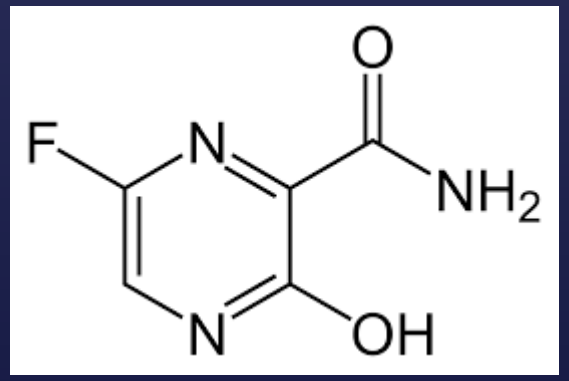
Session 6 Clinical Trials Updates

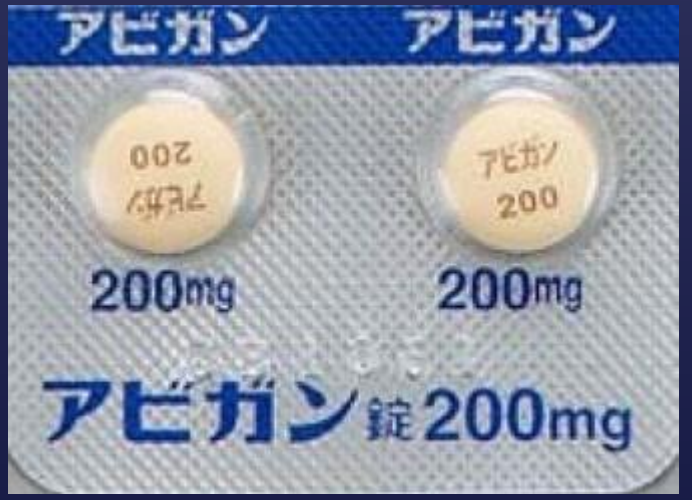
# Favipiravir

Yohei Doi, MD, PhD
Fujita Health University
University of Pittsburgh

# Favipiravir

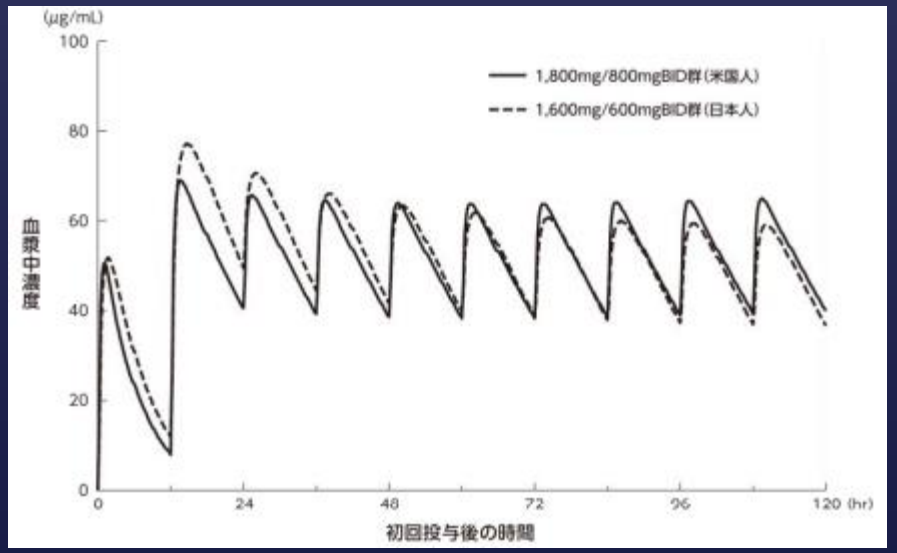
- Pyrazine carboxamide derivative
- Broad-spectrum, oral inhibitor of viral RNA-dependent RNA polymerase (RdRP) developed in Japan
- The active drug is favipiravir-ribofuranosyl-5’-triphosphate (favipiravir-RTP)
- Metabolized mainly by aldehyde oxidase in the liver



# Favipiravir

- Steady state plasma concentration of 40-60 mg/L when dosed at 1,800 mg x2 doses followed by 800 mg bid
- Approved as Avigan® in Japan for treatment of new or emerging influenza infection
- Shows *in vitro* activity against SARS-CoV-2



# RCTs on COVID-19

- **Russia, 60 patients**
- Open-label RCT
- FAVI vs SOC
- Primary endpoint
  - PCR negativity by day 10
- PCR negative by day 10
  - 92.5% vs 80%
- PCR negative by day 5
  - 62.5% vs 30%

+

- **Japan, 89 patients**
- Open-label RCT
- Early FAVI vs late FAVI
- Primary endpoint
  - PCR negativity by day 6
- PCR negative by day 6
  - 66.7% vs 56.1%
- Duration of fever shortened by 1.1 days

±

- **Japan, 156 patients**
- Single-blind RCT
- FAVI vs placebo
- Primary endpoint
  - Time to clinical improvement and PCR negativity
- Time to improvement/PCR negative
  - 11.9 days vs 14.7 days

+

# Russia, 60 patients

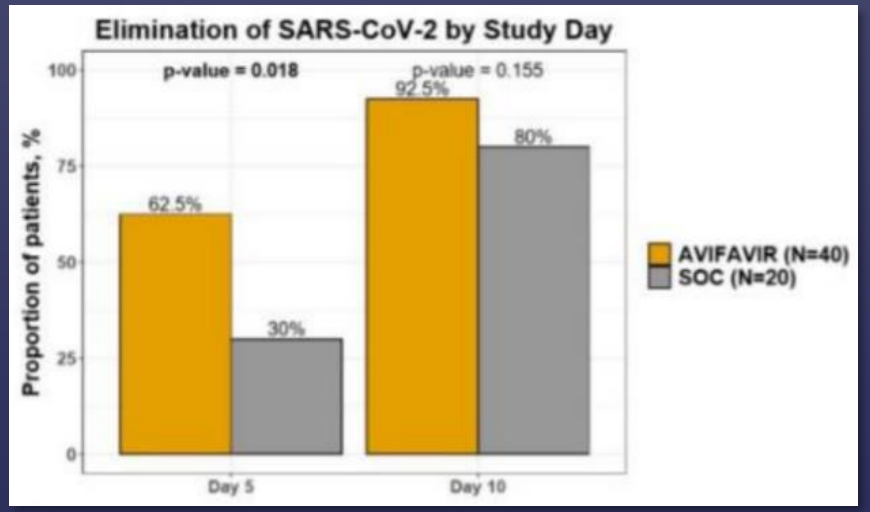
- 60 patients hospitalized with COVID-19 pneumonia
- Randomized to 3 treatment groups
  - FAVI 1,800 mg x2 followed by 800 mg bid
  - FAVI 1,600 mg x2 followed by 600 mg bid
  - Standard of care (SOC)
- ¼ of them required oxygen
- Primary endpoint
  - PCR negativity by day 10

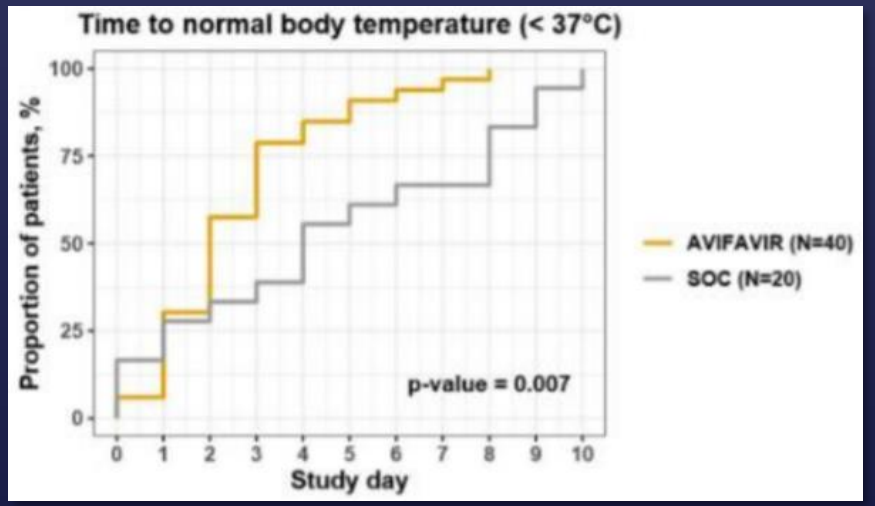
Ivashchenko AA, Clin Infect Dis 2020

# Russia, 60 patients

- PCR negative by day 5
  - FAVI = 62.5%, SOC = 30.0% (p = 0.018)
- PCR negative by day 10
  - FAVI = 92.5%, SOC = 80.0% (p = 0.155)
- Time to temperature <37°C (median)
  - FAVI = 2 days, SOC = 4 days (p = 0.007)

- FAVI associated with earlier viral clearance, shorter duration of fever
- No impact on duration of hospitalization

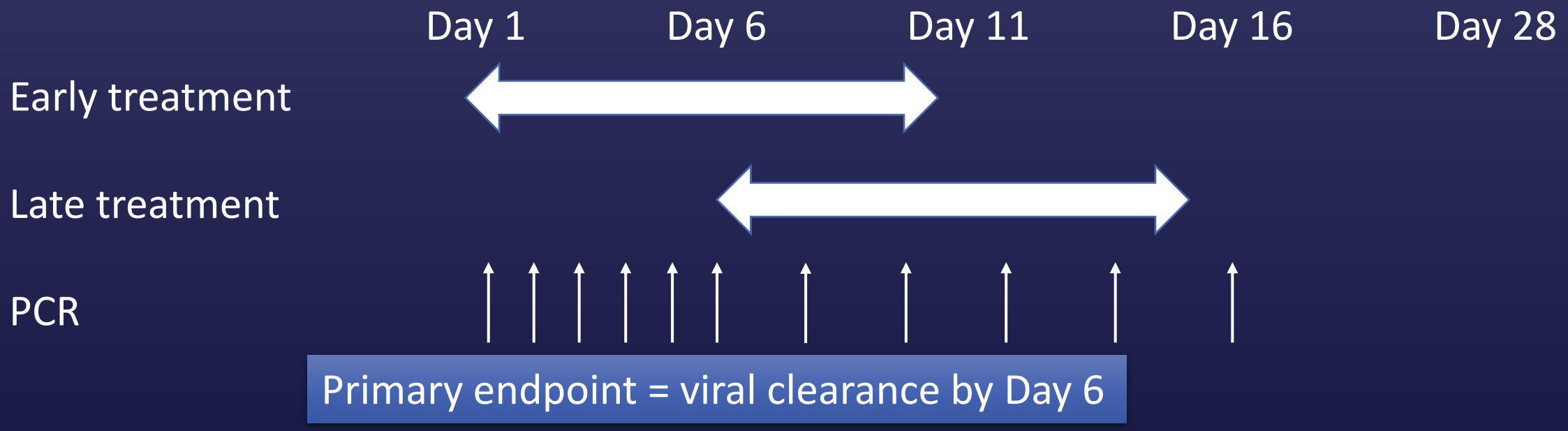



Ivashchenko AA, Clin Infect Dis 2020

# Japan, 89 patients

- We sought to determine the efficacy of favipiravir in reducing viral load among patients with asymptomatic or mild COVID-19
- 89 patients were randomized to early treatment arm and delayed treatment arm, favipiravir 1,800 mg x2 first day then 800 mg bid



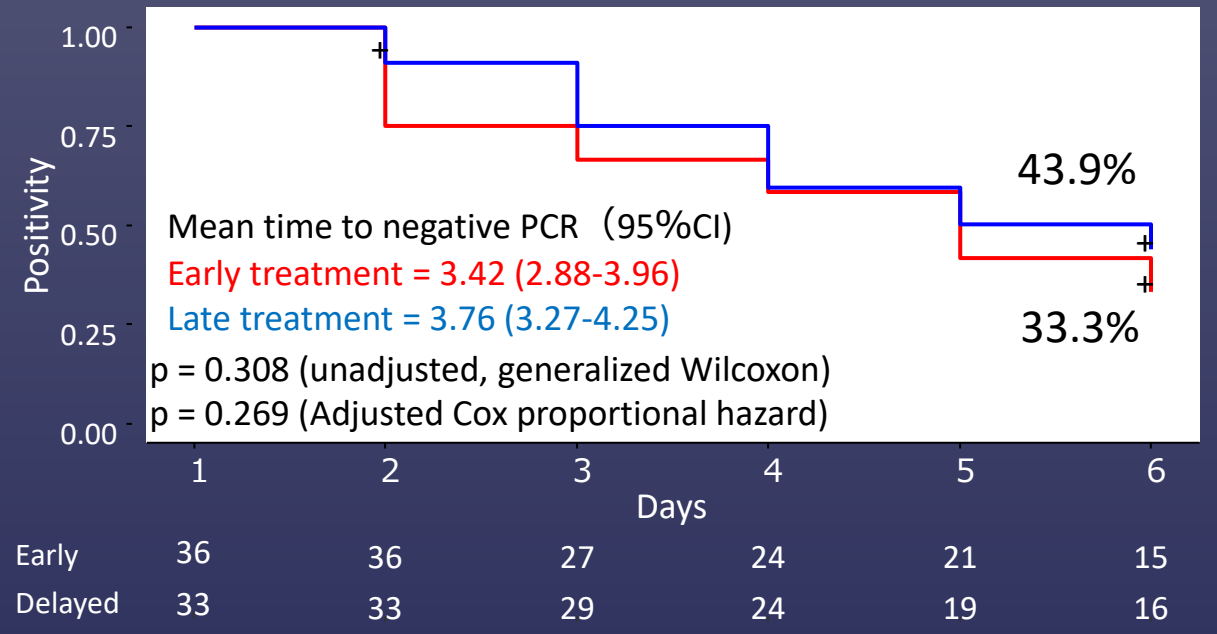
# Demographics

- The groups were well balanced except for sex (52.8% vs 70.5%)
- Median age = 50.0 years
- Median time from diagnostic PCR to randomization = 4.0 days
- Median time from first day of fever = 7.0 days

Doi Y, et al. Antimicrob Agents Chemother 2020

# Primary endpoint

- Negative PCR by Day 6
- 69 evaluable patients
- aHR for time to PCR negativity = 1.416




| | # of patients | % | 95% CI |
|---|---|---|---|
| Early treatment | 24 | 66.7% | 51.4%-81.2% |
| Late treatment | 18 | 56.1% | 40.1%-73.4% |

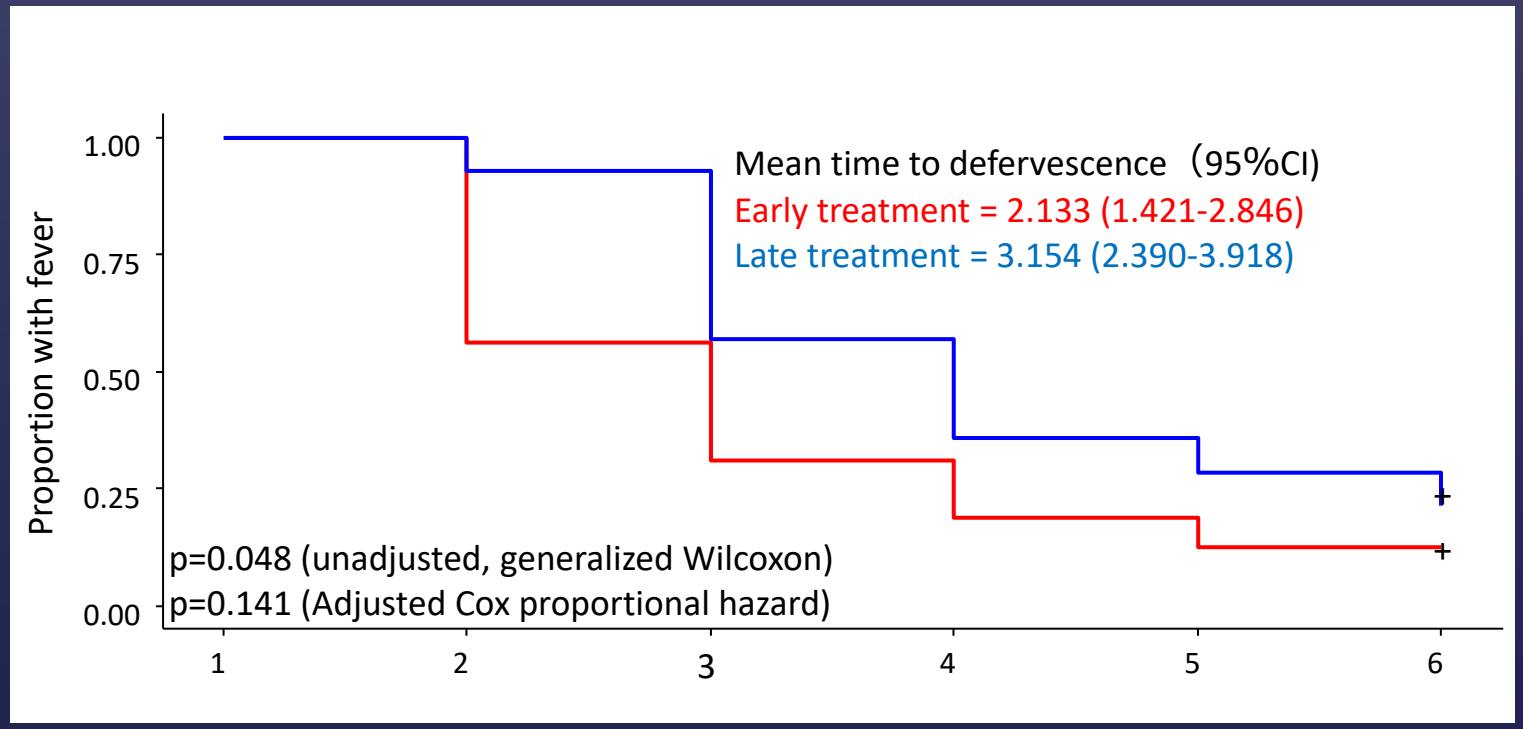
| | Hazard ratio | 95% CI | P value |
|---|---|---|---|
| Unadjusted | 1.340 | 0.726-2.472 | 0.350 |
| **Adjusted for age and time from first positive PCR** | **1.416** | **0.764-2.623** | **0.269** |

Doi Y, et al. Antimicrob Agents Chemother 2020

# Exploratory endpoint

- Time to defervescence (≤37.5°C)
- 30 evaluable patients
- aHR for time to defervescence = 1.880

| | Hazard ratio | 95% CI | P value |
|---|---|---|---|
| Unadjusted | 1.883 | 0.813-4.364 | 0.141 |
| **Adjusted for age and time from first positive PCR** | **1.880** | **0.812-4.354** | **0.141** |




Doi Y, et al. Antimicrob Agents Chemother 2020

# Common adverse events

- Hyperuricemia 69 (84.1%)
- Hypertriglyceridemia 9 (11.0%)
- ALT elevation 7 (8.5%)
- AST elevation 4 (4.9%)
- These values normalized in most patients after completion of treatment

- FAVI not clearly associated with viral reduction by Day 6
- FAVI associated with numerical reduction in time to defervescence
- None had progressive disease or death

- Supported by the Japan Agency for Medical Research and Development (AMED; JP19fk0108150)

Doi Y, et al. Antimicrob Agents Chemother 2020

# Japan, 156 patients

- 156 patients hospitalized with COVID-19 pneumonia
- Randomized, single-blind
  - FAVI 1,800 mg x2 followed by 800 mg bid
  - Placebo
- Primary endpoint = time to alleviation of symptoms (body temperature, oxygen saturation and chest images) AND PCR negativity
  - FAVI = 11.9 days
  - Placebo = 14.7 days (aHR = 1.593; p = 0.0136)

- The primary endpoint was met
- The MA holder plans to move forward with NDA in October in Japan

https://www.fujifilm.com/jp/en/news/hq/5451

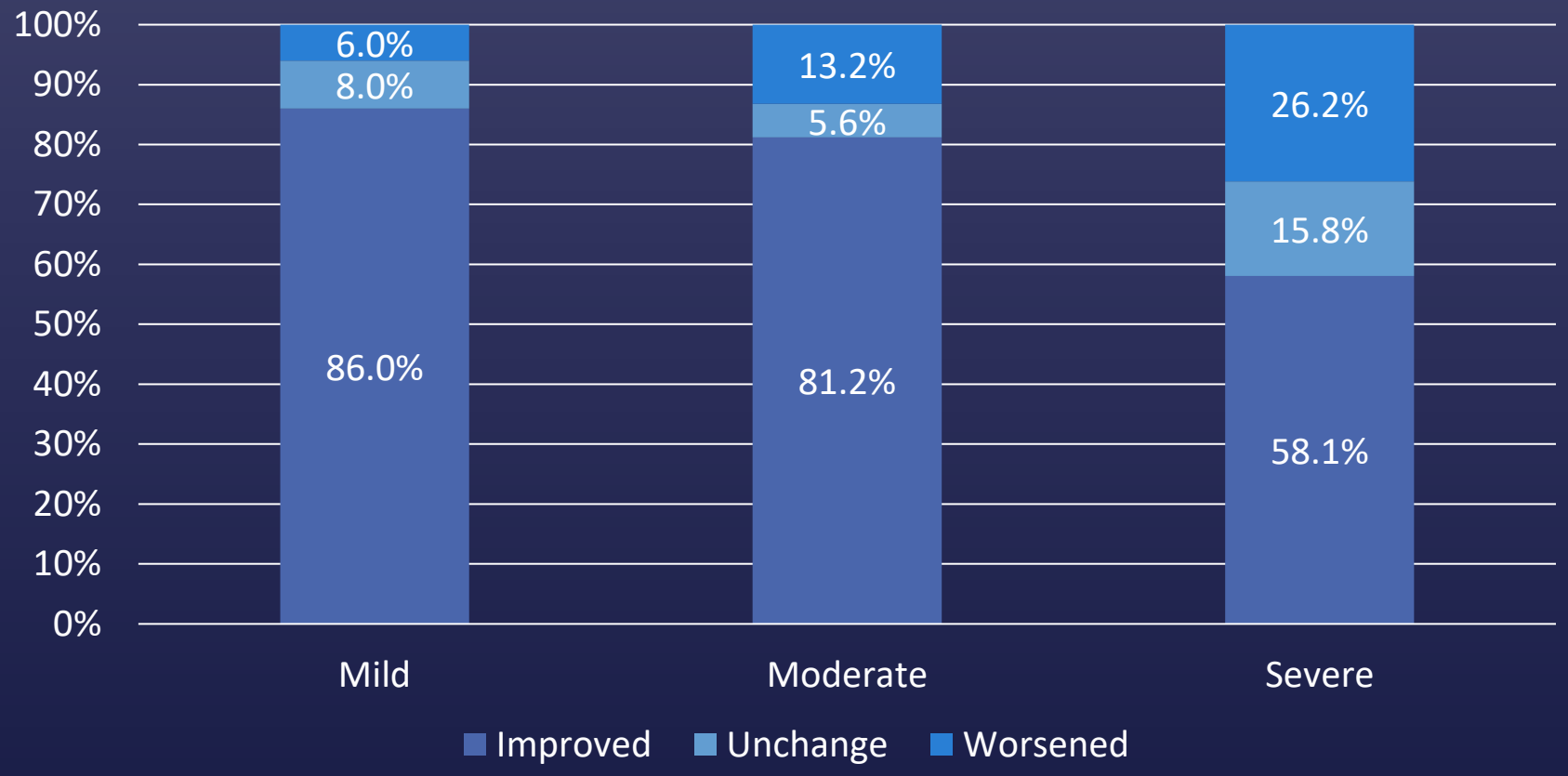
# Japan, observational study

- 2970 COVID-19 patients who received favipiravir on a compassionate use basis
- 497 hospitals across Japan, March through June 2020
- 55% were age ≥60 years
- 49.8% had comorbidities
- 93.6% took the high dose (2 doses of 1,800 mg followed by 800 mg bid)

http://www.kansensho.or.jp/uploads/files/topics/2019ncov/covid19_favip_eng_0928.pdf

# Outcomes

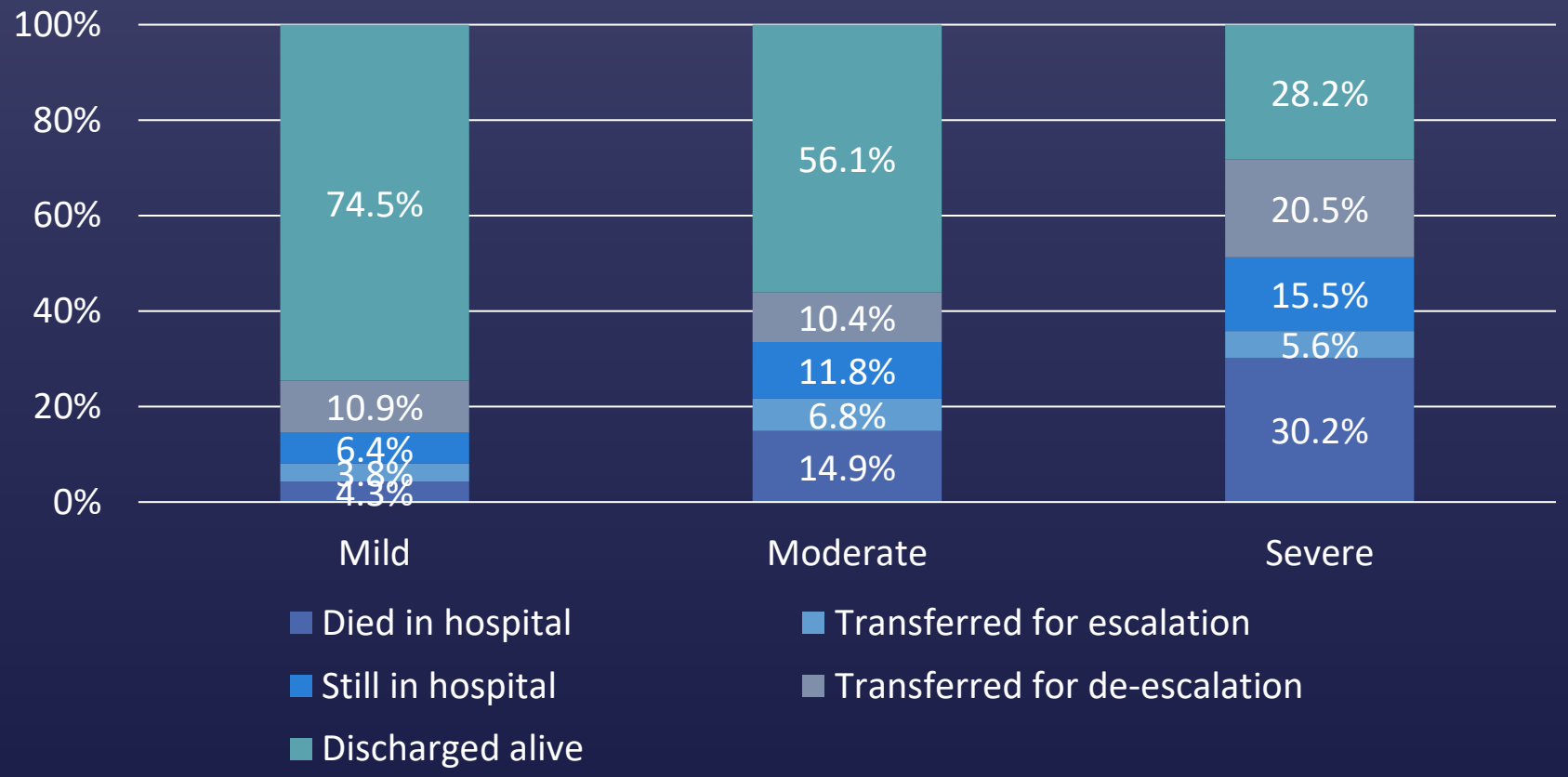
- Clinical status at 14 days after starting FAVI




http://www.kansensho.or.jp/uploads/files/topics/2019ncov/covid19_favip_eng_0928.pdf

# Outcomes

- Clinical outcome 1 month from hospital admission




http://www.kansensho.or.jp/uploads/files/topics/2019ncov/covid19_favip_eng_0928.pdf

# Adverse events associated with use

| | |
|---|---|
| • Hyperuricemia/elevated uric acid levels | 17.6% |
| • Hepatic function disorder/elevated LFT levels | 8.1% |
| • Skin eruption/toxicoderma | 1.9% |
| • Renal impairment/elevated creatinine levels | 0.8% |
| • Diarrhea/soft stool | 0.7% |
| • Fever | 0.6% |
| • Vomiting/nausea | 0.5% |
| • Gout | 0.3% |
| • Rhabdomyolysis/elevated creatine kinase levels | 0.2% |
| • Hyperkalemia | 0.2% |

http://www.kansensho.or.jp/uploads/files/topics/2019ncov/covid19_favip_eng_0928.pdf

# Conclusion

- ✓Favipiravir is one of few oral antiviral agents with SARS-CoV-2 activity already available
- ✓Clinical data suggesting the efficacy of favipiravir against COVID-19 are emerging
- ✓There appears to be modest to moderate impact on shortening periods of symptoms and PCR positivity
- ✓Hyperuricemia occurs frequently but is transient
- ✓Whether early administration of favipiravir leads to reduction in critical illness and death downstream remains as a knowledge gap