Should favipiravir be used in the treatment of COVID-19?

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KEY FINDINGS

In one randomized controlled trial, Favipiravir, compared to Arbidol, did not show significant difference in the clinical recovery rate for patients with moderate to severe COVID-19 infections. In one non-randomized open-label trial, Favipiravir significantly reduced viral clearance with higher chest CT scan improvement rates compared to Lopinavir/Ritonavir in patients with non-severe COVID-19. However, both studies have serious methodologic issues and results should be interpreted with caution.

- Favipiravir (6-fluoro-3-hydroxy-2-pyrazinecarboxamide, T-705, Avigan) is an antiviral drug previously approved as treatment for influenza virus in Japan in 2014 [1] and is currently undergoing several clinical trials as treatment for COVID-19.
- Favipiravir (FPV) selectively inhibits the RNA-dependent RNA polymerase (RdRp) of the influenza virus thus inhibiting viral replication [2]. As a prodrug, favipiravir, was shown to effectively inhibit the SARS-COV-2 infection in clinical isolates *in vitro* [3].
- In one unpublished open-label randomized controlled trial, there was no significant difference in the clinical recovery rate for favipiravir compared to arbidol for patients with moderate to severe COVID-19. In the subgroup of moderate COVID-19 patients, there was borderline significance favoring benefit in the favipiravir group [4]. In an unpublished open-label non-randomized trial, compared to the combination drug Lopinavir/Ritonavir (LPV/RTV), Favipiravir (FPV) showed earlier viral clearance (4 days vs 11 days) and higher chest CT scan improvement rate (91% vs 62%) for non-severe COVID-19 patients [5]. However, both studies have serious methodologic issues and results should be interpreted with caution.
- For COVID-19 patients, adverse reactions for favipiravir include diarrhea, liver and kidney injury, elevated serum uric acid and psychiatric symptoms [4,5]. In other studies, it was well tolerated in humans [6] but may cause prolongation of QTc interval at higher doses [7]. Teratogenic effects were seen in animal studies [6].
- There are 23 ongoing clinical trials on favipiravir with results expected between May 2020 to April 2021.
- As of this writing, Favipiravir has not been recommended as routine treatment for COVID-19 in any guidelines [8-12].

RESULTS

This review included two unpublished clinical trials in China [4,5] and 23 ongoing clinical trials globally. Characteristics of the included studies are seen in Table 1 and ongoing clinical trials are outlined in Table 2.

An unpublished open-label randomized controlled trial conducted by Chen et al. in Wuhan, China showed there was no significant difference between the clinical recovery rate after 7 days for moderate-severe cases for the two groups ($p = 0.1396$, computed RR 0.80, 95% CI 0.60, 1.08). In the subgroup analysis, there was also no significant difference seen for severe cases ($p = 0.4712$, RR 0.94, 95% CI 0.84, 1.06). For moderate COVID-19 patients, there was borderline significance favoring benefit in the clinical recovery rate for Favipiravir compared to arbidol ($p = 0.0199$, RR 0.65, 95% CI 0.44, 0.94). There was also significant time of fever reduction, shorter cough relief ($p < 0.0001$) and prevention of new-onset dyspnea ($p < 0.0174$) in the favipiravir group. Result for patients with hypertension and/or diabetes was not statistically significant ($p = 0.7704$ RR 0.93, 95% CI 0.58, 1.50). For adverse events, there was no significant difference between the cumulative adverse events for the two groups ($p = 0.1410$). However, elevated serum uric acid level was significantly more common in patients in the favipiravir group than those in the arbidol group ($p = 0.0014$, RR 5.52, 95% CI 1.65,18.44). There were no significant differences between the two groups on abnormal liver function tests, psychiatric and digestive tract symptoms. All adverse reactions resolved upon patients' hospital discharge.

The validity issues identified in this study were due to non-blinding and difference in the baseline characteristics among the participants. There were more patients >65 years old in the arbidol group but there were more patients who have severe cases in the favipiravir group. Other limitations were the lack of definition for standard care or routine therapy and the difference in the methods of diagnosing the patients. The potential bias seems to favor the Arbidol group.

The unpublished open-label non-randomized trial conducted by Cai et al. in Shenzen, China showed that viral clearance for patients was significantly shorter for the Favipiravir (FPV) group at 4 days (IQR: 2.5–9 days) compared to the Lopinavir/Ritonavir (LPV/RTV) group at 11 days (IQR: 8–13 days) ($p < 0.001$). For improvement based on Chest CT Scan, improvement rates were significantly higher only at Day 14 after treatment for FPV (32/35 or 91.4%) compared to LPV/RTV (28/45 or 62.2%) ($p = 0.004$, RR 0.23, 95% CI 0.07, 0.71). The total number of adverse reactions in the FPV arm was significantly lower than in the LPV/RTV arm ($p < 0.001$, RR 0.21, 95% CI 0.08, 0.54). The adverse reactions recorded for FPV were diarrhea (n = 2), liver injury (n = 1) and poor diet (n = 1).

Validity issues due to the lack of randomization and allocation concealment, non-blinding and difference in the baseline characteristics of the participants threaten the result of the study. The selection bias favored Favipiravir, because they had a younger population and patients in the LPV/RTV group had more pronounced leukopenia and higher CRP results which may indicate that there were more patients with potentially worse conditions compared to the FPV group. A multivariate analysis showed that antiviral therapy was an independent factor affecting chest CT scan and viral clearance.

CONCLUSION

Based on two unpublished clinical trials, Favipiravir may be potentially beneficial for patients with moderate COVID-19 infections. In one open-label randomized controlled trial, there was no significant difference in the clinical recovery rate for Favipiravir compared to Arbidol for moderate and severe COVID-19 cases but showed borderline significance favoring benefit in the subgroup of moderate COVID-19 patients. In the other study, Favipiravir (FPV) showed earlier viral clearance and higher chest CT scan improvement rate for non-severe COVID-19 patients compared to combination drug Lopinavir/Ritonavir (LPV/RTV). However, both studies have serious methodologic issues and results should be interpreted with caution. No serious or life-threatening adverse effects were noted after giving favipiravir but significant elevation of serum uric acid was documented in one clinical trial. High-quality randomized controlled trials are still warranted to strengthen the recommendation for favipiravir use in COVID-19.

Declaration of Conflict of Interest

No conflict of interest

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Table 1. Characteristics of included studies

No.	Title/Author	Study design	Country	Population	Intervention Group(s)	Comparison Group(s)	Outcomes	Key findings
1	Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial Chen C, Huang J, Cheng Z, Wu J, Chen S, Zhang Y, et al.	Multi-center, open-label, randomized controlled trial	Wuhan, China	Adult patients (> 18 years old) with COVID-19 (N = 236) Exclusion: elevated ALT/AST >6x or Child Pugh C, severe patients whose expected survival time<48 hours .	Favipiravir group (n = 116) Routine treatment + famiravir tablets (1600 mg/time on the first day, twice a day; 600 mg/time from the second day to the end of the experiment, twice a day). Course of treatment 7-10 days but may be extended according to researcher's judgment.	Arbidol group (n = 120) Routine therapy + arbidol (200 mg each time, 3 times a day, from the first day to the end of the trial). Course of treatment 7-10 days but may be extended according to researcher's judgment.	Primary outcome: Clinical recovery rate at 7 days or end of treatment, which was stratified as ordinary patients with COVID-19, critical patients with COVID-19, COVID-19 patients with hypertension and/or diabetes. Secondary outcomes: fever reduction, cough relief, auxiliary oxygen therapy or noninvasive mechanical ventilation, rate of respiratory failure Safety outcome: adverse events (abnormal liver function tests, serum uric acid, psychiatric symptoms, digestive tract reactions)	There was no significant difference between the clinical recovery rate after 7 days for the two groups ($p = 0.1396$). For moderate cases, there is a statistically significant difference for Favipiravir compared to arbidol ($p = 0.0199$) with Favipiravir showing beneficial results (RR 0.65, 95% CI 0.44 to 0.94). No significant difference was seen for severe cases ($p = 0.4712$, RR 0.94, 95% CI 0.84 to 1.06). Result for patients with hypertension and/or diabetes was not statistically significant ($p = 0.7704$) and were inconclusive (RR 0.93, 95% CI 0.58 to 1.50). For moderate COVID-19 patients and those with hypertension and/or diabetes, the time of fever reduction and cough relief in the favipiravir group was significantly shorter than that in the arbidol group ($p < 0.0001$). No significant difference was observed on the need for O2 support or noninvasive mechanical ventilation between the two groups but Favipiravir was beneficial in preventing new-onset dyspnea ($p = 0.0174$, RR 0.30, 95% CI 0.10 to 0.87). For adverse events, no significant difference between the cumulative adverse events for the two groups ($p = 0.1410$) but elevated serum uric acid level was significantly higher in the FPV group ($p = 0.0014$, RR 5.52, 95% CI 1.65 to 18.44). Adverse reactions resolved upon patient's hospital discharge.
2	Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study Cai, M. Yang, D. Liu et al	Open-label non-randomized trial	Shenzhen, China	Laboratory-confirmed COVID-19 patients aged 16-75 years old (N=80) Exclusion criteria: severe clinical condition,	Favipiravir (FPV) group FPV + IFN-α1b 60 μg + standard care (n=35)	Lopinavir (LPV)/Ritonavir (RTV) group LPV/RTV + IFN-α1b 60 μg + standard care	Viral clearance Improvement of chest CT scan on D14 after treatment	Viral clearance for patients was significantly shorter for the FPV group at 4 days (IQR: 2.5–9 days) compared to the LPV/RTV group at 11 days (IQR: 8–13 days) ($p < 0.001$).

				respiratory failure, shock, chronic liver and kidney disease	FPV 1600 mg twice daily on Day 1 and 600 mg twice daily on Days 2–14, continued until the viral clearance was confirmed or until 14 d had passed.	(n=45) LPV 400 mg/RTV 100 mg twice daily, continued until the viral clearance was confirmed or until 14 d had passed.		For improvement on Chest CT Scan, there were no significant differences for Days 4 and 8 between the two groups. But improvement rates were significantly higher for FPV (32/35 or 91.4%) compared to LPV/RTV (28/45 or 62.2%) (p = 0.004, computed RR 0.23, 95% CI 0.07 - 0.71). Adverse reactions were lower in the FPV group (4/35 or 11.43%) versus LPV/RTV group (25/45 or 55.56%) and were statistically significant ($p < 0.001$, computed RR 0.21, 95% CI 0.08 – 0.54). The adverse reactions recorded for FPV were diarrhea (n = 2), liver injury (n = 1) and poor diet (n = 1). For the LPV/RTV group, adverse reactions were nausea (n = 6), vomiting (n = 5), diarrhea (n = 5),rash (n = 4), liver injury (n = 3), chest tightness and palpitations (n = 2).

Table 2. Characteristics of clinical trials

No.	Clinical Trial ID / Title	Status	Start and estimated primary completion date	Study design	Country	Population	Intervention Group(s)	Comparison Group(s)	Outcomes
1	NCT04319900 / ChiCTR2000030987 Clinical Trial of Favipiravir Tablets Combine With Chloroquine Phosphate in the Treatment of Novel Coronavirus Pneumonia	Recruiting	03/05/20 – 04/30/20	Multi-center, three-armed, RCT, double-blind	China	Adults 18-75 years old w/ COVID-19 (n = 150) Inclusion: Course of illness not more than 14 days or if disease >14 days need to fulfill criteria Exclusion: severe illness (i.e. respiratory failure, shock, organ failure requiring ICU, clinical prognostic non-survival)	Favipiravir tablets + Chloroquine phosphate tablets - Favipiravir (1600mg BID day 1; 600mg BID day 2-10), max 10 days oral - Chloroquine phosphate (1000mg BID day 1; 500mg OD day 2-3; 250mg OD day 4-10), max 10 days, oral Favipiravir tablets group (1600mg BID day 1; 600mg BID day 2-10), max 10 days oral	Placebo group Placebo for favipiravir tablets is produced by Zhejiang Haizheng pharmaceutical co, LTD. Placebo for chloroquine phosphate tablets is produced by the Chinese people's liberation army academy of military science military medical research institute production.	Time of improvement/ recovery of respiratory symptoms in 10 days Number of days virus nucleic acid shedding in 10 days Frequency of improvement or recovery of respiratory symptoms in 10 days

2	NCT04310228 / ChiCTR2000030894 Favipiravir Combined With Tocilizumab in the Treatment of Corona Virus Disease 2019-A Multicenter, Randomized and Controlled Clinical Trial Study	Recruiting	03/08/20 – 05/20	Multi-center RCT, open-label	China	Adult > 18 w/ COVID-19 (clinically diagnosed, with increased IL-6) (n = 150) Exclusion: severe illness (i.e. respiratory failure, shock, organ failure requiring ICU, predicted clinically without hope of survival; ALT or AST > 5 times of upper limit of normal, tuberculosis, and definite bacterial and fungal infections; organ transplant patients	Favipiravir with tocilizumab - Favipiravir (1600mg BID day 1; 600mg BID day 2-7), oral - Tocilizumab (4 ~ 8mg/kg (up to a maximum of 800mg per dose)), IV	Favipiravir group (1600mg BID day 1; 600mg BID day 2-7), oral Tocilizumab group (4 ~ 8mg/kg (up to a maximum of 800mg per dose)), IV	Clinical cure rate in 3 months (i.e. viral load negative for 2 consecutive nucleic acid tests, improvement in lung image, normal body temperature for > 3 days, improved clinical manifestation)
3	NCT04303299 Various Combination of Protease, Inhibitors, Oseltamivir, Favipiravir and Hydroxychloroquine for Treatment of COVID19: A Randomized Control Trial (THDMS-COVID19)	Not yet recruiting	03/15/20 – 10/31/20	Multi-center, RCT, open-label	Thailand	COVID 19 patients 16 – 100 years old (n=320) Inclusion Reliable for compliance for taking medication and can record effects of medication Exclusion: For elective surgery; used other antiviral agents	Multiple antiviral drug combinations including Favipiravir	Conventional Quarantine for mild COVID19	SARS-CoV-2 eradication time up to 24 weeks (i.e. eradication of nasopharyngeal SARS-CoV-2)
4	ChiCTR2000030113 Randomized controlled trial for safety and efficacy of Favipiravir in the treatment of novel coronavirus pneumonia (COVID-19) with poorly responsive ritonavir/ritonavir	Recruiting	2/22/20-5/31/20	Randomized controlled trial	Shenzhen, Guangdong, China	COVID-19 patients 16-75 years old Exclusion Patients with chronic liver and kidney disease and reaching end-stage	Favipiravir (n = 15)	Ritonavir/Ritonavir (n = 15)	Blood routine tests, liver function examination, renal function examination, blood gas analysis, Chest CT examination
5	ChiCTR2000029600 Clinical study for safety and efficacy of Favipiravir in the treatment of novel coronavirus	Recruiting	01/30/20 – 4/29/20	Non-randomized controlled trial	Shenzhen, Guangdong China	COVID-19 patients 16-75 years old Exclusion Patients with chronic liver and kidney disease and reaching end-stage	Favipiravir + Alpha-interferon atomization (n = 30) Lopinavir and Ritonavir + Alpha-interferon atomization (n = 30)	Alpha-interferon atomization (n = 30)	Primary Declining speed of novel coronavirus by PCR Negative time of novel coronavirus by PCR

	pneumonia (COVID-19)								Incidence rate of chest imaging Incidence rate of liver enzymes Incidence rate of kidney damage
6	ChiCTR2000029548 Randomized, open-label, controlled trial for evaluating of the efficacy and safety of Baloxavir Marboxil, Favipiravir, and Lopinavir-Ritonavir in the treatment of novel coronavirus pneumonia (COVID-19) patients	Not yet recruiting	02/04/20 – 06/03/20	Randomized, open-label, controlled trial	Hangzhou, Zheujang China	Adult COVID-19 patients 18-75 years old (N = 30) Exclusion Severe disease, known kidney and liver dysfunction	Baloxavir marboxil (80mg on day1,80mg on day4; and 80mg on day7 as necessary. No more than 3 times administration in total.) (n = 10) Favipiravir (600 mg TID with 1600mg first loading dosage for no more than 14 days.) (n = 10) Lopinavir-Ritonavir (200mg/50 mg), twice daily, for 14days.) (n = 10)		Time to viral negativity by PCR Time to clinical improvement (time from start of study drug to hospital discharge or to NEWS2 < 2 for 24 hours)
7	ChiCTR2000029544 A randomized controlled trial for the efficacy and safety of Baloxavir Marboxil, Favipiravir tablets in novel coronavirus pneumonia (COVID-19) patients who are still positive on virus detection under the current antiviral therapy	Not yet recruiting	02/04/20 – 05/31/20	Randomized controlled trial	Zhejiang China	Adult COVID-19 patients 18-75 years old (n = 30) Exclusion Severe disease, known kidney and liver dysfunction	Current antiviral treatment + Baloxavir marboxil tablets (n = 10) Current antiviral treatment + Favipiravir tablets (n = 10)	Current antiviral treatment (n = 10)	Time to viral negativity by RT-PCR Time to clinical improvement
8	JPRN-jRCTs031190226 A prospective multi-center open trial to evaluate the safety and efficacy of favipiravir in patients infected with COVID-19	Recruiting		Prospective multi-center open trial	Gunma Japan	COVID-19 patients ≥ 20 years old (n = 50)	Favipiravir (oral administration)		Primary C-reactive protein before and after treatment Secondary Disappearance rate of COVID-19

9	JPRN-jRCTs041190120 Multicenter, open-label, randomized trial of favipiravir in asymptomatic and minimally symptomatic patients infected with SARS-CoV2 to evaluate viral load reduction	Recruiting		Multi-center, open-label, randomized trial	Aichi Japan	COVID-19 patients ≥ 16 years old Exclusion: 7 days or more since the onset of COVID-19, as diagnosed by fever, pneumonia or other relevant findings, liver and kidney dysfunction, History of hereditary xanthine oxidase deficiency, history of hypouricemia (less than 1 mg/dL) or xanthine urolithiasis, gout	Immediate favipiravir arm (Administered orally between Day 1 and Day 10, 1800 mg twice a day on Day 1 followed by 800 mg twice a day from Day 2) Delayed favipiravir arm (Administered orally between Day 6 and Day 15, 1800 mg twice a day on Day 6 followed by 800 mg twice a day from Day 7)	No treatment control	Primary Proportion of subjects with clearance of SARS-CoV2 in nasopharyngeal swab on Day 6 Secondary Proportion of subjects with 90% reduction in SARS-CoV2 copy number in nasopharyngeal swab between Day 1 and Day 6 Change of SARS-CoV2 copy number in nasopharyngeal swab
10	NCT04336904 Clinical Study To Evaluate The Performance And Safety Of Favipiravir in COVID-19	Active, not recruiting	03/25/20-07/2020	Multi-center, randomized, double-blind, placebo-controlled (1:1) clinical study	Italy	Adult moderate COVID-19 patients, 18-75 years old (n=100) Exclusion: cannot swallow drug of underwent bowel resection that interferes with drug absorption, severe liver or renal disease, hyperuricemia, SpO2 ≤93%, pregnancy and lactation	Favipiravir Day 1: 1800mg, BID; Day 2 and thereafter: 600mg, TID, for a maximum of 14 days	Placebo Day 1: 1800mg, BID; Day 2 and thereafter: 600mg, TID, for a maximum of 14 days.	Primary Clinical Recovery Secondary Negative RT-PCR nucleic acid test Deterioration/aggravation of pneumonia Fever resolution, relief of cough, dyspnea Need for O2 support ICU admission Mortality
11	NCT04358549 Study of the Use of Favipiravir in Hospitalized Subjects With COVID-19	Recruiting	04/17/20 – 08/2020	Open label, randomized, controlled, multicenter Phase 2 proof-of-concept study	USA	Adult COVID-19 patients, 18-80 years old, within 48 hours if hospitalization, PCR positive (n=50) Exclusion: Concomitant bacterial respiratory infection, hyperuricemia, use of adrenocorticosteroids, serious chronic disease, renal disease on dialysis, severe liver impairment, alcohol or drug abuse, psychiatric disease, ventilator use at study entry	Favipiravir + Standard of Care Day 1: 1800 mg favipiravir BID Day 2-14: followed by 1000 mg BID favipiravir (800 mg BID for subjects with Child-Pugh A liver impairment)	Standard of Care	Primary Viral clearance Secondary Clinical recovery Clinical effect using National Early Warning Score 2 (NEWS2) Characterized the pharmacokinetics (PK) of favipiravir in plasma
12	NCT04359615	Not yet recruiting	04/20/20 – 05/03/20	Randomized, double-blind, controlled, clinical trial	Tehran, Iran	Adult, symptomatic, COVID-19 patients, RT-PCR confirmed, SpO2 ≤93% (n=40)	Favipiravir + Hydroxychloroquine	Hydroxychloroquine	Primary Clinical improvement Secondary

	Favipiravir in Hospitalized COVID-19 Patients (FIC)					Exclusion: Prolonged QT or PR intervals, heart blocks and arrhythmias, pregnancy and lactation, alcohol or drug addiction, liver enzymes > 5 times upper limit of normal			Mortality Oxygen saturation (SpO2) Mechanical ventilation use Duration of hospitalization Serious adverse events
13	NCT04349241 Efficacy and Safety of Favipiravir in Management of COVID-19 (FAV-001)	Not yet recruiting	04/20/20 – 10/01/20	Phase 3 Randomized controlled interventional trial	Cairo, Egypt	Adult, laboratory-confirmed COVID-19 patients with mild to moderate symptoms, 18-80 years old, (n=100) Exclusion: Severe disease, pregnancy and lactation	Favipiravir (n=50) 3200 mg (1600 mg 12 hourly) loading dose on day-1 followed by 1200 mg maintenance dose (600 mg 12 hourly daily) on day-2 to day-10	Standard of care (n=50) Oseltamivir 75 mg 12 hourly for 5-10 days and hydroxychloroquine 400mg 12 hourly day -1 followed by 200mg 12 hourly daily on day- 2 to day-5-10	Primary Viral clearance Clinical improvement Secondary Radiologic improvement
14	NCT04376814 Safety and Efficacy of Hydroxychloroquine + Favipiravir Drug Regimen in Comparison With Hydroxychloroquine + Kaletra on the Need for Intensive Care Unit Treatment in Patients With COVID-19	Enrolling by invitation	03/29/20 – 04/04/20	open-label, non-randomized clinical trial	Tehran, Iran	COVID-19 patients, 16 to 100 years old, diagnosed by chest CT scan or RT-PCR requiring hospitalization (n=40) Exclusion Chronic liver or renal failure, HIV, GI bleeding, pregnancy or lactation, QT interval > 500ms	Hydroxychloroquine Plus Favipiravir Stat dose of 1600mg Favipiravir tablets for the first time, and for next time they will be given 600mg of favipiravir tablets three times per day for 7 days, plus 200mg of Hydroxychloroquine two times per day will be given to patients for 7 days	Hydroxychloroquine Plus Kaletra Stat dose of 400mg Hydroxychloroquine tablets plus 200/50 mg of Kaletra two times per day for seven days	Primary ICU admission Secondary Mortality Length of hospital stay Radiologic treatment response Treatment response (CBC, CRP) Resolution of fever, dyspnea O2 saturation without O2 support Need for O2 support Adverse drug reaction
15	NCT04333589 Corona Virus Disease 2019 Patients Whose Nucleic Acids Changed From Negative to Positive	Recruiting	04/01/20 – 06/01/20	multi-center, randomized controlled, open label trial	China	Adult COVID-19 patients, 18-80 years old, diagnosed by nucleic acid test (n=210) Exclusion pregnancy or lactation, unstable liver, kidney or heart disease, mental disorder, substance abuse	Favipiravir Day 1: 1600mg each time, twice a day Day 2-7: 600mg each time, twice a day. Oral administration, not more than 14 days	Regular treatment Treatments other than lopinavir and ritonavir, chloroquine phosphate, hydroxychloroquine sulfate, arbidol, and colomycin can be given.	Primary Viral nucleic acid test negative conversion rate Secondary Clinical cure
16	NCT04373733 EudraCT Number: 2020-001449-38 A Randomised Controlled Trial of Early Intervention in COVID-19: Favipiravir Verses HydroxycholorquiNe & Azithromycin & Zinc	Not yet recruiting	05/01/20 – 03/31/21	randomized, open label study	London, United Kingdom	Adult suspected or confirmed COVID-19 patients (n=450) Exclusion pregnancy or lactation, hepatic or renal impairment, retinopathy, G6PD deficiency. Myasthenia gravis, QT prolongation, cannot take medication via oral or NGT route, immunocompromised patients	Favipiravir Day 1: 1800mg twice per day Days 2-10: 800mg twice per day Hydroxychloroquine, azithromycin, zinc & standard of Care	Standard of care	Primary Clinical improvement Secondary Clinical status Overall survival Time to improvement by two points on the NEWS score Admission to ICU Requirement for mechanical ventilation, non-invasive ventilation

	vErsEs Standard CaRe (PIONEER)						Hydroxychloroquine: Day 1 400mg twice per day, Days 2-10 200mg twice per day; Azithromycin: Day 1-3 250mg once per day; Zinc-sulfate: Days 1-10 125mg twice per day		Incidence of bacterial/fungal infections Adverse event
17	NCT04346628 Oral Favipiravir Compared to Standard Supportive Care in Subjects With Mild COVID-19	Not yet recruiting	04/2020 – 04/2021	Randomized, Open Label Study	California. USA	Adult, laboratory-confirmed COVID-19 patients either asymptomatic or mild disease (n=120) Exclusion Bacterial respiratory infection, hyperuricemia, adrenocorticosteroids, serious chronic disease, renal insufficiency on dialysis, liver impairment, alcohol or drug abise, psychiatric illness	Favipiravir Day 1: 1800 mg on the first dose Day 2-10: 800 mg twice daily for the next 9 days	Standard of care	Primary Cessation of viral shedding Secondary Clinical worsening Viral load Development of SARS-CoV-2 antibodies Cessation of symptoms Pharmacokinetics of favipiravir
18	NCT04351295 Efficacy of Faviprevir in COVID-19 Treatment	Not yet recruiting	04/17/20 – 12/01/30	Randomized Open Label Study	Egypt	COVID-19 patients (n=40) Exclusion Allergy or contraindications	Favipiravir	Placebo	Cure rate
19	NCT04356495 Treatments to Decrease the Risk of Hospitalization or Death in Elderly Outpatients With Symptomatic SARS-CoV-2 Infection (COVID-19) (COVERAGE)	Not yet recruiting	04/15/20 – 07/31/20	Randomized controlled, open-label, multi-arm multi-stage trial	Bordeaux, France	Adult COVID-19 patients, 65 years old and older, positive virology test, onset of symptoms less than 3 days, non-hospitalized (n=1057) Exclusion Dementia, Long QT syndrome, pacemaker, bradycardia, hyperkalemia, severe disease, treatment with medications that can interfere with drugs under study	Hydroxychloroquine (Plaquenil® 200 mg) Day 1: 2 tablets twice a day on the first day Day 2-10: 2 tablets daily Imatinib (Imatinib TEVA® 400 mg) 1 tablet daily for 10 days Favipiravir (Avigan® 200 mg) Day 1: 12 tablets twice a day Day 2-10: 6 tablets twice a day Telmisartan (Micardis® 20 mg) 1 tablet daily for 10 days	Vitamins ("AZINC forme et vitalité®") 2 tablets daily for 10 days	Primary Occurrence of hospitalization Death Secondary Hospitaliztion Cause of death ICU admission Negative RT-PCR test Loss of autonomy Hematologic markers (CBC, Prothrombin, INR) Biochemical marker (ferritin, serum creatinine, urea, sodium, potassium, chlorine, calcium, magnesium, albumin, bicarbonates / tCO2, LDH, CPK, ASAT, ALAT, uricemia) Inflammatory markers Adverse events Plasma concentration

20	NCT04345419 A Real-life Experience on Treatment of Patients With COVID 19	Not yet recruiting	04/30/20 – 12/2029	Randomized, clinical trial	Egypt	COVID-19 patients (n=120) Exclusion Allergy or contraindications	Chloroquine Favipiravir Nitazoxanide Ivermectin Niclosamide Other drugs as oseltamivir or combination of any of the above treatment	None	Decrease in viral load
21	IRCT20150808023559N20 Efficacy of hydroxychloroquine plus favipiravir drug regimen in comparison with hydroxychloroquine plus kaletra in hospitalized patients with COVID-19	Recruiting	04/29/20 – 07/31/20	Randomized, open-label	Iran	COVID-19 patients by chest CT scan or positive RT-PCR test; Requiring hospitalization; 16-100 years old (n=100) Exclusion Receiving other antiviral medications; renal failure; HIV; Pregnancy and Lactation	Favipiravir plus Hydroxychloroquine Stat dose of eight 200 mg Favipiravir tablets (total 1600 mg) followed by Favipiravir 600 mg three times a day for 7 days plus Hydroxychloroquine 200mg two times per day for 7 days.	Kaletra plus Hydroxychloroquine Stat dose of two 200 mg Hydroxychloroquine tablets (total 400 mg) followed by Kaletra(Lopinavir/Ritonavir) 200/50 mg two times a day for 7 days.	Mortality Length of stay in hospital
22	IRCT20151227025726N14 Evaluation the effects of Favipiravir in COVID-19 patients	Recruiting	04/05/20 – 07/07/20	Prospective clinical trial with parallel randomized groups	Iran	COVID-19 patients by RT-PCR test, 18 years old and above, O2 sats < 93%, fever > 72 hours, bilateral pulmonary infiltration Exclusion: Chronic kidney Disease, Acute kidney injury, Pregnancy or breastfeeding, history chronic liver disease, mild COVID-19, critical COVID-19	Favipiravir 1600 mg BID for one day and then 600 mg BID for totally 7 days Supportive care	Lopinavir-ritonavir 200/50 mg two tablets BID for 7 days Supportive care	Resolution of fever, cough, dyspnea Length of hospital stay Change in lung findings based on radiography
23	JPRN-JapicCTI-205238 Phase 3 Clinical Study of Favipiravir in Patients with COVID-19 Non-Severe Pneumonia	Recruiting	03/31/20 – 06/30/20	Multicenter, Adaptive, Randomized, Placebo-Controlled, Comparative Study	Japan	Adult hospitalized, laboratory-confirmed, COVID-19 patients, aged 20-74 years old, with lung involvement in chest imaging (n=96) Exclusion: more than 10 days since onset of fever, pregnancy or lactation, severe hepatic and renal impairment	Favipiravir	Placebo	Primary Time to alleviation of body temperature, SpO2, and chest image findings, and time to SARS-CoV-2 RT-PCR negativity. Secondary: Adverse events