Title: Evaluation of Financial Conflicts of Interest and Drug Statements in the Coronavirus Disease 2019 Clinical Practice Guideline in Japan

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To the Editor (704 words)

Since its outbreak in late 2019, evidence on coronavirus disease 2019 (COVID-19) treatment has rapidly accumulated. Accordingly, many countries subsequently drafted COVID-specific clinical practice guidelines (CPGs). While CPGs allow healthcare professionals to standardize and improve patient care, inappropriate biases may arise when the authors have financial conflicts of interest (FCOI) directly related to those recommendations [1]. In Japan, the Ministry of Health, Labour and Welfare (the Ministry) funded the COVID-19 clinical practice guideline development. Originally published in March of 2020, the COVID-19 CPG has undergone multiple revisions. The most recent of these, the fifth edition, was published on May 26, 2021.

Consequently, we considered this latest version for this study [2].

We examined all COVID-19 CPG fifth edition authors and their financial relationships with pharmaceutical companies from 2017 to 2019. These data were voluntarily published by all 79 pharmaceutical companies belonging to the Japanese Pharmaceutical Manufacturers Association. However, this Association does not impose penalties for non-compliance with the guidelines mandating payment disclosure.

First, we descriptively analyzed the authors’ demographic characteristics and financial
relationships with the pharmaceutical companies manufacturing the drugs listed in the COVID-19 CPG. We also assessed the CPG management policy on FCOI. We then reviewed the statements of the COVID-19 drugs listed in the CPG and the evidence cited supporting them. Details of the methodology are summarized in Supplementary Material 1.

The 23 COVID-19 CPG authors were all male and content experts. For further details, refer to Supplementary Material 2. Twenty (87.0%) of these authors received at least one payment from a pharmaceutical company. In all, 50 (63.3%) companies made combined payments totaling $2,823,477, of which $1,915,196 (67.8%) consisted of scholarship donations, and another $908,281 (32.2%) in personal payments (Table 1). The combined 3-year average total payment per author was $122,760 (standard deviation (SD): $233,538). Additionally, payments from three of the manufacturers of the COVID-19 drugs included in the CPG (Supplementary Table 3) accounted for 8.4% ($236,294) of the total payments. Of these, Chugai Pharmaceutical Co. (the distributor of tocilizumab in Japan) contributed the most at $153,368, while FUJIFILM Toyama Chemical Co. (the manufacturer of favipiravir) paid the least at $32,574 (Table 1). Nine authors (39.1%) received at least one payment from these three companies. Since there were no COI statements in the CPG, we contacted the Ministry about its management of CPG author-related FCOI. Despite four such attempts between June and August, we have received no formal
response as of October 15, 2021.

Supplementary Material 3 provides summaries for the drugs recommended in the COVID-19 CPG. As of June 2021, of the five drugs listed in the CPG, remdesivir, dexamethasone, and baricitinib received approval for COVID-19 patient treatment in Japan. The other two, tocilizumab and favipiravir, have not. Interestingly, while tocilizumab received a mixture of positive and neutral findings for COVID-19 treatment, the CPG discouraged its use. In contrast, favipiravir received a positive assessment with the embedded description inviting participants in a Ministry sponsored observational study.

Overall, our study found significant FCOI between the government COVID-19 CPG authors and pharmaceutical companies. We further note poor management of these FCOI by the Ministry. The $39,490 average personal payments and high prevalence of CPG authors with FCOI were consistent with our previous studies[3, 4]. Although government-sponsored CPGs are reportedly more transparent and associated with less FCOI than those not sponsored by the government[1], we did not observe this with the Japanese COVID-19 CPG.

Additionally, we observed inconsistencies between the tone of recommendations and underlying
evidence supporting the use of included COVID-19 drugs. For example, the CPG recommended favipiravir without rigorous evidence supporting its efficacy. Indeed, neither the World Health Organization nor the United States National Institute of Health recommended favipiravir. In contrast, tocilizumab was not recommended despite a recent rigorous systematic review confirming efficacy for the treatment of COVID-19[5]. Interestingly, while both manufacturers of these drugs made payments to COVID-19 CPG authors, the manufacturer of tocilizumab paid more. Therefore, the discrepancies in the recommendations suggest that FCOI do not always result in potentially inappropriate recommendations.

We propose that the Ministry ensures a more transparent and rigorous approach to CPG development. This should include a more balanced author selection process, full COI disclosure, systematic evidence quality assessment, and appropriate recommendations based on established CPG development methodology.

**Funding and Acknowledgements**

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independent non-profit news organization dedicated to investigative journalism. However, none
of the entities providing financial support for this study contributed to the design, execution,
data analyses, or interpretation of study findings and the drafting of this manuscript.

Conflicts of interest

As non-financial conflicts of interest, Anju Murayama, Akihiko Ozaki, and Tetsuya Tanimoto
have several research articles related to the conflicts of interest among healthcare professionals
in Japan. Drs. Ozaki and Tanimoto received personal fees from Medical Network Systems
outside the scope of the submitted work. Dr. Tanimoto also received personal fees from Bionics
Co., Ltd, outside the scope of the submitted work.

Author Contributions:

All authors had full access to all the data in the study and take responsibility for the data’s
integrity and the accuracy of the data analysis.

Study concept and design: All authors.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: All authors.
Statistical analysis: Takanao Hashimoto and Anju Murayama

Study supervision: Anju Murayama, Akihiko Ozaki and Tetsuya Tanimoto

References


Table 1. Pharmaceutical company author payment breakdown. (n=23)

<table>
<thead>
<tr>
<th></th>
<th>All companies</th>
<th>Companies manufacturing COVID-19 drugs*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total payments, US$</strong></td>
<td>2,823,477</td>
<td>236,294</td>
</tr>
<tr>
<td><strong>Type of payments, US$ (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scholarship donations</td>
<td>1,915,196 (67.8)</td>
<td>212,751 (90.0)</td>
</tr>
<tr>
<td>Personal payments</td>
<td>908,281 (32.2)</td>
<td>23,543 (10.0)</td>
</tr>
<tr>
<td><strong>Average (Standard Deviation), US$</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scholarship donations</td>
<td>83,269 (171,034)</td>
<td>9,250 (24,089)</td>
</tr>
<tr>
<td>Personal payments</td>
<td>39,490 (67,676)</td>
<td>1,024 (2,599)</td>
</tr>
<tr>
<td>Overall</td>
<td>122,760 (233,538)</td>
<td>10,274 (26,036)</td>
</tr>
<tr>
<td><strong>Median (Interquartile Range), US$</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scholarship donations</td>
<td>15,881 (0–87,987)</td>
<td>0 (0–5,411)</td>
</tr>
<tr>
<td>Personal payments</td>
<td>13,274 (2,289–33,910)</td>
<td>0 (0–0)</td>
</tr>
<tr>
<td>Overall</td>
<td>34,605 (4,482–98,020)</td>
<td>0 (0–6,564)</td>
</tr>
</tbody>
</table>

Ranking of top five pharmaceutical companies with largest payments (US$) and recommended drugs if available

1<sup>st</sup> Nippon Boehringer Ingelheim Chugai Pharmaceutical (Tocilizumab) 153,368
2<sup>nd</sup> Astellas Pharma Eli Lilly Japan (Baricitinib) 50,353
3<sup>rd</sup> Shionogi FUJIFILM Toyama Chemical (Favipiravir) 32,574
4<sup>th</sup> Chugai Pharmaceutical (Tocilizumab) –
5<sup>th</sup> Pfizer Japan –

Authors with payments (n, %)

<table>
<thead>
<tr>
<th></th>
<th>All companies</th>
<th>Companies manufacturing COVID-19 drugs*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any payments</td>
<td>20 (87.0)</td>
<td>9 (39.1)</td>
</tr>
<tr>
<td>≥ $10,000</td>
<td>16 (69.6)</td>
<td>4 (17.4)</td>
</tr>
<tr>
<td>≥ $50,000</td>
<td>9 (39.1)</td>
<td>2 (8.7)</td>
</tr>
<tr>
<td>≥ $100,000</td>
<td>6 (26.1)</td>
<td>1 (4.3)</td>
</tr>
</tbody>
</table>
We evaluated the personal payments, including speaking, consulting, and writing reimbursements, and scholarship donations from pharmaceutical companies using the payment data from 2017 to 2019, which were disclosed on those companies’ websites. Scholarship donations represent funds provided to medical institutions and various departments to encourage educational and academic activities related to the development of new drugs.

*Three pharmaceutical companies were included as companies manufacturing COVID-19 drugs: Eli Lilly Japan K.K. (Baricitinib), Chugai Pharmaceutical Co., Ltd. (Tocilizumab), and FUJIFILM Toyama Chemical Co., Ltd. (Favipiravir). Dexamethasone (DECADRON® Table released in 1959) was previously developed and distributed by MSD K.K. in Japan. However, MSD transferred the manufacturing and marketing approval of dexamethasone to generic companies such as Nichi-Iko Pharmaceutical Co., the largest pharmaceutical companies marketing generic drugs in Japan. Since only generic dexamethasone was available in Japan during the study period we excluded payments from companies marketing dexamethasone from the list of companies manufacturing COVID-19 drugs. Also, Gilead (remdesivir) is not a member of the Japan Pharmaceutical Manufacturers Association, so the payments from this company to healthcare professionals were undisclosed.

Japanese yen (¥) were converted to U.S. dollars ($) using the 2017 average monthly exchange rate of ¥112.1 per $1, 2018 average exchange rate of ¥110.4 per $1, and ¥112.1 per $1, 2019 average exchange rate of ¥109.0 per $1. Abbreviation: COVID-19, coronavirus disease 2019
Supplementary Material 1. Details of COVID-19 drug assessments applied in this study.

We first evaluated the tone of recommendations concerning the drugs stated with a detailed description of efficacy and safety in the CPG. Further, we reviewed the underlying evidence of positive or negative statements on the listed drugs. In the review of underlying evidence, we extracted study design, study setting, number of participants, the preset primary endpoint, enrollment duration, results concerning primary endpoints, and sponsors of the trial from the published articles and the US ClinicalTrials.gov (https://clinicaltrials.gov/ct2/home), a database of clinical trials operated by the US National Institutes of Health. Then we evaluated whether the underlying evidence correctly backed the statements in the CPG.
## Supplementary Material 2. Demographic characteristics of authors.

<table>
<thead>
<tr>
<th>Variables</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>23 (100)</td>
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<tr>
<td>Female</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Affiliation</strong></td>
<td></td>
</tr>
<tr>
<td>University school of medicine</td>
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<tr>
<td>Professor</td>
<td>10 (43.5)</td>
</tr>
<tr>
<td>Non-professor</td>
<td>5 (21.7)</td>
</tr>
<tr>
<td><strong>Hospital</strong></td>
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<tr>
<td>National</td>
<td>5 (21.7)</td>
</tr>
<tr>
<td>Public</td>
<td>2 (8.7)</td>
</tr>
<tr>
<td>Private</td>
<td>1 (4.3)</td>
</tr>
<tr>
<td><strong>Median h-index (IQR)</strong></td>
<td>17 (9.5–26.5)</td>
</tr>
<tr>
<td><strong>Specialty, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Infectious disease</td>
<td>9 (39.1)</td>
</tr>
<tr>
<td>Pediatrics</td>
<td>4 (17.4)</td>
</tr>
<tr>
<td>Pulmonology</td>
<td>4 (17.4)</td>
</tr>
<tr>
<td>Acute care</td>
<td>2 (8.7)</td>
</tr>
<tr>
<td>Anesthesiology</td>
<td>2 (8.7)</td>
</tr>
<tr>
<td>Microbiology</td>
<td>2 (8.7)</td>
</tr>
</tbody>
</table>
## Supplementary Material 3. Characteristics of clinical trials referred to in the clinical practice guideline for novel coronavirus disease 2019 in Japan

<table>
<thead>
<tr>
<th>Drug name (Pharmaceutical companies)</th>
<th>Approval status in Japan</th>
<th>Main clinical trial reviewed</th>
<th>Reference (trial number)</th>
<th>Study Design</th>
<th>Setting</th>
<th>Participants</th>
<th>Primary endpoint, enrollment duration, and main results</th>
<th>Sponsors and relationships with the pharmaceutical companies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td>Remdesivir (N=243) Not remdesivir (N=2725)</td>
<td>Age: &lt;50 yr: 35.1% 50–69 yr: 47.1% ≥70 yr: 17.8%</td>
<td>Primary endpoint: Effects on in-hospital mortality (i.e., death during the initial hospitalization; follow-up ceased at discharge), regardless of whether death occurred before or after day 28</td>
<td>Duration: March 22 to October 4, 2020</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>Remdesivir (N=541) Placebo (N=521)</td>
<td>Average age, yr: 58.9 (SD 15.0)</td>
<td>Primary endpoint: Time to recovery, defined by either discharge from the hospital or hospitalization for infection-control purposes only</td>
<td>Duration: February 21 to April 19, 2020</td>
</tr>
<tr>
<td></td>
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<td></td>
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<td></td>
<td>Remdesivir (N=197) 5-day course of remdesivir (N=199) Standard care (N=200)</td>
<td>10-day course of remdesivir (N=197)</td>
<td>Primary endpoint: Clinical status on day 11 on a 7-point ordinal scale ranging from death (category 1) to discharged (category 7)</td>
<td>Duration: March 15 to April 18, 2020</td>
</tr>
</tbody>
</table>

Pan H., et al. N Engl J Med. 2021;384:497. (NCT04315948) Adapative, Randomized, Open-Label, Multicenter Study | 405 hospitals from 30 countries (Australia, Canada, France, Germany, India, Indonesia, Israel, Peru, South Africa, Thailand, and others) | Remdesivir (N=243) Not remdesivir (N=2725) | Primary endpoint: Effects on in-hospital mortality (i.e., death during the initial hospitalization; follow-up ceased at discharge), regardless of whether death occurred before or after day 28 | Duration: March 22 to October 4, 2020 |

Beigel JH., et al. N Engl J Med. 2020;383:1813. (NCT04280705) A Multicenter, Adaptive, Randomized Double-Band Placebo-Controlled Study | 60 trial sites and 13 subsites (the United States, Denmark, the United Kingdom, Greece, Germany, Korea, Mexico, Spain, Japan, and Singapore) | Remdesivir (N=541) Placebo (N=521) | Average age, yr: 58.9 (SD 15.0) | Duration: February 21 to April 19, 2020 |

Spinner CD., et al. JAMA 2020;324:1048. (NCT04292730) A Phase 3 Multicenter, Randomized, Open-label Study | 105 hospitals (the United States, Italy, Spain, the United Kingdom, Germany, France, Switzerland, Japan, and Singapore) | Remdesivir (N=197) 5-day course of remdesivir (N=199) Standard care (N=200) | 10-day course of remdesivir (N=197) | Duration: March 15 to April 18, 2020 |

Company contribution: Both remdesivir and placebo were provided by Gilead Sciences, Foster City, CA, USA

Company contribution: Remdesivir was donated by Gilead Sciences, hydroxychloroquine by Mylan, lopinavir by AbbVie, Cipla, Mylan, and interferon beta-1a by Merck (subcutaneous) and Faron Pharmaceuticals (intravenous).

Company contribution: Gilead Sciences provided remdesivir for use in the trial but did not provide any financial support. Employees of Gilead Sciences participated in discussions about protocol development and weekly protocol team calls.

Company contribution: Gilead Sciences was the sponsor of the trial.
Dexamethasone
Drug approved for COVID-19 in Japan
Multicenter, Randomized, Open-label Study
176 National Health Service organizations in the United Kingdom
Standard care + Dexamethasone (N=2104)
Standard care alone (N=4321)
Average age, yr: 66.1 (SD: 15.7)
Primary endpoint: All-cause mortality within 28 days of randomization
Duration: March 19 to June 8, 2020
Results: Positive
Mortality at 28 days was significantly lower in the dexamethasone group than in the usual care group, with deaths reported in 482 of 2,104 patients (22.9%) and in 1100 of 4,321 patients (25.7%), respectively (rate ratio, 0.83; 95% CI 0.75-0.93; p-value=0.001), among those receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2%; rate ratio, 0.82; 95% CI 0.72-0.94) but not among those who were receiving no respiratory support at randomization (17.8% vs. 14.0%; rate ratio, 1.19; 95% CI 0.92-1.55).

Baricitinib
Drug approved for COVID-19 in Japan
Multicenter, Randomized, Double-Blinded Placebo-Controlled Study
55 trial sites (the United States, Singapore, the Republic of Korea, Mexico, Spain, Japan, the United Kingdom, and Denmark)
Remdesivir + Baricitinib (N=515)
Remdesivir + placebo (N=518)
Average age, yr: 55.4 (SD: 15.7)
Primary endpoint: Time to recovery
Duration: May 8 to July 1, 2020
Results: Positive
Patients with Baricitinib plus remdesivir recovered a median of 1 day faster than patients with remdesivir and placebo (median, 7 days vs. 8 days; rate ratio for recovery, 1.16; 95% CI, 1.01-1.32; p-value=0.03 by log-rank test stratified according to actual baseline severity).

Tocilizumab
(Sponsor: Roche)
Drug considered for oﬀ-label use for COVID-19
Multicenter, Randomized, Open-label study
131 trial sites in the United Kingdom
Standard care + Tocilizumab (N=2022)
Standard care alone (N=2094)
Average age, yr: 63.6 (SD: 13.6)
Primary endpoint: All-cause mortality at 28 days after randomization to tocilizumab vs. standard care alone.
Duration: April 23, 2020, to January 2021
Results: Positive
Allocation to tocilizumab was associated with a significant reduction in the 28-day mortality compared with standard care alone (621 [31%] of 2,022 patients in the tocilizumab group vs. 729 [36%] of 2,094 patients in the standard care group; p-value = 0.018 by Wilcoxon rank sum test).

Sponsor: Medical Research Council of UK Research and Innovation National Institute for Health Research (NIHR) NIHR Oxford Biomedical Research Centre Bill and Melinda Gates Foundation Department for International Development, Health Data Research UK Other UK national organisations Company contribution: Tocilizumab was provided free of charge for this study by Roche. AbbVie contributed some supplies of lopinavir-ritonavir for use in the trial. Regeneron contributed supplies of a combination of two monoclonal antibodies directed against the SARS-CoV-2 spike protein for use in the clinical trial.

Sponsor: National Institute for Allergy and Infectious Diseases Company contribution: Eli Lilly, the manufacturer of Baricitinib, supported writing protocol by providing information on Baricitinib.

Sponsor: NIHR BHR Oxford Biomedical Research Centre Bill & Melinda Gates Foundation Department for International Development, Health Data Research UK Medical Research Council Population Health Research Unit NIHR Health Protection Research Unit in Emerging and Zoonotic
(35%) of 2,094 patients in the standard care group; rate ratio 0.85; 95% CI, 0.76–0.94; p-value=0.0028).

Infections
NIHR Clinical Trials Unit Support Funding
Company contribution: Roche Products (Welwyn Garden City, UK) supported the trial by providing tocilizumab. AbbVie contributed some supplies of lopinavir–ritonavir for use in this study. Regeneron contributed two monoclonal antibodies against the SARS-CoV-2 spike protein for use in the trial.


Multicenter, Randomized, Open-label Study
113 trial sites from the United Kingdom
Tocilizumab (N=353)
Sarilumab (N=48)
Standard care (N=402)

Primary endpoint: Number of respiratory and cardiovascular organ support–free days
Duration: March 9 to November 19, 2020
Results: Positive
The median number of organ support–free days was 10 (IQR, −1 to 16) in the tocilizumab group, 11 (IQR, 0 to 16) in the sarilumab group, and 0 (IQR, −1 to 15) in the control group. The median adjusted odds ratios (primary model) were 1.64 (95% CI, 1.25 to 2.14) for tocilizumab and 1.76 (95% CI, 1.17 to 2.91) for sarilumab as compared with control, yielding posterior probabilities of superiority of more than 99.9% and 99.5%, respectively.


Multicenter, Randomized, Double-blind, Placebo-controlled Study
7 hospitals in Boston, US
Standard care + Tocilizumab (N=161)
Standard care + placebo (N=81)

Primary endpoint: Intubation (or death, for patients who died before intubation) after administering tocilizumab or placebo, assessed in a time-to-event analysis.
Duration: April 20 to June 15, 2020
Results: Neutral.
By day 28, 17 patients (10.6%) in the tocilizumab group and 10 patients (12.5%) in the placebo group had died or undergone intubation. Specifically for the tocilizumab group, 11 were intubated, and 6 died before intubation. Similarly, for the placebo group, 8 were intubated, and 2 died before
intubation. The hazard ratio for intubation or death in the tocilizumab group compared with the placebo group was 0.83 (95% CI, 0.38 to 1.81; P=0.64 by log-rank test).

Multicenter, Randomized, Double-Blind, Placebo-controlled Study
50 trial sites (the United States, Brazil, Peru, Mexico, Kenya, and South Africa)
Standard care + Tocilizumab (N=249)
Standard care + placebo (N=128)
Primary endpoint: Mechanical ventilation (invasive mechanical ventilation or extracorporeal membrane oxygenation) or death by day 28
Duration: Not reported
Results: Positive.
The cumulative percentage of patients who had received mechanical ventilation or who had died by day 28 was significantly lower in the tocilizumab group (12.0%; 95% CI, 8.5 to 16.9) than in the placebo group (19.3%; 95% CI, 13.3 to 27.4) (hazard ratio, 0.56; 95% CI, 0.33 to 0.97; p-value=0.04 by the log-rank test).

Multicenter, Randomized, Open-label Study
25 hospitals in Italy
Tocilizumab (N=60)
Standard care (N=66)
Primary endpoint: Clinical worsening within 14 days since randomization, defined by the occurrence of one of the following events: admission to intensive care unit with invasive mechanical ventilation, death from all causes, or clinical aggravation documented by the finding of a Pao2/Fio2 ratio < 150 mm Hg, whichever came first.
Duration: March 31 to June 11, 2020
Results: Neutral.
17 patients of 60 (28.3%) in the tocilizumab arm and 17 of 63 (27.0%) in the standard care group showed clinical worsening within 14 days since randomization (rate ratio, 1.05; 95% CI, 0.59-1.86; p-value=0.87).

Multicenter, Randomized, Open-label Study
9 university hospitals in France
Standard care + Tocilizumab (N=64)
Standard care alone (N=67)
Primary endpoint: (1) the proportion of patients dead or needing noninvasive or mechanical ventilation on day 4 (>5 on the WHO-CPS); and (2) survival with no need for noninvasive or mechanical ventilation at day 14
Duration: March 31 to April 18, 2020
Results: Positive
In the tocilizumab group, 12 patients had a WHO-CPS score greater than 5 at day 4 vs. 19 in the usual care group (median posterior absolute risk difference [ARD] −9.0%; 95% CI, −21.0 to 3.1), with a posterior probability of negative ARD of 89.0% not achieving the 95% predefined efficacy threshold. At day 14, 12% (95% CI −28% to 4%) fewer patients needed noninvasive ventilation or mechanical ventilation or died in the tocilizumab group than in the usual care group (24% vs. 36%, median posterior hazard ratio 0.58; 95% CI, 0.33-1.00), with a posterior probability of hazard ratio
Favipiravir (Fujifilm Toyama Chemical) was considered for off-label use for COVID-19. Doi Y., et al. *Antimicrob Agents Chemother.* 2020;64:e01897 (jRCTs041190120) conducted a multicenter, randomized, open-label study in 25 hospitals in Japan. Receiving favipiravir from day 1 (N=44) and receiving favipiravir from day 6 (N=45). Median age, yr: 48.0 (IQR: 34.5-68.0).

Primary endpoint: Proportion of subjects with clearance of SARS-CoV2 in nasopharyngeal swab by Day 6. Duration: March 2 to May 18, 2020. Results: Neutral. Achieved clearance of SARS-CoV2 by day 6 in 66.7% (95% CI: 51.4-81.2) of the early treatment group and 56.1% (95% CI: 40.1-73.4) of the delayed treatment group (adjusted HR, 1.42; 95% CI, 0.76-2.62).

Sponsor: Japan Agency for Medical Research and Development. Company contribution: Fujifilm Toyama Chemical provided favipiravir and members of the Independent Data Monitoring Committee.

**Abbreviations:** ARD, absolute risk difference; SD, standard deviation; IQR, Interquartile range; ICU, Intensive care unit; CI, confidence interval; UK, United Kingdom; HR, hazard ratio; yr, year

*Chugai Pharmaceutical Co., Ltd. is a member of the Roche Group and manufactured and marketed tocilizumab in Japan on behalf of F. Hoffmann-La Roche Ltd.*
Supplemental Material 4. Payment data