Chen C, Huang J, Yin P, et al. Favipiravir versus arbidol for COVID-19: a randomized clinical trial. April 2020. Available from: https://www.medrxiv.org/content/10.1101/2020.03.17.20037432v3. Accessed April 10, 2020.

BACKGROUND – THE STUDY QUESTION?		
Background	• Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus that is highly contagious, spreads rapidly, and causes mild to severe respiratory illness (COVID-19), including pneumonia and acute respiratory distress syndrome. • Arbidol is a potent, broad-spectrum antiviral approved in Russia and China for treatment and prophylaxis of influenza viruses and is recommended for COVID-19 treatment in Chinese guidelines. It has also shown activity against arthropod-born flaviviruses, such as the Zika and West Nile viruses. • Favipiravir is a broad-spectrum antiviral agent that selectively and potently inhibits the RNA-dependent RNA polymerase of RNA viruses.	
Previous trials	• Currently, there is a lack of evidence for a definitive therapeutic agent in the prevention and treatment of COVID-19 • An open-label, controlled study of 340 patients with COVID-19 showed more improvements in chest imaging and more rapid viral clearance in patients who received favipiravir versus those who did not (Cai Q, et al. doi:10.1016/j.eng.2020.03.007; study has been temporarily removed from journal)	
Why this study?	• Favipiravir has shown *in vitro* and *in vivo* animal model efficacy against RNA viruses and might provide another treatment option to patients with COVID-19	
Null Hypothesis	• There is no difference in clinical outcomes between favipiravir and arbidol for the treatment of COVID-19	
GENERAL STUDY OVERVIEW		
	Summary	Critique
Funding	• National Key Research and Development program of China	• Funder of study did not have a role in study design, operation of study, or data analysis
Trial design	• Prospective, multicenter, open-labeled, randomized superiority trial • Patients randomized 1:1	• Participants and clinicians were not blinded • Arbidol is recommended for COVID-19 treatment in Chinese guidelines
Objectives	• To determine if favipiravir can serve as an acceptable treatment option in patients with COVID-19	
Enrollment	• Patients enrolled from three hospitals in Wuhan, China • Patients were enrolled for the study between February 20, 2020 to March 12, 2020	
METHODS		
Inclusion criteria	• 18 years or older, Initial symptoms within 12 days of enrollment and diagnosed with COVID-19 pneumonia	• Clinical diagnoses without a positive nucleic acid test result for COVID-19 were included
Exclusion criteria	• Allergy to study drug • ALT/AST increased to over 6 times of normal upper range or Child-Pugh score of C • Expected survival time <48 hours • Pregnant • HIV infection • Deemed “unsuitable” by researchers	• “Unsuitable by researchers” not defined

Interventions	• Experimental group received favipiravir 1600mg twice daily on day one, then 600mg twice daily until completion • Control group received arbidol 200mg three times daily • Both groups given treatment for 7-10 days as well as supportive therapy	• Treatment duration extended to 10 days according to researchers' judgment
Monitoring	• Patients were followed by clinicians daily during hospitalization • Each primary endpoint measurements were repeated twice each day, spaced out by at least 15 minutes	• Patients were not monitored for any follow up upon discharge from hospital
Primary Endpoints	• Clinical recovery rate at 7 days or end of treatment. Defined as >72 hours recovery of body temperature (axillary temp ≤36.6°C), respiratory rate (≤24 BPM), oxygen saturation (≥98%), and cough relief	• Body temperature measurements were taken from the armpit, which provides a less accurate reading compared to oral or rectal • Defined quantitative criteria for factors in clinical recovery • Low temperature threshold for fever definition
Secondary Endpoints	• Time from randomization to fever reduction and cough relief • Rate of auxiliary oxygen therapy or noninvasive mechanical ventilation • Rate of respiratory failure • All-cause mortality	• Defined quantitative criteria for secondary endpoints
Statistical analyses	• A sample size estimate of 240 participants was based on an expected clinical recovery rate of 70% in the experimental group vs 50% in the control group with a one-sided α-level of 0.025, 80% power, and a 20% sample size increase for factors like viral shedding • 95% bilateral CI were calculated for differences between experimental group and control group. Experimental group considered superior if lower limit of CI was >0 • Secondary endpoints were calculated using T-test or Wilcoxon rank sum test for safety indicators, continuous variables, and grade variables • Chi-square test or Fisher's exact test were used for comparison between the two groups for frequency percentages of statistical description of classification indexes	• All statistical analyses were performed using SAS • Censoring performed on time to event analyses but not explained in trial protocol or manuscript
RESULTS		
Enrollment	• 236 total patients enrolled • 116 randomized to favipiravir, 120 randomized to arbidol	• Did not meet estimated sample size but power calculation demonstrated power >80%

Baseline characteristics	• Favipiravir group: 59 male /57 female, 75% <65 years old, 31% had hypertension, 12% had diabetes • Arbidol group: 51 males/69 females, 66% <65 years old, 25% had hypertension, 11% had diabetes • 98 out of 116 cases in favipiravir group classified as moderate, 18 classified as severe • 111 out of 120 cases in arbidol group classified as moderate, 9 classified as severe • 199/236 (84.32%) patients received ancillary treatments • In moderate cases, patients in the arbidol group received more antivirals (p=0.0045) and immunomodulators (p=0.0391) vs the favipiravir group	• Double the amount of severe cases in favipiravir group vs arbidol group • No statistically significant difference in baseline characteristics between groups • Patients received many other therapies including anti-infectives (viral and bacterial), steroids, Chinese herbal medicines, and immunomodulators
Primary Outcome	• 71/116 (61.21%) patients in favipiravir group vs 62/120 (51.67%) patients in arbidol group experienced clinical recovery for an overall difference in recovery rate of 0.0954 (95% CI: -0.0305, 0.2213) • For moderate cases, 70/98 (71.43%) in favipiravir group vs 62/111 (55.86%) in arbidol group experienced clinical recovery for a difference in recovery rate of 0.1557 (95% CI: 0.0271, 0.2843) • For severe cases, 1/18 (5.56%) in favipiravir group vs 0/9 (0%) in arbidol group experienced clinical recovery for a difference in recovery rate of 0.0556 (95% CI: -0.0503, 0.1614)	• Subgroup analyses of different clinical classifications suggest increased clinical recovery in moderate cases in the favipiravir group, but analyses were performed post-hoc • Did not meet expected clinical recovery rate in favipiravir group, but power calculation demonstrated power >80%
Secondary Outcomes	• All cause mortality: 0 patients for both groups • **In moderate cases**, 57 in the favipiravir group had fever at enrollment with all experiencing fever reduction by day 5 (2 patients censored) vs 65 at enrollment in the arbidol group with 54 experiencing fever reduction by day 5 (5 patients censored) (p<0.0001) • **In moderate cases**, 60 in the favipiravir group had cough at enrollment with all experiencing cough relief by day 9 vs 64 at enrollment in arbidol group with 52 experiencing cough relief by day 9 (p<0.0001) • **In moderate cases**, auxiliary oxygen therapy was required in 8/98 (8.16%) in the favipiravir group vs 19/111 (17.12%) in the arbidol group for a difference in incidence rate of -0.0895 (95% CI: -0.01781, -0.0009) • In severe cases, auxiliary oxygen therapy was required in 13/18 (72.22%) in the favipiravir group vs 8/9 (88.89%) in the arbidol group for a difference in incidence rate of -0.1667 (95% CI: -0.4582, 0.1248)	• Roughly 11% of patients had severe or critical disease; it is highly unusual that no deaths were observed • Low rates of respiratory failure (n=5) and ICU transfer (n=4) • Cough relief is a subjective endpoint, and criteria for assessment of this outcome were not provided • For cough relief in moderate cases, difference by 1 patient was found to be statistically significant; however, 12 patients in arbidol group vs 0 in favipiravir group were censored • Time to negative SARS-CoV-2 PCR listed as secondary endpoint in trial protocol but not reported in manuscript • Mean/median treatment durations in each group were not reported

Adverse Effects	• 37 adverse effects with favipiravir vs 28 with arbidol • Raised serum uric acid: 2.50% in arbidol group vs 13.79% in favipiravir group (p=0.0014) • Digestive tract reactions: 11.67% in arbidol group vs 13.97% in favipiravir group (p=0.6239) • All reported events were level 1; most resolved by discharge	• Both agents were well tolerated with only mild adverse effects reported • No reported therapy discontinuations due to adverse effects • No reported treatment for study-related adverse effects

AUTHORS' CONCLUSIONS

- Favipiravir did not improve clinical recovery rate in the total population at day 7 vs arbidol
- Favipiravir had a higher clinical recovery rate compared to arbidol in moderate cases
- Favipiravir treatment resulted in significantly shorter time to cough and fever reduction
- Adverse effects of favipiravir are mild and reversible
- In moderate COVID-19 cases, favipiravir can be considered as a possible treatment option

GENERALIZABILITY/CRITIQUE/DISCUSSION

- Arbidol is a current clinical recommendation in China, although clinical efficacy is unknown, leaving an unproven therapy to serve as the control arm
- Only 42% of patients were SARS-CoV-2 nucleic-acid-positive at day 0, but sensitivity of nucleic acid assays by throat swab sampling was a known issue in China at the time of study
- Some outcome criteria were not well defined (cough relief) or did not have optimal definitions (axillary temp ≤36.6°C)
- Patient data was only collected for at most 10 days, based on treatment recommendations from clinicians; outcomes of patients that did not experience clinical recovery in the timeframe, including ventilation requirements and mortality rates, remain unclear
- Most results did not achieve statistical significance
- Lower end of 95% CI was not greater than 0 for both overall difference in recovery rate and for difference in recovery rate of severe cases, therefore favipiravir did not demonstrate superiority to arbidol
- Small, post-hoc analyses in the severe group limit interpretation and conclusions
- Given the above critique, the ability to make meaningful conclusions concerning the role of favipiravir in the treatment of COVID-19 is severely limited