the disease, its manifestations and course, as well as frequent changes in guidelines for its diagnosis and management. Although protocol changes during a study are generally not endorsed, unless a study evolves as relevant information becomes available along a pandemic, its results may be deemed irrelevant by the end of it. We avoided major changes to the study's design and its endpoints, while updating the sample size to achieve the pre-specified number of events, therefore, maintaining study's objectives and integrity. The primary endpoint of this study is subjective and difficult to measure. To overcome this challenge, we used PRO with a 4-point scale for severity designed to be completed in real time in an electronic diary by the patient.[33] This validated standardized approach and the large sample size helped reduce documentation bias. Another challenge was ensuring adequate representation of all affected by COVID-19 regardless of their ability to use an electronic diary. To address this challenge, we allowed the use of a paper diary with frequent reminders from the study team. In this study, the proportion of patients with COVID-19 progression was relatively small. Yet, the complete lack of favipiravir efficacy on progression in this study suggests that a larger sample size would have been unlikely to show a favorable effect.

In summary, adequately designed clinical trials are important, particularly during pandemic times, when favorable study results can be immediately translated to better care and outcomes. Conversely, inconclusively designed trials can produce misleading results and drain the pool of

study candidates for the meaningful trials. Contradicting much of the data from quasi-experimental studies and despite signals of in vitro potency, in this multicenter RCT, favipiravir showed no evidence of clinical efficacy or viral shedding cessation. Until data from additional adequately designed studies using different regimens of favipiravir formulations or dosing becomes available, we advise against the use of favipiravir in the treatment of COVID-19.

NOTES

ACKNOWLEDGMENTS

The authors would like to thank Prasann Bavaniya and Lussia Kim for their critical contribution to the conduct of this clinical trial.

SOURCES OF FUNDING

The conduct of this clinical trial and the preparation of this manuscript were funded by Appili Therapeutics, Inc., Halifax, NS, CANADA

CONFLICT OF INTEREST

Yoav Golan, MD, MS, FIDSA: Employee of Appili Therapeutics in the capacity of Chief Medical Officer. Speaker: Pfizer, Sanofi, AbbVie, Paratek, Shionogi, Merk. Consultant/advisor: Pfizer, Seres, Sanofi. Stock options: Appili Therapeutics, Inc. Grants from NIH, CO-PI, niclosamide in COVID-19.

Jesus Abraham Simon Campos, MD: Advisor and speaker: Pfizer, Astra Zeneca, and Regeneron (paid to author). Served as site PI in this clinical trial and reimbursed for subject enrollment. Consulting fees include ADVISORY BOARD ASTRAZENECA and ADVISORY BOARD PFIZER (paid to author).

Rob Woolson, MS: Employee of Rho, Inc., Durham, NC, USA. Served as the study's statistician.

Donald Cilla, Pharm.D., MBA: Employee of Appili Therapeutics in the capacity of Chief Development Officer. Stock options: Appili Therapeutics, Inc.

Rodolfo Hanabergh, MD: No COI to report. Served as site PI in this clinical trial and reimbursed for subject enrollment.

Yaneicy Gonzales-Rojas, MD: No COI to report. Served as site PI in this clinical trial and reimbursed for subject enrollment.

Reynaldo Lopez, MD: No COI to report. Served as site PI in this clinical trial and reimbursed for subject enrollment.

Robert Finberg, M.D. (deceased): No COI to report. Served as site PI in this clinical trial and reimbursed for subject enrollment.

Armand Balboni, MD, PhD: Employee of Appili Therapeutics, Inc. in the capacity of Chief Executive Officer. Stock options: Appili Therapeutics, Inc; includes grant or contracts from US DoD – Research Grants unrelated to COVID-19/Favipiravir.

REFERENCES

1. World Health Organization. Infection prevention and control in the context of coronavirus disease (COVID-19): A living guideline. March 07, 2022 (https://www.who.int/publications/i/item/WHO-2019-nCoV-ipc-guideline-2022.1).
2. Center for Disease Control. Guidance for COVID-19. March 15, 2021 (https://www.cdc.gov/coronavirus/2019-ncov/communication/guidance.html).
3. Reuters. COVID-19 vaccination tracker. Accessed June 09. 2022 (https://graphics.reuters.com/world-coronavirus-tracker-and-maps/vaccination-rollout-and-access/).
4. Lazarus JV, Ratzan SC, Palayew A, et al. A global survey of potential acceptance of a COVID-19 vaccine. Nat Med. 2021;27:225-8.
5. Comirnaty. Package insert. Pfizer; 2021.
6. SPIKEVAX. Package insert. Moderna; 2022.
7. Lucas C, Vogels CBF, Yildirim I, et al. Impact of circulating SARS-CoV-2 variants on mRNA vaccine-induced immunity. Nature. 2021;600:523-9.
8. Chen RE, Zhang X, Case JB, et al. Resistance of SARS-CoV-2 variants to neutralization by monoclonal and serum-derived polyclonal antibodies. Nat Med. 2021;27:717-26.
9. Tao K, Tzou PL, Nouhin J, et al. The biological and clinical significance of emerging SARS-CoV-2 variants. Nat Rev Genet. 2021;22:757–73.
10. Strengert M, Becker M, Morillas Ramos G, et al. Cellular and humoral immunogenicity of a SARS-CoV-2 mRNA vaccine in patients on haemodialysis. EBioMedicine. 2021;70:103524.

11. Kawasuji H, Morinaga Y, Tani H, et al. Age-dependent reduction in neutralization against alpha and beta variants of bnt162b2 sars-cov-2 vaccine-induced immunity. Microbiol Spectr. 2021;9:e00561-21.
12. Lai A, Caimi B, Franzetti M, et al. Durability of humoral responses after the second dose of mrna bnt162b2 vaccine in residents of a long term care facility. Vaccines (Basel). 2022;10:446.
13. Furuta Y, Komeno T, Nakamura T. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. Proc Jpn Acad Ser B Phys Biol Sci. 2017;93:449-63.
14. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020;30:269-71.
15. Choy KT, Wong AY, Kaewpreedee P, et al. Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication in vitro. Antiviral Res. 2020;178:104786.
16. Manabe T, Kambayashi D, Akatsu H, Kudo K. Favipiravir for the treatment of patients with COVID-19: a systematic review and meta-analysis. BMC Infect Dis. 2021;21:489.
17. Cai Q, Yang M, Liu D, et al. Experimental treatment with favipiravir for COVID-19: an open-label control study. Engineering (Beijing). 2020;6:1192-8.
18. Tiwaskar M, Dhar R, Talwar D, et al. Real-world experience with favipiravir for treatment of COVID-19 among Indian healthcare professionals. J Assoc Physicians India. 2022;69:11-2.
19. Yamamura H, Matsuura H, Nakagawa J, Fukuoka H, Domi H, Chujoh S. Effect of favipiravir and an anti-inflammatory strategy for COVID-19. Crit Care. 2020;24:413.

20. Murohashi K, Hagiwara E, Kitayama T, et al. Outcome of early-stage combination treatment with favipiravir and methylprednisolone for severe COVID-19 pneumonia: a report of 11 cases. Respir Investig. 2020;58:430-4.
21. Joshi S, Parkar J, Ansari A, et al. Role of favipiravir in the treatment of COVID-19. Int J Infect Dis. 2021;102:501-8.
22. FDA News. Favipiravir earns temporary approval in Russia. June 02, 2020 (https://www.fdanews.com/articles/197395-favipiravir-earns-temporary-approval-in-russia).
23. Department of Disease Control (Thailand). Treatment guidelines for COVID-19. March 11, 2020 (https://ddc.moph.go.th/viralpneumonia/eng/file/guidelines/g_treatment.pdf).
24. The Indonesian Food and Drug Authority. Informatorium of COVID-19 Drugs in Indonesia. March 2020 (https://www.pom.go.id/new/admin/dat/20201203/Informatorium_COVID-19_Indonesian_FDA_(english_version)_edit.pdf).
25. Dubai Health Authority. United Arab Emirates, National Guidelines of COVID-19. June 2020 (https://www.dha.gov.ae/uploads/022022).
26. Dabbous HM, Abd-Elsalam S, El-Sayed MH, et al. RETRACTED ARTICLE: Efficacy of favipiravir in COVID-19 treatment: a multi-center randomized study. Archives of Virology. 2021;166:949–54.
27. Chen C, Zhang Y, Huang J, et al. Favipiravir versus arbidol for clinical recovery rate in moderate and severe adult COVID-19 patients: a prospective, multicenter, open-label, randomized controlled clinical trial. Front Pharmacol. 2021;12:683296.

28. Holubar M, Subramanian A, Purington N, et al. Favipiravir for treatment of outpatients with asymptomatic or uncomplicated COVID-19: a double-blind randomized, placebo-controlled, phase 2 trial. Clin Infect Dis. 2022:ciac312. Online ahead of print.
29. Doi Y, Hibino M, Hase R, Yamamoto MA. Prospective, randomized, open-label trial of early versus late favipiravir therapy in hospitalized patients with COVID-19. Antimicrob Agents Chemother. 2020;64:e01897-20.
30. Fujifilm. Fujifilm to terminate the enrollment of subjects in the phase III clinical trial of anti-influenza drug Avigan® Tablet in Japan, targeting COVID-19 patients. March 11, 2022 (https://www.fujifilm.com/jp/en/news/hq/7721).
31. Munjal S (2020, August 22 – 2021, January 27). Clinical trial evaluating the efficacy and safety of favipiravir in moderate to severe COVID-19 patients. Identifier NCT04529499. https://clinicaltrials.gov/ct2/show/NCT04529499.
32. Food and Drug Administration. Guidance for Industry: COVID-19: developing drugs and biological products for treatment or prevention. May 2020.
33. Food and Drug Administration. Guidance for Industry: Assessing COVID-19-related symptoms in outpatient adult and adolescent subjects in clinical trials of drugs and biological products for covid-19 prevention or treatment. September 2020.
34. Food and Drug Administration. Guidance for Industry: Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency. June 2020
35. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline: Maintenance of the ICH guideline on clinical safety data management: data elements for transmission of individual case safety reports. February 05, 2001.

36. Center for Disease Control. Symptoms of COVID-19. March 22, 2022 (https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fabout%2Fsymptoms.html).

Table 1. Demographics and Baseline Characteristics of the Patients (Modified Intent-to-Treat Population)

Patient Characteristic	**n (%)**	
	Placebo (n = 588)	**Favipiravir (n = 599)**
Male	261 (44.4%)	282 (47.1%)
Female	327 (55.6%)	317 (52.9%)
Age Group		
<60 years	506 (86.1%)	506 (84.5%)
≥60 years	82 (13.9%)	93 (15.5%)
Race		
American Indian or Alaska Native	59 (10.0%)	63 (10.5%)
Asian	2 (0.3%)	3 (0.5%)
Black or African American	26 (4.4%)	43 (7.2%)
Native Hawaiian or Pacific Islander	1 (0.2%)	0
White	491 (83.5%)	485 (81.0%)
Other or Not Reported	9 (1.5%)	5 (0.8%)
Ethnicity		
Hispanic or Latino	495 (84.2%)	494 (82.5%)
Non-Hispanic or Latino	93 (15.8%)	102 (17.0%)
Not Reported or Unknown	0	3 (0.5%)
Country		
United States	480 (81.6%)	482 (80.5%)
Mexico	78 (13.3%)	82 (13.7%)
Brazil	30 (5.1%)	35 (5.8%)
Vaccinated for COVID-19 at Enrollment	72 (12.2%)	59 (9.8%)
Seropositive at Enrollment	173 (29.4%)	159 (26.5%)

Risk Status at Enrollment for COVID-19 Progression*		
High Risk	453 (77.0%)	470 (78.5%)
Age ≥65 years	44 (7.5%)	56 (9.3%)
BMI (kg/m^2) ≥25	420 (71.4%)	435 (72.6%)
Any Qualifying Comorbidity (at least one condition #4-12)*	151 (25.7%)	62 (27.0%)
More Than One Risk Factor or Comorbidity (#1-12)*	145 (24.7%)	152 (25.4%)
Not High Risk	135 (23.0%)	129 (21.5%)
COVID-19 Symptom Severity at Enrollment		
Multiple Moderate or Severe Symptoms (≥4)	306 (52.0%)	293 (48.9%)
Few Moderate or Severe Symptoms (2-3)	281 (47.8%)	305 (50.9%)
Days from First Positive SARS-CoV-2 Test to Randomization**	2 (0,3)	2 (0,3)
≤2 days	521 (88.6%)	528 (88.1%)
2-5 days	66 (11.2%)	71 (11.9%)
No. of Days from Onset of COVID-19 Symptoms to Randomization**	3 (0,7)	3 (0,6)

*High risk for COVID-19 progression is defined as meeting at least one of the following: 1) 65 years of age or older OR 2) Overweight (BMI ≥25) OR 3) Pregnancy OR 4) Chronic kidney disease OR 5) Diabetes OR 6) Weakened immune system OR 7) Currently receiving immunosuppressive treatment OR 8) Cardiovascular disease/hypertension OR 9) Chronic lung disease OR 10) Sickle cell disease OR 11) Neurodevelopmental disorders OR 12) Medical-related technological dependence.

**Median (min, max)

Table 2. Summary of Adverse Events (Safety Population)

Adverse Event Category	n (%) [no. of events]	
	Placebo (n = 601)	Favipiravir (n = 610)
Any Adverse Event	89 (14.8%) [160]	84 (13.8%) [149]
Serious Adverse Event	14 (2.3%) [17]	12 (2.0%) [16]
CTCAE Grade 3 or 4 TEAE	17 (2.8%) [18]	14 (2.3%) [18]
Related Adverse Event	20 (3.3%) [25]	14 (2.3%) [18]
Related Serious Adverse Event	2 (0.3%) [2]	0
Related CTCAE Grade 3 or 4 TEAE	2 (0.3%) [2]	1 (0.2%) [1]
Adverse Event Leading to Treatment Discontinuation	7 (1.2%) [10]	9 (1.5%) [14]
Adverse Event Leading to Study Discontinuation	9 (1.5%) [11]	7 (1.1%) [9]
Adverse Event Leading to Death*	1 (0.2%) [4]	0
Most Common Adverse Events by PT**		
Nausea	5 (0.8%) [7]	8 (1.3%) [9]
Cough	5 (0.8%) [5]	7 (1.1%) [7]
Dizziness	10 (1.7%) [10]	5 (0.8%) [5]
Most Common Serious Adverse Events by PT***		
COVID-19 Pneumonia	5 (0.8%) [5]	5 (0.8%) [5]
Pneumonia	1 (0.2%) [1]	3 (0.5%) [3]
COVID-19 Worsening	3 (0.5%) [3]	2 (0.3%) [2]
Dyspnea	2 (0.3%) [2]	1 (0.2%) [1]
Blood Uric Acid % Increase from Baseline****	6.6% (21.2)	30.1% (51.6)
Alanine Aminotransferase % Increase from Baseline****	16.4% (94.6)	27.3% (95.0)

Aspartate Aminotransferase % Increase from Baseline****	-1.1% (41.1)	9.3% (93.2)

*1 subject in the placebo group died as a result of COVID-19 pneumonia, acute respiratory failure, pneumomediastinum, and hypoxia.

**reported in ≥1% of patients, overall

***reported in ≥0.2% of patients, overall

****Mean (SD)

FIGURE LEGENDS

Figure 1. Study Flow Diagram

Figure 2. Efficacy of Favipiravir as an Outpatient Treatment for Patients with Early Mild to Moderate COVID-19 (Modified Intent-to-Treat Population)

Figure 2A. Sustained Clinical Recovery and Progression to Severe COVID-19 Overall and Stratified by Patient's Characteristics

Figure 2B. Time to Sustained Clinical Recovery, Favipiravir vs. Placebo

Figure 3. Time to Negative Conversion of Detectable SARS-CoV-2 Viral RNA in RT-PCR Assays of Saliva (Modified Intent-To-Treat Population). P=0.94.

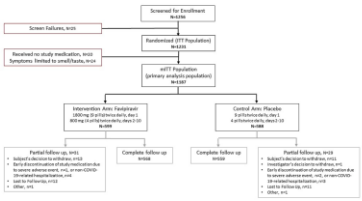

Figure 1
59x33 mm (x DPI)

Patient Characteristic	Time to Sustained Clinical Recovery (Days) [Median (95% CI)]			Progression to Severe COVID-19 (Proportion [95% CI]) (Narrow definition*)		
	Placebo (n = 588)	Favipiravir (n = 599)	p-value **	Placebo	Favipiravir	p-value ***
Overall	7 (6, 8)	7 (7, 8)	0.80	0.019 (0.008, 0.030)	0.018 (0.008, 0.029)	0.97
Age Group						
<60 years	7 (6, 8)	7 (6, 7)	0.42	0.020 (0.008, 0.032)	0.020 (0.008, 0.032)	1.00
≥60 years	8 (6, 9)	9 (7, 10)	0.19	0.012 (0.00, 0.066)	0.011 (0.00, 0.058)	1.00
Geographical Region						
North America	7 (6, 8)	7 (7, 8)	0.95	0.018 (0.007, 0.029)	0.018 (0.007, 0.029)	0.98
South America	6 (5, 8)	6 (4, 7)	0.47	0.033 (0.001, 0.172)	0.029 (0.001, 0.149)	1.00
Race						
White Race Group	7 (6, 8)	7 (7, 8)	0.98	0.018 (0.006, 0.030)	0.021 (0.008, 0.033)	0.80
Non-White Race Group	7 (6, 8)	7 (5, 8)	0.67	0.021 (0.003, 0.073)	0.009 (0.00, 0.48)	0.60
Serostatus at Enrollment						
Seronegative	7 (6, 8)	7 (7, 8)	0.85	0.022 (0.008, 0.037)	0.026 (0.011, 0.040)	0.76
Seropositive	7 (6, 8)	7 (6, 8)	0.55	0.006 (0.00, 0.032)	0.00 (0.00, 0.023)	1.00
Days from First Positive SARS-CoV-2 Test to Enrollment						
≤2 days	7 (6, 8)	7 (7, 8)	0.50	0.015 (0.005, 0.026)	0.019 (0.007, 0.031)	0.65
2-5 days	6 (5, 9)	7 (6, 10)	0.34	0.045 (0.009, 0.127)	0.014 (0.00, 0.076)	0.35
Risk-Status for COVID-19 Progression at Enrollment						
High Risk	7 (6, 8)	7 (7, 8)	0.57	0.024 (0.010, 0.038)	0.021 (0.008, 0.034)	0.76
Low to Intermediate Risk	7 (6, 8)	7 (6, 8)	0.59	0.00 (0.00, 0.027)	0.008 (0.00, 0.042)	0.49
% Increase from Baseline in Uric Acid at Day 10/EOT						
≥10% from baseline	7 (6, 8)	6 (6, 7)	0.23	--	--	--
<10% from baseline	7 (6, 8)	7 (7, 8)	0.29	--	--	--

*Defined as the occurrence from study Day 1 onward of an emergency department visit or hospitalization for COVID-19 worsening OR shortness of breath OR death.
**P-values were based on a two-sided Gehan-Wilcoxon test, comparing the 2 treatment groups.
***P-values were based on a two-sided Chi-square test, comparing the 2 treatment groups.
-- analysis was not performed.

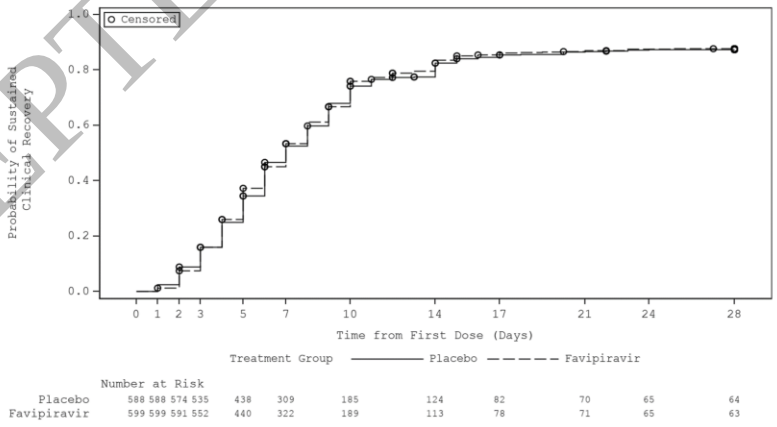

Figure 2
105x127 mm (x DPI)

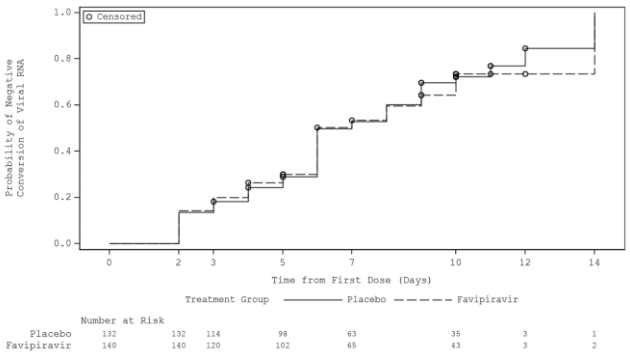

Figure 3

84x48 mm (x DPI)