
### 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

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<th>Summary</th>
<th>Critique</th>
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<td>Funding</td>
<td>National Key Research and Development program of China</td>
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<tr>
<td>Trial design</td>
<td>Prospective, multicenter, open-labeled, randomized superiority trial</td>
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<td>Objectives</td>
<td>Patients randomized 1:1</td>
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<td>Enrollment</td>
<td>Patients randomized 1:1</td>
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<td>Patients enrolled from three hospitals in Wuhan, China</td>
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<td>Patients were enrolled for the study between February 20, 2020 to March 12, 2020</td>
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### METHODS

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<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
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<td>18 years or older, Initial symptoms within 12 days of enrollment and diagnosed with COVID-19 pneumonia</td>
<td>Allergy to study drug</td>
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<td>ALT/AST increased to over 6 times of normal upper range or Child-Pugh score of C</td>
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<td>Expected survival time &lt;48 hours</td>
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<td>Pregnant</td>
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<td>HIV infection</td>
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<td>Deemed “unsuitable” by researchers</td>
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<td>Clinical diagnoses without a positive nucleic acid test result for COVID-19 were included</td>
<td>“Unsuitable by researchers” not defined</td>
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| 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  
8 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 antivirals (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 (88.99%) 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