INVESTIGATOR'S BROCHURE

INVESTIGATIONAL PRODUCT:	favipiravir 6-fluoro-3-hydroxypyrazine-2-carboxamide, T-705
EDITION NUMBER:	Twelfth Edition (US Version)
RELEASE DATE:	20 March, 2020
PREVIOUS EDITION NUMBER:	Eleventh Edition (US Version)
PREVIOUS EDITION DATE:	19 February, 2019
UTN:	U1111-1147-8470
DATA CUT OFF DATE:	18 March 2020
SPONSORED BY:	FUJIFILM Pharmaceuticals U.S.A., Inc. One Broadway, Cambridge, MA 02142 USA Telephone: +1 617-674-8224

SPONSOR'S SIGNATORY FOR INVESTIGATOR'S BROCHURE

DocuSigned by:
Mikihiko Kato
Signer Name: Mikihiko Kato
Signing Reason: I approve this document
Signing Time: 3/20/2020 | 11:46:29 AM EDT
A0EE84BF3A6041668084F91A3C304823

3/20/2020

Signature Date

Mikihiko Kato
FUJIFILM Pharmaceuticals U.S.A., Inc.

1. TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse event
AFT	Accelerated failure time
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration vs time curve
BID	Twice daily
BLQ	Below lower limit of quantitation
CI	Confidence interval
CKD	Chronic kidney disease
ClCr	Creatinine clearance
CL/F	Apparent total body clearance after extravascular administration
C_{max}	Maximum plasma concentration
C_{min}	Minimum plasma concentration
CV	Coefficient of variation
CYP	Cytochrome P450
DDI	Drug-drug interaction
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
EC_{50}	Effective concentration to 50%
FDA	Food and Drug Administration
GD	Gestation day
GI	Gastrointestinal
GLP	Good Laboratory Practices
hERG	Human ether-a-go-go-related gene
hOAT	Human organic anion transporter
hOCT	Human organic cation transporter
hURAT	Human urate transporter
ICH	International Conference on Harmonisation
IC_{50}	Inhibitory concentration to 50%
IL	Interleukin
IND	Investigational New Drug
ITT	Intent-to-treat
ITTI	Intent-to-treat infected
IV	Intravenous
LS	Least squares
MDVI	MDVI, LLC
NOAEL	No observed adverse effect level
PK	Pharmacokinetics
PT	Prothrombin time or preferred term
PCR	Polymerase chain reaction

Abbreviation	Description
qPCR	Quantitative polymerase chain reaction
RBC	Red blood cell
RNA	Ribonucleic acid
SAE	Serious adverse event
SD	Standard deviation
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
T-705	Favipiravir
T-705M1	Metabolite (hydroxide) of T-705, ie, 6-fluoro-3,5-dihydroxy-2-pyrazinecarboxamide
T-705M2	Glucuronide conjugate of T-705
T-705RTP	T-705 ribosyl triphosphate
$TCID_{50}$	50% tissue culture infectious dose
TEAE	Treatment-emergent adverse event
TID	Three times daily
$t_{1/2}$	Half-life
t_{max}	Time to maximum plasma concentration
US	United States of America
UVA	Ultraviolet A
WBC	White blood cell

CHANGES TO PREVIOUS EDITION

The Investigator's Brochure (IB) was updated with information related to favipiravir's effect on other RNA viruses than influenza.

2. SUMMARY

Favipiravir (6-fluoro-3-hydroxypyrazine-2-carboxamide; T-705) has been shown to be an antiviral drug with broad spectrum capabilities in nonclinical studies and has been investigated in clinical studies for its efficacy in uncomplicated influenza in adult subjects. Favipiravir has also been employed in the treatment of Ebola in a clinical trial sponsored by the French Government in Guinea during the 2014 epidemic, where favipiravir showed suggestions of efficacy. Additional indications under consideration or used under compassionate use include severe fever with thrombocytopenia virus, rabies, Lassa fever, Jamestown Canyon virus, and norovirus.

2.1. Physical, Chemical, and Pharmaceutical Properties and Formulation

Favipiravir is a novel nucleic acid (pyrazine molecule) analogue that interferes with viral ribonucleic acid (RNA) replication. Favipiravir is supplied as a light yellow, film-coated tablet for oral administration containing 200 mg favipiravir. Favipiravir tablets are to be kept in a dry area, stored at 15° C to 30° C (59° F to 86° F) and shielded from direct light.

2.2. Pharmacology

The mechanism of action of favipiravir differs from currently approved drugs for influenza infection, which include neuraminidase inhibitors (eg, oseltamivir) and viral M2 protein ion channel inhibitors (eg, amantadine). Preclinical data have demonstrated that host cellular enzymes convert favipiravir to T-705 ribosyl triphosphate (T-705RTP). In turn, T-705RTP is mistaken for natural nucleotide triphosphates by influenza viral RNA polymerase, selectively inhibiting viral RNA synthesis and thus interfering with replication of influenza viruses. (Furutaet al., 2002; Furuta et al., 2005; Sangawa et al., 2013)

Preclinical studies of favipiravir have shown potent *in vitro* inhibitory activity against seasonal influenza A (H1N1[2009], H2N2, H3N2, H5N1), avian influenza A (H7N9), influenza B, and influenza C viruses, as well as against oseltamivir-resistant and amantadine-resistant strains. (Furutaet al., 2013)

In vitro studies of favipiravir have also shown activity against Ebola [*Filoviridae*] and other RNA viruses (eg, Lassa fever [*Arenaviridae]*, *Bunyaviridae*, Ch ikungunya virus [*Alphavirus*], etc.) via a similar mechanism of action (Gowen et al., 2007; Jochmans et al., 2013; Safronetz et al., 2013; Smithers et al., 2014). Recently there is published data demonstrating *in vitro* activity against Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). (Wang et al., 2020)

2.3. Pharmacokinetics

In adults, favipiravir is rapidly and completely absorbed following oral administration. Across the dose range and formulations utilized, the time to maximum plasma concentration (t_{max}) of favipiravir occurs between 0.5 to 4.0 hours, the median time being 1.0 hour after a single dose of favipiravir and 2.0 hours following multiple doses.

A repeat-dose study over 5 days has shown that favipiravir in plasma accumulates due to an inhibition of the major drug metabolizing enzyme, aldehyde oxidase, by favipiravir. Favipiravir

administered twice daily (BID) resulted in a greater than proportional increase in favipiravir blood levels. The average dose-adjusted Day 5 area under the plasma concentration vs time curve (AUC) ratio comparing 600 mg BID with 800 mg BID was 1.5 in one study and 1.9 in a second study of healthy volunteers.

Favipiravir plasma protein binding averages 53 to 54%, of which 65% is bound to albumin and 6.5% to alpha-1-acid glycoprotein.

Favipiravir, metabolite (hydroxide) of T-705 (T-705M1) and glucuronide conjugate of T-705 (T-705M2) are excreted predominately in urine and to a small extent into the feces. In healthy volunteers following administration of a single oral 400 mg dose, 86.7% of the dose was recovered in the urine as the T-705M1 metabolite, 3.6% as a glucuronide conjugate, and 0.2% as favipiravir, totaling 90.5% at 48 hours.

The major metabolite, T705M1, is formed by aldehyde oxidase in human liver cytosol and other tissues. The cytochrome mixed function oxidase systems do not significantly contribute to the metabolism of favipiravir. Favipiravir exhibits only weak inhibitory effects on cytochrome P450 (CYP) 1A2, 2C9, 2C19, 2D6, 2E1, or 3A4 (inhibitory concentration to 50% [IC_{50}] >800 µmol/L, 126 µg/mL). Favipiravir does inhibit CYP2C8 in human liver microsomes. Favipiravir showed little or no induction of CYP1A2, CYP2C9, CYP2C19 and CYP3A4 in human hepatocytes. Both favipiravir and T-705M1 moderately inhibit human organic anion transporter (hOAT) 1, hOAT3, and human urate transporter (hURAT) 1 (30.9 to 65.7% of control). Additionally, hURAT1-mediated uric acid uptake was increased by T-705M1, suggesting T-705M1 may stimulate the reabsorption of uric acid in human renal proximal tubules.

Food interaction studies have shown favipiravir absorption from the 200 mg tablet formulation was not altered when taken with a high fat meal. The extent of absorption of favipiravir plasma concentrations over time, as determined by AUC, was 316.3 µg•hr/mL vs. 299.8 µg•hr/mL following tablet administration alone and with food, respectively.

2.3.1 Special Populations

No alteration of dosing is needed in subjects with renal impairment. Total (AUC_{inf}) exposure for plasma favipiravir for subjects with severe renal impairment (Stage 4) was 1.3-fold higher compared to subjects with normal renal function. No obvious effect of renal impairment on safety was observed and favipiravir treatment was generally well tolerated in subjects with renal impairment. No data on renal failure with or without dialysis are available. The maximum plasma concentration (C_{max}) and AUC values in elderly subjects in a single and a multiple-dose study completed in Japan were higher than in young subjects. Comparing AUC values on Day 5, the differences were 40 and 80% after 600 mg once a day and 400 mg BID, respectively. In the companion study completed in the United States of America (US), there were no differences between young and elderly populations based on Day 5 AUC comparison in subjects receiving either 600 or 800 mg BID.

2.4. Nonclinical Data

Nonclinical safety pharmacology studies showed that favipiravir did not affect the central nervous system in rats, cardiovascular system in dogs, or respiratory system in rats. Although a statistically significant inhibition was reported in the human ether-a-go-go-related gene (hERG) channel at the highest concentration tested, the magnitude of this change was slight (8.1%

inhibition at the highest concentration, 1000 μM, tested vs. 2.7% in controls). Results also showed that the major metabolite, T705M1, has no effect on the hERG channel or cardiovascular parameters in dogs following an intravenous (IV) dose.

Repeat dose toxicity studies for 28-days were conducted in rats and dogs and for 14 days in monkeys. For rats, the no observed adverse effect level (NOAEL) was 32 mg/kg/day. The threshold effect level was 80 mg/kg/day and reduction in weight gain and minor alterations in various clinical pathology parameters were observed. Mortality was seen at 200 mg/kg/day. Histopathological effects were limited to decreased hematopoiesis. In the dog, the NOAEL was 10 mg/kg/day. The major effect was in the male reproductive organs where decreased weights were seen in the testes and accessory glands at all doses, particularly at 100 mg/kg/day, but were not statistically significant nor dose related. Histopathological effects (hypospermatogenesis) were limited to the high dose of 300/100 mg/kg/day (animals were first dosed at 300 mg/kg/day then the dose was reduced to 100 mg/kg/day). The other threshold effect level was 30 mg/kg/day where emesis and decreased weight gain were noted. Mortality was seen at 300 mg/kg/day. In monkeys, the NOAEL was 100 mg/kg/day following 14 days of treatment. At higher dose, body weight gain was reduced and some alterations in some clinical pathology parameters were noted. Histopathological effects were limited to vacuolar degeneration of hepatocytes and minor necrotic changes in the seminal vesicles in some but not all males. The testicular effects seen in the dog were not observed in the monkey.

Male and female fertility studies were conducted in rats and embryo-fetal development studies were conducted in the mouse, rat, rabbit, and monkey. Initial reproductive and developmental toxicity studies on favipiravir showed the NOAEL for fertility effects in rats was <30 mg/kg/day. Favipiravir was shown to be teratogenic in rats and rabbits. Additional studies conducted in mice and monkeys also showed teratogenic effects. A total of nine additional embryo-fetal studies were conducted to further clarify this observation. The NOAELs for developmental effects were 100, 20, 300 and 100 mg/kg/day for mice, rats, rabbits and monkeys, respectively.

Testicular effects seen in the initial toxicity studies were followed up with 13 additional studies, most of which were two weeks in duration. The NOAELs for testicular effects were 300, 60, 200 and 150 mg/kg/day for mice, rats, rabbits and monkeys, respectively.

Phototoxic effects have been observed with favipiravir in mice and guinea pigs.

For the major metabolite T-705M1, an early embryonic development study has been completed in rats, and embryo-fetal development studies have been completed in rats and rabbits. T-705M1 was not teratogenic and did not cause any other signs of developmental or reproductive toxicity. The Food and Drug Administration (FDA) agrees that the T-705M1 teratology studies in rabbits support the contraception period reduction from three months to seven days after the last dose for both men and women.

2.5. Clinical Experience in Influenza

Overall, 40 clinical studies with favipiravir have been completed and analyzed. Studies designated as "US" were designed and conducted primarily in the US Studies designated as "JP" were designed and conducted in Japan. Of the 40 completed clinical studies, 33 were Phase 1 studies (17 JP studies, 16 US studies), three were Phase 2 studies (one JP study and two US studies of which one was a global study excluding Asia), and four were Phase 3 studies (two JP

studies of which one was a multinational study in Asia and two US studies that were global studies excluding Asia). 3160 study subjects have received at least one dose of favipiravir.

In addition, several studies in patients with severe influenza have been conducted in China, using drug manufactured by another company. Data on these studies have been released by the investigators. (Wang et al., 2019)

Influenza Clinical Efficacy and Virology

Favipiravir has been administered at 1800 mg BID on Day 1 followed by 800 mg BID on Days 2 through 5 in three key influenza studies (phase 2 US213b and phase 3 US316 and US317) that support the efficacy of favipiravir in uncomplicated influenza. Part B of study US213 included two favipiravir treatment arms, a BID regimen and a three times daily (TID) regimen. Favipiravir administered in subjects confirmed as having influenza (intent-to-treat infected [ITTI]) when compared with placebo subjects resulted in:

- A significant reduction in median time to alleviation of symptoms and resolution of fever in studies US213b and US316 (15 hours, p=0.010 and 14.4 hours, p=0.004, respectively), and a similar trend in reduction was observed in US317 (6.1 hours, p=0.303).
- A comparison of the time until 25% and 75% of subjects had achieved alleviation suggests a greater benefit in those subjects who took longer to resolve in Studies US213b BID regimen (26.7-hour and 33.0-hour differences, respectively) and in US316 (9.4-hour and 36.3-hour differences, respectively) but not in US213b TID regimen (13.5-hour and 9.4-hour differences, respectively) or in US317 (1.8-hour and 0.2-hour differences, respectively).
- A greater reduction in mean viral load with titers dropping below the lower limit of quantification (LLOQ) on Day 3 compared to Day 4 or 5 for the placebo group ($p<0.001$) in studies US316 and US317.
- A significantly shortened time when 75% of subjects had undetectable virus (ie, cessation of viral shedding) as assessed by the 50% tissue culture infectious dose ($TCID_{50}$) across the three studies by approximately 24 hours (US213b BID and TID, p=0.035 and p=0.030, respectively; US316 and US317, $p<0.001$).

2.5.1 Clinical Safety

A five-day regimen of favipiravir was well-tolerated when administered to adult and elderly subjects. The safety profile at the intended influenza dose (ie, 1800 mg BID on Day 1 followed by 800 mg BID on Days 2 through 5) is broadly comparable to placebo with the exception of mild to moderate asymptomatic elevations in uric acid. These asymptomatic elevations in uric acid either resolved or trended towards baseline without clinical intervention after discontinuation of favipiravir. Since favipiravir was associated with asymptomatic elevations in uric acid, in most Phase 2 and 3 studies, investigators were blinded to the uric acid results to prevent inadvertent unblinding of subject treatment assignments. Thus, elevations in serum uric acid were identified from the safety laboratory assessments but were not captured as adverse events (AEs).

Repeated administration of favipiravir for 22 days (1800 mg BID on Day 1, followed by 800 mg BID from Day 2 to Day 21, and a single dose of 800 mg on Day 22) in healthy Japanese subjects was well tolerated. Asymptomatic blood uric acid levels, aspartate aminotransferase (AST), and

alanine aminotransferase (ALT) increases trended towards normal after the completion of the study . No other clinically significant findings were observed.

No consistent trend in favipiravir effect on QTc interval has been observed, suggesting favipiravir's potential to prolong QTc interval is low. A thorough QTc study in Japan showed favipiravir had no adverse effect on electrocardiogram (ECG) parameters at doses of 1200 and 2400 mg.

Testicular safety studies in healthy males to evaluate the effects of favipiravir versus placebo on a regimen of 1200 mg twice daily (BID) for 1 day followed by 800 mg BID for 4 days found no statistically significant differences between favipiravir and placebo for changes from baseline semen parameters, and semen favipiravir concentrations were below the limit of quantitation by 7 days after last dose.

2.6 Clinical Experience in Other RNA Viral Diseases

Favipiravir has been administered under compassionate use to small numbers of patients with rabies, Lassa fever, and norovirus. The French National Institute of Health & Medical Research (Inserm) has conducted historical controlled studies in patients with Ebola, and the data showed a trend toward improved survival in favipiravir-treated patients. Subjects with lower viral titers have a higher survival rate, compared to historical controls.(Sissoko et al., 2016) More recently, patients with SARS-CoV-2 have been treated with favipiravir, and the data showed significantly better treatment effects on COVID-19 in terms of disease progression and viral clearance than control group. (Cai et al., 2020)

3. INTRODUCTION

Favipiravir is a novel nucleic acid (pyrazine molecule) analogue that interferes with viral RNA replication and was discovered by Toyama Chemical Co., Ltd. Preclinical data have demonstrated that host cellular enzymes convert favipiravir to T-705RTP. In turn, T-705RTP is mistaken for natural nucleotide triphosphates by influenza viral RNA polymerase, selectively inhibiting viral RNA synthesis and thus interfering with viral replication. (Sangawa et al., 2013)

Preclinical studies of favipiravir have shown potent in vitro inhibitory activity against seasonal influenza A (H1N1[2009], H2N2, H3N2, H5N1), avian influenza A (H7N9), influenza B, and influenza C viruses, as well as against oseltamivir-resistant and amantadine-resistant strains. (Furuta et al., 2013)

Favipiravir has been studied for the treatment of uncomplicated influenza. (Furuta et al., 2013) Influenza epidemics occur on an annual basis and have a significant impact worldwide: they are estimated to affect five to 10% of adults and 20 to 30% of children each year. (http://www.who.int/en/news-room/fact-sheets/detail/influenza-[seasonal]) Globally, approximately 3 to 5 million cases of severe illness occur annually, resulting in 290,000 to 650,000 deaths. In the US, an average of 30,000 influenza-associated deaths occur annually. (https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5933a1.htm) The pathogenicity of a circulating influenza strain results in significant year-to-year variations in morbidity and mortality. Emerging lethal and highly virulent strains and rising resistance to existing antiviral drugs exacerbate the need for agents against influenza that have novel mechanisms of action. Literature reports suggest that early antiviral drug intervention, ideally within 24 hours of symptom onset, can significantly reduce the time to symptom alleviation and accelerate reduction in viral load and shedding. (https://www.cdc.gov/flu/antivirals/whatyoushould.htm, Sleeman et al., 2010)

In vitro studies have demonstrated activity against Ebola and other RNA viruses (eg, Lassa fever [*Arenaviridae]*, *Bunyaviridae*, Chikungunya virus [*Alphavirus*], etc) via a similar mechanism of action. (Furuta et al., 2013) There is currently no proven treatment for Ebola infection. However, the current standard of care in several West African nations includes favipiravir in addition to supportive care.

Favipiravir has been in clinical development since 2007. On 10 January 2012 Toyama Chemical Co., Ltd. transferred sponsorship of Investigational New Drug (IND) 73,727 to Fujifilm Pharmaceuticals USA, Inc. for the development of T-705a (favipiravir) in the US. On 16 May 2013 Fujifilm Pharmaceuticals USA, Inc. transferred sponsorship of IND 73,727 to MDVI, LLC (MDVI). The clinical development program of favipiravir was financially supported by the US Department of Defense (Joint Project Manager—Transformational Medical Technologies, Emerging Infectious Disease Medical Counter Program Transformational Medical Technologies, Emerging Infectious Disease Medical Counter Measure Program, T-705 Development, contract No. HDTRA1-12-C-0031). Then, on 10 April 2018 this IND was placed on Inactive status after the development of favipiravir in uncomplicated influenza was discontinued in the US. Favipiravir has been approved for stockpile for pandemic of a new strain of influenza in Japan. In February 2020, the Chinese regulatory agency approved favipiravir for use in China under similar conditions.

4. PHYSICAL, CHEMICAL, AND PHARMACEUTICAL PROPERTIES AND FORMULATION

4.1. Drug Substance and Nomenclature

The physical and chemical properties of favipiravir and the finished favipiravir tablet are summarized below in Table 1 and Table 2 respectively. The tablet chosen for further development contains 200 mg of favipiravir as the active ingredient and includes inactive ingredients commonly used in oral tablet formulations.

Table 1: Physical and Chemical Properties of Favipiravir Drug Substance

US Adopted Name/ International nonproprietary name:	Favipiravir
Chemical name:	6-fluoro-3-hydroxypyrazine-2-carboxamide
Lab Code:	T-705
Chemical Abstracts Service number:	259793-96-9
Molecular formula:	$C_5H_4FN_3O_2$
Molecular weight:	157.10
Description:	Favipiravir is a white to light yellow powder. Favipiravir is sparingly soluble in acetonitrile and methanol, and slightly soluble in ethanol and water.
Melting point:	191°C
Stability:	Favipiravir is stable for 5 years at 15 to 30° C (59 to 86° F).

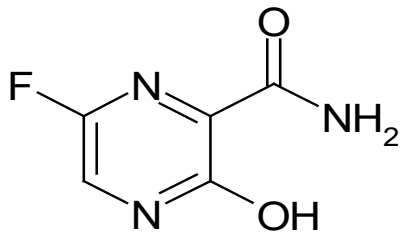
Table 2: Physical and Chemical Properties of Favipiravir Drug Product: 200 mg Tablet

Description:	Light yellow round tablet 8.7 mm in diameter.
Active Ingredient:	One tablet contains 200 mg of favipiravir.
Preparation	Tablets are manufactured using a wet granulation process.
Inactive Ingredients:	Compendial grade excipients commonly used in oral tablet formulations: colloidal silicon dioxide (diluent), povidone K30 (binder), low-substituted hydroxypropyl cellulose (disintegrant), crospovidone (disintegrant) and sodium stearyl fumarate (lubricant) and film coated with OPADRY, which includes hypromellose (2910, 6mPa·s), titanium dioxide, talc and yellow ferric oxide.
Release test items:	Description, identification, related compounds, uniformity of dosage units, dissolution, assay, microbial evaluation
Stability:	Stability studies are in progress (container: carded blister/aluminum pouch with desiccant). Favipiravir tablets are stable at 30°C/65% RH for 60 months.

4.2. Chemical Structure

The chemical structure of favipiravir, 6-fluoro-3-hydroxypyrazine-2-carboxamide, is presented in Figure 1.

Figure 1: Chemical Structure of Favipiravir



4.3. Storage, Handling and Investigational Product Accountability

The investigational product kit is supplied in an aluminum-coated pouch containing desiccant and a blister card. The blister card contains 50 favipiravir tablets or matching placebo reflecting the dosing schema. The drug has been supplied in bottles in Phase 1 studies and for several patients with a variety of RNA viruses who were treated under compassionate use.

All study medication is to be kept in a dry area, stored at 15° to 30°C (59° to 86°F) and shielded from direct light. A record of the minimum and maximum daily temperatures during storage is to be maintained at depots and sites prior to dispensing.

5. NONCLINICAL STUDIES

The nonclinical development program for favipiravir has followed the International Conference on Harmonisation (ICH) M3 (R2), Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (February, 2013) guideline as well as several other ICH guidelines related to genetic toxicology and developmental toxicity studies, and most studies, including pivotal studies, have been conducted in compliance with Good Laboratory Practices (GLP).

Repeat dose toxicity studies consist of 28-day studies in rats and dogs and 14 days in monkeys. For rats, the NOAEL was 32 mg/kg/day. The threshold effect level was 80 mg/kg/day, at which reduction in weight gain and minor alterations in various clinical pathology parameters were observed. Mortality was seen at 200 mg/kg/day. Histopathological effects were limited to decreased hematopoiesis.

In the 28-day dog study, the NOAEL was 10 mg/kg/day. The major effect was in the male reproductive organs where decreased weights were seen in the testes and accessory glands at all doses, particularly at 100 mg/kg/day. These findings were not statistically significant nor dose related. Histopathological effects (hypospermatogenesis) were limited to the high dose of 300/100 mg/kg/day (animals were first dosed at 300 mg/kg/day then the dose was reduced to 100 mg/kg/day). The other threshold effect level was 30 mg/kg/day where emesis and decreased weight gain were noted. Mortality was seen at 300 mg/kg/day.

In monkeys, the NOAEL was 100 mg/kg/day following 14 days of treatment. At higher doses, body weight gain was reduced and some alterations in clinical pathology parameters were noted. Histopathological effects were limited to vacuolar degeneration of hepatocytes and minor necrotic changes in the seminal vesicles in some but not all males. The testicular effects seen in the dog were not observed in the monkey.

Testicular effects seen in the initial toxicity studies were followed up with 13 additional studies, most of which were two weeks in duration. The NOAELs for testicular effects were 300, 60, 200, 100 and 150 mg/kg/day for mice, rats, rabbits, dogs and monkeys, respectively. A discussion of the effects on the male reproductive system is presented in a later section.

In a male and female fertility study conducted in rats, a reduced pregnancy rate occurred at doses of ≥100 mg/kg/day, and increases in pre- and post-implantation loss occurred at doses down to 30 mg/kg/day. Male reproductive organ weights were affected at ≥30 mg/kg/day, abnormal sperm were noted at ≥60 mg/kg/day, and decreases in sperm motility occurred at all doses (≥30 mg/kg/day). In a subsequent study, no male reproductive effects were seen at doses up to 30 mg/kg/day, however, early embryonic development (pre- and post-implantation loss) were mediated through treatment effects of females. The antiviral drugs valacyclovir and ribavirin had similar effects on early embryonic development to favipiravir. Effects with ribavirin occurred at subclinical exposures, which may be attributed to its accumulation in tissues and longer biological half-life. By contrast, effects with favipiravir and valacyclovir occurred at clinical or low multiples of clinical exposures and therefore showed a more favorable safety profile.

Embryo-fetal development was evaluated in mouse, rat, rabbit, and monkey. Teratogenicity (fetal malformations) occurred in all species at doses causing mild to marked maternal toxicity

and was accompanied by embryolethality in rat and mouse but not in rabbit or monkey. Fetal malformations occurred at doses of 300, 100, 600, and 200 mg/kg/day in the mouse, rat, rabbit, and monkey, respectively. NOAELs for developmental toxicity, based primarily on fetal body weight changes, were 100, 20, 300, and 100 mg/kg/day in those species, respectively, and were similar to NOAELs demonstrated for general toxicity in 14- or 28-day pivotal studies. When compared to two other antiviral drugs, favipiravir had a margin of safety (ie, low multiples of clinical exposure) for developmental toxicity similar to valacyclovir (Pregnancy Category B) and a more favorable margin than ribavirin (Pregnancy Category X), which caused teratogenicity at subclinical exposures.

Early embryonic and embryo-fetal developmental toxicity studies with the T-705M1 metabolite revealed no teratogenicity or other developmental effects at doses of up to 100 mg/kg/day in rats and 300 mg/kg/day in rabbits. Based on dose range finding studies in rabbits and cesarean section data from the definitive study in rabbits, T-705M1 does not appear to be teratogenic in rabbits. The T-705M1 teratology studies in rabbits provided the rationale for contraception period reduction from three months to seven days after the last dose for both men and women.

Phototoxic effects have been seen with favipiravir in mice at 100 mg/kg and 300 mg/kg groups and in guinea pigs at 100 mg/kg. In mice at the 100 mg/kg dose, erythema was observed at 0.5 and 24 hours after ultraviolet A (UVA) irradiation and was alleviated or disappeared at 48 and 72 hours. In the 300 mg/kg dose in mice, erythema was observed at 0.5 to 72 hours after UVA irradiation. No skin reactions were observed in non-irradiated animals receiving favipiravir. In guinea pigs, slight erythema was noted at 24 hours after UVA exposure but subsided after 48 hours.

Two proof-of-concept studies of favipiravir in cynomolgus macaques infected with Ebola Zaire were conducted. Both studies showed antiviral activity, as measured by prolonged survival, a 2 log reduction in plasma viral titer, and delay in onset of Ebola virus specific organ toxicities (specifically, renal toxicity and hepatotoxicity).

Favipiravir has been extensively studied in rodent and nonrodent toxicology and safety pharmacology evaluations. These studies show that the threshold effects can be monitored clinically and are reversible. Specific effects observed in animals at doses lower than the proposed clinical doses have been shown not to occur in humans (testicular changes) or have been addressed by requirements included in the clinical protocol (teratogenic effects).

5.1. Nonclinical Pharmacology

5.1.1 Mechanism of Action

Favipiravir is a nucleic acid analogue that is ribosylated and phosphorylated within cells forming T-705-ribosylmonophosphate (T-705RMP) which can be further phosphorylated to the di- and triphosphate analogues (T-705RDP & T-705RTP respectively). As with other nucleoside analogues, studies suggest favipiravir interferes with viral RNA replication.

Initial studies (Furuta et al., 2005) demonstrated that T-705RTP but not T-705RMP or favipiravir inhibited influenza viral RNA synthesis by viral polymerase in vitro at low micromolar concentrations. In infected Madin-Darby canine kidney cells favipiravir inhibition of viral replication was reversed by the addition of a 10-fold excess of purines or purine nucleosides but not by pyrimidines or pyrimidine nucleosides. No effect on human deoxyribonucleic acid (DNA)

polymerases (alpha, beta, gamma) or RNA polymerase II was observed at concentrations up to 2650- and 80-fold above the effective antiviral concentrations, respectively.

Additional work has demonstrated T-705RTP competes with purine nucleotide incorporation into nascent viral RNA strands resulting in early chain termination. These findings have been independently confirmed with recombinant influenza viral polymerase. (Jinet al., 2013) A polymerase complex was incubated with guanosine triphosphate, adenosine triphosphate, T-705RTP and 3'deoxyguanosine triphosphate following which viral RNA production was monitored. T-705RTP in low micro molar concentrations was observed to both incorporate into growing RNA chains (hence causing mutations (Baranovich et al., 2013) as well as early chain termination).

In Vitro and In Vivo Bioactivity in Influenza:

In vitro studies have shown that favipiravir is active against isolates of influenza A (H5N1) avian influenza virus, with mean effective concentration to 50% (EC_{50}) values ranging from 0.4 to 1.9 µg/mL. In addition, favipiravir was effective against multiple clinical strains of influenza A (seasonal H1N1, H1N1 pandemic 2009 and H3N2), including those resistant to existing treatments (eg, oseltamivir and amantadine). Watanabe et al., demonstrated in vitro and in vivo activity against three different strains of H7N9. (Watanabe et al., 2013)

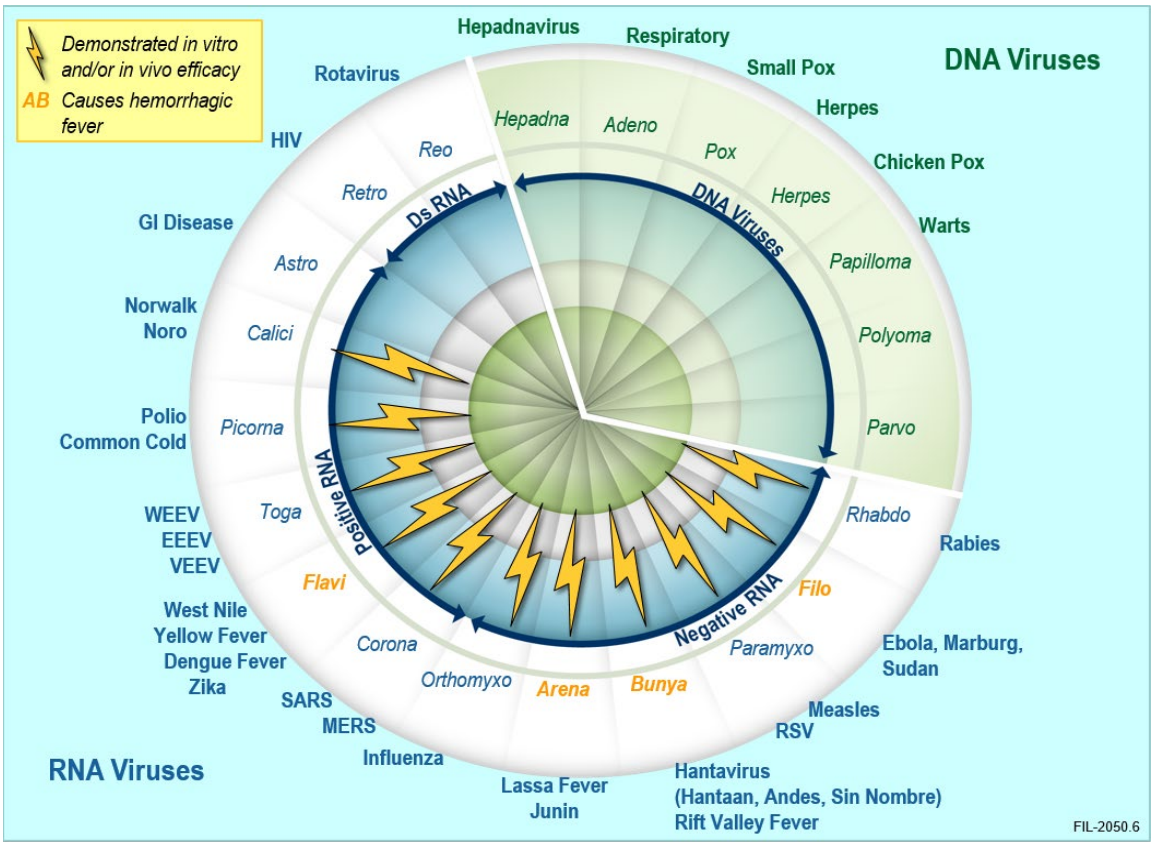
Growing patient specimens in vitro in the presence of favipiravir did not generate resistance to favipiravir. More than 500 isolates (consisting of subtype A/H1N1 pdm09, A/H3N2 and Type B) were isolated during two Japanese Phase 3 clinical studies. The EC_{50} values were in the range of 0.045 – 3.8 µg/mL. Similar results were obtained on testing 525 isolates obtained in the more recent US Phase 2 clinical study US204, from Day 1 samples (prior to exposure to favipiravir) and last virus positive samples (from all treated patients in whom nasopharyngeal samples were virus positive on Day 2 or beyond). EC_{50} values in the range of 0.05 – 3.99 µg/mL were documented.

In combination studies in infected mice a synergistic effect between favipiravir and oseltamivir in the inhibition of growth of influenza A (H1N1 and H3N2) virus strains was demonstrated. An in vitro assessment of the combination effect of favipiravir with zanamivir, peramivir, or laninamivir demonstrated a synergistic effect in the inhibition of growth of the influenza A (H3N2) virus. The major metabolite of favipiravir, T-705M1, with an IC_{50} >100 µg/mL against influenza A (H1N1) virus, had no detectable antiviral activity.

Five in vivo studies have shown that mice challenged with a lethal dose of different serotypes of influenza that were treated with favipiravir had a significant dose-dependent improvement in survival with doses of >30 mg/kg for five days associated with increased survival in mice infected with the H1N1 virus or the H3N2 virus. Mice that survived the initial challenge were protected against rechallenge with the same strain. The combination of favipiravir with oseltamivir showed a synergistic effect compared to treatment with favipiravir alone (>50 mg/kg for 7 days).

In Vitro and In Vivo Bioactivity in Other RNA Viruses

A study of the RNA-dependent RNA polymerase from the 20 different RNA viruses, both positive and negative strand, demonstrated they share structural similarities (Jacome et al., 2015) which may explain why favipiravir has been shown to inhibit growth of viruses from the twelve different families tested, including arenaviruses.



IC50 data indicate that therapeutic levels for many of these viruses can be reached in humans. Most may require a higher dose regimen than that used for influenza.

Concentration at which viral growth in cultured cells is inhibited by 50%

Virus	USAMRIID	Literature
	IC_{50} (µg/ml)	
Lassa Fever (Josiah strain)	10	4.6[1]
SARS-CoV-2		9.7[2]
Marburg	9.9	
Ebola	66	47[3], 10.5[4]
Influenza		< 4[5]

[1] Oestereich, et al.,2016
[2] Wang, et al.,2020
[3] Smithers, et al.,2014
[4] Oestereich, et al.,2014
[5] Sleeman, et al.,2010

Group	Family	Virus	EC50 (µg/mL)	Reference
(+) strand RNA virus	Flaviviridae	West Nile virus	53	Antiviral Res. 2008
		Yellow fever virus	42	Antimicrob Agents Chemother. 2009
	Togaviridae	Western equine encephalitis virus	49 (EC_{90})	Antiviral Res. 2009
		Chikungunya virus	0.3-9.4	J Antimicrob Chemother. 2014
	Picornaviridae	Poliovirus	4.8	Antimicrob Agents Chemother. 2002
		Rhinovirus	23	Antimicrob Agents Chemother. 2002
	Caliciviridae	Norovirus	13-25	Biochem Biophys Res Commun. 2012
(-) strand RNA virus	Orthomyxoviridae	Influenza A virus (seasonal)	0.01-0.94	Antimicrob Agents Chemother. 2002, 2010
		Influenza A virus (H5N1)	0.2-1.9	Antimicrob Agents Chemother. 2007, 2010
		Influenza A virus (H7N9)	0.38-0.74	Antivir Chem Chemother. 2014
		Influenza B virus	0.04-0.8	Antimicrob Agents Chemother. 2002, 2010
		Influenza C virus	0.03-0.06	Antimicrob Agents Chemother. 2002
	Paramyxoviridae	Respiratory syncytial virus	41	Antimicrob Agents Chemother. 2002
	Bunyaviridae	La Crosse virus	5	Antimicrob Agents Chemother. 2007
		Rift Valley fever virus	4.2-5.0	Antimicrob Agents Chemother. 2007, Antiviral Res. 2010
		Sandfly fever virus	4.7-18	Antimicrob Agents Chemother. 2007, Antiviral Res. 2010
		Andes virus	2.5-5.0 (EC_{90})	Antimicrob Agents Chemother. 2013
		Crimean-Congo hemorrhagic fever virus	0.6-2.8	PLoS Negl Trop Dis. 2014
	Arenaviridae	Junin (Candid 1)	0.8-1.4	Antimicrob Agents Chemother. 2007, Antiviral Res. 2010
		Pichinde	0.9-3.9	Antimicrob Agents Chemother. 2007, Antiviral Res. 2010
		Guanarito	2.6	Antimicrob Agents Chemother. 2011
		Machupo	2.2	Antimicrob Agents Chemother. 2011
	Filoviridae	Ebola	10.5	Antiviral Res. 2014

5.1.2 Secondary Pharmacology

Favipiravir (1 mM) was tested for off-target reactivity in in vitro radioligand binding assays against 25 purified receptors, including CYP 19, steroid 5α-reductase, androgen, cholecystokinin, dopamine, estrogen, histamine, progesterone, opiate, the serotonin family of receptors, thyroid hormone, and vasoactive intestinal peptide. Favipiravir showed no inhibition of any receptor except human progesterone PR-B, which showed 96% inhibition at 1 mM.

In another study, investigators evaluated the effect of favipiravir on progesterone receptors via a human progesterone receptor–binding assay. Six concentrations of favipiravir were tested (31.25 – 1000 μmol/L). Favipiravir showed no effect on progesterone receptors at concentrations up to 1000 μmol/L.

5.1.3 Safety Pharmacology

In a series of safety pharmacology studies, favipiravir did not affect the central nervous system in mice (up to 500 mg/kg), cardiovascular system in dogs (up to 150 mg/kg), or respiratory system in rats (up to 2000 mg/kg). Although a statistically significant inhibition was observed on the hERG channel, in vitro, the magnitude of this change was slight (8.1% inhibition at the highest concentration, 1000 μM, tested vs. 2.7% in controls). In dogs dosed with favipiravir up to 150 mg/kg or T-705M1 dosed at 30 mg/kg, no QTc effects were observed.

5.2. Pharmacokinetics and Product Metabolism in Animals

Single doses administered to mice (8 mg/kg) by both oral and IV routes demonstrated favipiravir half-lives of 2 and 1.8 hours, respectively with an oral absolute bioavailability of 97.6% in this species.

Toxicokinetics was determined as a part of the 28-day toxicity studies in rats and dogs and in the two-week study in monkeys. In the rat and dog studies, plasma C_{max} and AUC increased with increasing dose. Female rats exhibited slightly higher plasma levels than males with a slightly longer half-life. In monkeys, plasma levels increased with increasing dose, but the increases were nonlinear. Half-lives were increased 2 to 3 times at the highest dose (300 mg/kg/day) compared to 100 and 200 mg/kg/day. Plasma levels were four times higher after two weeks of treatment than they were on the first day. Gender differences were not apparent.

Metabolic studies in rats and monkeys indicate that favipiravir is extensively metabolized and primarily excreted in the urine. In the rat, excretion in the urine was 80% with approximately 18% excreted in the feces. The major metabolite was identified as T-705M1 with smaller amounts of the glucuronide T-705M2. Favipiravir was metabolized to the major metabolite by aldehyde oxidase in human liver cytosol. Protein binding was primarily (near 100%) to albumin.

Favipiravir inhibited CYP2C8 in human liver microsomes; however, the IC_{50} was 477 μM. Favipiravir showed little or no induction or inhibition of CYP1A2, CYP2C9, CYP2C19 and CYP3A4 in human hepatocytes.

Tissue distribution studies utilizing ^{14}C-labeled favipiravir have shown the plasma-to-tissue ratio in the cynomolgus monkey range between 0.42 to 0.72 in the liver, lung, adrenal gland, and spleen. All other plasma-to-tissue ratios were less than 0.39 at 4 hours after a single oral dose.

5.3. Toxicology

5.3.1 Single-Dose Studies

Single oral doses of favipiravir given to rats and mice at doses of 1000 and 2000 mg/kg, respectively, produced no mortality in primary studies. In a study designed to compare toxicity between two drug substance lots, a single female rat died at 2000 mg/kg with each lot. Transient suppression of weight gain or weight loss was observed. Favipiravir given intravenously to rats and mice at 2000 mg/kg likewise produced no mortality, but decreased activity was observed.

5.3.2 Repeat-Dose Studies

Repeat-dose toxicology studies consist of a 4-week study in rats, a 4-week study in dogs, and a 2-week study in monkeys, with a one-month recovery period in the rat and dog studies and an eight-week recovery period in the monkey study. Prior to conducting the studies in rats, monkeys and dogs, a series of dose-ranging studies were conducted in order to establish appropriate doses for the IND-enabling studies. These pilot studies were conducted in rats and dogs as well as in mice and rabbits (to support other types of studies such as teratology). These studies were generally non-GLP and are not summarized in this document.

5.3.2.1. Rats

In the IND-enabling study in rats, Sprague Dawley rats (n = 10/sex/group) were administered favipiravir orally via gavage at total daily doses of 0 (0.5% methylcellulose vehicle), 13, 32, 80 and 200 mg/kg/day for 28 days. The total daily dose was administered as equally divided doses and administered approximately 8 hours apart. An additional 5 rats/sex were added to the control, 80 and 200 mg/kg/day groups and were included to evaluate recovery over a 28-day period. Parameters evaluated included clinical observations, body weight, food consumption, ophthalmology, clinical pathology, gross pathology, organ weights and histopathology (all tissues in the control and high-dose groups at the terminal necropsy and target tissues in the low- and mid-dose groups at the terminal necropsy and in all groups at the recovery necropsy). An additional 44 animals/sex/group were included for toxicokinetic analyses on Days 1 and 28; all samples were terminal bleeds.

No toxicologically meaningful effects were observed among any of the evaluated parameters at doses up to and including 32 mg/kg/day and this dose was considered the NOAEL. At 80 and 200 mg/kg/day, the following effects were noted: a reduction in weight gain; reductions in red blood cell (RBC) parameters; and increased alkaline phosphatase. Additional effects seen at 200 mg/kg/day included mortality (one male), broken incisors, decreased reticulocytes, prolongation of prothrombin time (PT) and activated partial thromboplastin time (APTT), and increases in ALT and bilirubin. Some changes in relative organ weights were a consequence of reduced weight gain. Histopathological effects were limited to decreased hematopoiesis at 200 mg/kg/day which were not apparent at the end of the recovery period. However, no effects were seen in the liver to support the described liver enzyme observations.

5.3.2.2. Dogs

Beagle dogs (n = 3 or 6/sex/group) were administered favipiravir orally via capsule at total daily doses of 0 (empty capsules), 10, 30, 100 and 300 (males only) mg/kg/day for 28 days. The doses were equally divided and administered approximately 8 hours apart. The dose of 300 mg/kg/day was reduced to 100 mg/kg/day beginning with the second week of treatment due to observed toxicity. An additional 2 dogs/sex were added to the control, 100 mg/kg/day (female only) and 300 mg/kg/day groups and were subjected to a 28-day recovery period. Parameters evaluated included clinical observations, body weight, food consumption, ophthalmology, clinical pathology, toxicokinetics, gross pathology, organ weights and histopathology (all tissues in all groups at the terminal and the recovery necropsy).

No toxicologically meaningful effects were observed among any of the evaluated parameters at 10 mg/kg/day and this dose was considered the NOAEL. At 30 mg/kg/day and above, emesis, and decreased body weights and food consumption was observed. Additional effects observed at 100 mg/kg/day included body weight loss and decreased food consumption (also seen at 30 mg/kg/day), increased white blood cell (WBC) counts, fibrinogen, urea nitrogen, and lactate dehydrogenase values as well as a prolongation of APTT (females only). At 300 mg/kg/day, two animals died (likely due to severely decreased food consumption), and animals in this group also showed decreased RBC parameters (including reticulocytes), a prolongation of activated partial prothrombin time, and elevated ALT and AST in the animals that were sacrificed in a moribund condition and decreased prostate weights. Creatinine values were increased only at Week 1 with no subsequent identified effects in the kidney. Histopathological evaluation in the two high-dose males that were moribund and sacrificed or found dead revealed degeneration of germinal epithelial cells, hypospermatogenesis, prostatic atrophy, and atrophy of the epididymides, as well as effects in some other tissues. For survivors, slight degeneration of germinal epithelial cells and severe hypospermatogenesis were also noted in one male at 300 mg/kg/day. No other tissues were affected. The hypospermatogenesis persisted in two recovery males.

5.3.2.3. Monkeys

In the definitive study in monkeys, cynomolgus monkeys (n = 5/sex/group) were administered favipiravir orally by gavage at total daily doses of 0, 100, 200 and 300 mg/kg/day for 14 days. The doses were equally divided and administered approximately 8 hours apart. Two (2) monkeys/sex were subjected to an 8-week recovery period. Parameters evaluated included clinical observations, body weight, food consumption, ophthalmology, clinical pathology, serum testosterone and inhibin B levels (males only), toxicokinetics, gross pathology, organ weights and histopathology (all tissues in all groups the terminal and recovery necropsy).

No toxicologically meaningful effects were observed among any of the evaluated parameters at 100 mg/kg/day and this dose was considered the NOAEL. At 200 and 300 mg/kg/day, body weights and food consumption were reduced and at 300 mg/kg/day weight loss occurred. Fibrinogen and triglycerides were elevated at 200 mg/kg/day and above. At 300 mg/kg/day, animals exhibited salivation, prolongation of PT, decreased red cell parameters, increased AST and ALT, and decreased albumin, cholesterol and glucose. Histopathological effects considered toxicologically significant were limited to vacuolar degeneration of hepatocytes at 300 mg/kg/day. However, very slight single cell death in the epithelium of the seminal vesicles was noted in two

males each at 200 and 300 mg/kg/day. It was reported that the toxicological significance of this finding was unclear since there was no change in incidence and severity with dose.

5.3.3 Genetic Toxicology

Genotoxicity studies have been conducted with favipiravir, and additional studies were conducted evaluating T-705M1.

Three studies were negative: the Ames test; the in vivo micronucleus assay in rats, following two daily doses at up to 1000 mg/kg (a near lethal dose of 2000 mg/kg produced a positive response by a secondary mechanism); and the in vivo unscheduled DNA synthesis assay, conducted in rats at single doses up to 2000 mg/kg.

Two in vitro studies produced positive responses. Both the chromosomal aberration (without metabolic activation) and mouse lymphoma assays (with and without metabolic activation) produced a dose related increase in mutation frequencies. A series of additional studies were completed demonstrating that the original findings were influenced by experimental conditions including cell density and excess nucleoside concentrations, as well as an imbalance of the intracellular nucleotides pool in the cells used in the chromosomal aberration assay. MDVI believes that these responses do not represent a risk to humans since they have been observed with other nucleoside analogues.

In the evaluation of T-705M1 the Ames test, the chromosomal aberration assay, and the in vitro micronucleus assay were all negative.

5.3.4 Reproductive and Developmental Toxicity

Reproductive and developmental toxicity studies have been completed with favipiravir according to ICH guidelines, including male and female fertility and early embryonic development studies in rats, embryo-fetal development studies in multiple species, and a pre-/postnatal development study in rats. In addition, the major metabolite, T-705M1, has been evaluated for effects on early embryonic and embryo-fetal development in the rat and rabbit. The developmental and reproductive toxicity of favipiravir has also been compared to two other marketed nucleotide analogue antiviral drugs in two separate studies.

Studies on favipiravir showed the NOAEL for fertility effects in rats was <30 mg/kg/day. Favipiravir was shown to be teratogenic in mice, rats, rabbits and monkeys. The NOAELs for developmental effects were 100, 20, 300 and 100 mg/kg/day for mice, rats, rabbits and monkeys, respectively. Developmental toxicity studies on the T-705M1 metabolite revealed no reproductive or teratogenic effects in rats or rabbits.

5.3.4.1. Fertility and Early Embryonic Development Studies

A fertility and embryonic development study was conducted in which both male and female rats were administered total doses of 0, 30, 60 100, 200, and 300 mg/kg (males only; the dose was subsequently lowered to 200 mg/kg/day) by oral gavage (BID). In males, dosing occurred from 63 days prior to mating through sacrifice; in females, dosing occurred from 14 days prior to mating through gestation day (GD) 7, and cesarean sections were performed on GD20. Parameters evaluated in the parental animals included clinical observations, body weight, food

consumption, gross pathology, organ weights, sperm analysis in males, and histopathology in select animals. Endpoints evaluated in the offspring included cesarean parameters and fetal weight, sex ratio, and external morphology.

Significant mortality occurred in males at the original high dose of 300 mg/kg/day, resulting in a lowering of the high dose to 200 mg/kg/day in males and the use of this dose as the high dose in females. Prostatitis accompanied by hemorrhage and seminal vesiculitis was observed in premature decedents and urination disorders due to prostatic inflammation and consequent postrenal renal failure was considered the cause of death. Significant reductions in body weight and body weight gain occurred premating in males and females at ≥100 mg/kg/day, and postmating in females at ≥60 mg/kg/day. Clinical signs of yellow hair and nails, and teeth fractures occurred at ≥30 mg/kg/day. Mating behavior was not affected by treatment, but a significant reduction in the percentage of mated females that were pregnant (fertility index) occurred at ≥100 mg/kg/day. In female animals there were dose related increases in pre-implantation loss which resulted in decreased implantation rates, and increases in post-implantation loss (embryo-fetal lethality) at all doses. In males, the percentage of motile sperm and sperm activity was slightly, but statistically significantly, decreased at all doses, with morphologically abnormal sperm noted at ≥60 mg/kg/day.

In a follow-up study conducted at total doses of 0, 3, 10, and 30 mg/kg/day (BID), treated males were mated to untreated females, and treated females were mated with untreated males under the same treatment conditions as the original study. No male reproductive effects were noted at any dose. After treatment of females, mating parameters were not affected, but post-implantation loss was significantly increased at 30 mg/kg/day, resulting in a reduction in fetuses per litter, and fetal weights were also significantly reduced at this dose. Reproductive parameters were generally not affected after treatment of females at 3 or 10 mg/kg/day, with the exception of female fetal weight which was significantly reduced at 10 mg/kg/day. The NOAEL was 30 mg/kg/day for male and female reproductive function and 3 mg/kg/day for early embryonic development. The results suggest that effects on early embryonic development (pre- and post-implantation loss) observed in the previous study were mediated through effects in the female.

An investigative study was conducted to evaluate susceptible periods during early embryonic development (pre-conception through implantation). Groups of 10 – 12 female rats were administered a total dose of 30 mg/kg/day (BID) during the following periods: 14 days prior to mating through mating; GD0-7; GD0-3; or GD4-7. Cesarean sections were conducted on GD20. Treatment with favipiravir prior to and through mating did not adversely affect embryo-fetal development. As shown in previous studies, there was a significant increase in post-implantation loss when treatment occurred during the entire preimplantation period or GD0-7. Embryo-fetal survival was not affected when treatment occurred for shorter durations within this window, but fetal body weights were significantly reduced after treatment on GD0-3.

5.3.4.1.1. Early Embryonic Antiviral Comparison Study

The early embryonic development of favipiravir (10, 30 mg/kg/day) was compared to two other nucleic acid analogue antivirals, ribavirin (30, 100 mg/kg/day) and valacyclovir (100, 200, 400 mg/kg/day) in a study in which test articles were administered by oral gavage on GD0-7 and cesarean sections were performed on GD20. Increased post-implantation loss (including total litter loss) and reductions in fetal body weight occurred at doses of 30, ≥30, and 400 mg/kg/day

for favipiravir, ribavirin and valacyclovir, respectively. The lowest observed adverse effect level for ribavirin on early embryonic development was an order of magnitude lower than recommended clinical exposure levels, which may be attributed to its accumulation in tissues and longer biological half-life. By contrast, favipiravir and valacyclovir exhibited comparable rat: human clinical AUC ratios based on developmental toxicity: 1.2 for favipiravir and 4.9 for valacyclovir.

5.3.4.2. Embryo-Fetal Development Studies

Embryo-fetal development studies have been completed in the mouse, rat, and rabbit, and a non-pivotal embryo-fetal development study was completed in the non-human primate. Developmental toxicity including fetal abnormalities, embryo-fetal lethality and decreased fetal weights occurred in all species. In general, teratogenic effects (fetal malformations) occurred at doses that also caused maternal toxicity and in some species at higher doses than those causing other forms of developmental toxicity. Teratogenicity was seen at doses of 300, 100, 600, and 200 mg/kg/day in the mouse, rat, rabbit, and monkey, respectively, and NOAELs for developmental toxicity were 100, 20, 300, and 100 mg/kg/day in those same species based primarily on fetal body weight changes and minor morphologic alterations.

5.3.4.2.1. Rat Embryo-Fetal Development Study

Favipiravir was administered by oral gavage (BID) to groups of 20 Sprague Dawley rats at total doses of 0, 6, 20, 60, and 200 mg/kg/day from GD7-17, and cesarean sections were performed on GD20 . Parameters evaluated included clinical observations, body weight, food consumption, gross pathology, cesarean section parameters, fetal and placental weight, sex ratio, and fetal external, visceral and skeletal morphology.

Maternal toxicity occurred in the form of significant reductions in body weight, body weight gain and food consumption, and few or loose stools at the high dose of 200 mg/kg/day, and yellow coloring of hair and nails at ≥60 mg/kg/day. Favipiravir caused an increase in post-implantation loss, including total litter loss, and a marked decrease in the number of live fetuses per litter in the 200 mg/kg/day group. In addition, an increased incidence of visceral malformations (membranous ventricular septum defect and thymic remnant in the neck), skeletal fetal variations, and significant reductions in fetal weight (24 – 25% lower than control weights) were observed at 200 mg/kg/day. No teratogenic effects occurred at doses of 60 mg/kg/day or below. A slight, non-statistically significant, reduction in fetal weights (3 – 4% lower than control weights), decreased male placental weights and an increased incidence of a skeletal variation (supernumerary lumbar vertebra) occurred at 60 mg/kg/day, and the NOAEL for maternal and developmental toxicity was considered 20 mg/kg/day.

5.3.4.2.2. Mouse Embryo-Fetal Development Study

Favipiravir was administered (BID) by oral gavage to groups of 22 Crlj:CD1(ICR) mice at total doses of 0, 30, 100, 300, or 1000 mg/kg/day from GD6-15, and cesarean sections were performed on GD18 . Parameters evaluated included clinical observations, body weight, food consumption, gross pathology, organ weights, cesarean section parameters, fetal and placental weight, sex ratio, and fetal external, visceral and skeletal morphology.

One nonpregnant female died on GD17 and abortion was observed in 7 females in the 1000 mg/kg/day group. Lower body weight and lower body weight gain were observed in the 1000 mg/kg/day group in the latter half of the gestation period that was considered related to decreased food consumption and lower uterine weight (caused by fetal death). Lower mean daily food consumption during the last stage of gestation was observed in the 300 and 1000 mg/kg/day groups. Significant increases in relative organ weights occurred at ≥300 (lung) and 1000 (heart, liver, kidneys, spleen, ovaries) mg/kg/day. Yellow-colored hair and claws (≥300 mg/kg/day) and decreased activity (100 mg/kg/day) were also observed. Increased embryo-lethality (including total litter loss), decreased live fetuses per litter, and reductions in fetal body weight (24 – 27% relative to control) and placental weights were observed at 1000 mg/kg/day. Slight reductions in fetal body weights (4 – 6%) were also observed at 300 mg/kg/day. External fetal malformations occurred at ≥300 mg/kg/day (bent and/or short tail, exencephaly, meningocephalocele, short snout) and 1000 mg/kg/day (anal atresia, cleft palate). Visceral malformations (primarily cardiovascular and brain defects) and skeletal malformations (misshapen or fused skull, sternebrae, ribs, or vertebrae) occurred at 1000 mg/kg/day. There was also an increase in minor skeletal variations and incomplete ossifications at ≥300 mg/kg/day. No teratogenic effects or other signs of developmental toxicity were seen at 30 or 100 mg/kg/day, and the NOAEL for maternal and developmental toxicity was 100 mg/kg/day.

5.3.4.2.3. Rabbit Embryo-Fetal Development Study

Favipiravir was administered (BID) to groups of 22 (N=11 at 600 and 1000 mg/kg/day) mated New Zealand White rabbits at total doses of 0, 30, 100, 300, 600, or 1000 mg/kg/day on GD6-18, and cesarean sections were conducted on GD29 . Parameters evaluated included clinical observations, body weight, food consumption, gross pathology, organ weights, cesarean section parameters, fetal and placental weight, sex ratio, and fetal external, visceral and skeletal morphology.

Treatment-related maternal mortality occurred in 5 of 11 females in the 1000 mg/kg/day groups, respectively, and the remaining does were euthanized on GD12 or 13. At 600 mg/kg/day, mortality occurred in 3 of 11 females and one female aborted. Body weight loss occurred in survivors at the 600 mg/kg/day dose, and a 40% reduction in body weight gain (non-significant) occurred in the 300 mg/kg/day group. Reductions in food consumption of 19% (non-significant) and 49% occurred for the 300 and 600 mg/kg/day groups, respectively, and yellow coloring of hair was noted at ≥300 mg/kg/day. No external or visceral malformations and no differences in fetal body weights relative to controls occurred at any doses. At the lethal dose of 600 mg/kg/day, an increased incidence of a single skeletal malformation (hemicentric cervical centrum) occurred in addition to non-significant increases in a subset of skeletal variations. Therefore, the maternal NOAEL was considered to be 100 mg/kg/day, and the NOAEL for developmental toxicity was 300 mg/kg/day (favipiravir AUC = 1300 µg•h/mL; T-705M1 AUC = 402 µg•h/mL).

5.3.4.2.4. Monkey Embryo-Fetal Development Dose-Range Study

Favipiravir was evaluated in a dose-range finding study in which total doses of 0, 50, 100, or 200 mg/kg/day were administered (BID) to groups of 5 pregnant cynomolgus monkeys on GD20-50, and cesarean sections were conducted on GD100 . Endpoints evaluated included

clinical observations, body weight, food consumption, hematology, clinical chemistry, fetal and placental weight, and fetal external, visceral (including organ weights) and skeletal morphology, and toxicokinetic evaluations were performed on GD20 and 50.

A slight reduction in body weight gain was noted for 3 of 5 females in the 200 mg/kg/day group. There were no significant effects on fetal mortality, fetal weight, placental weight, fetal measurements, or organ weights. Three fetuses in the 200 mg/kg/day had fetal malformations (2 fetuses with cleft palate and one fetus with subcutaneous edema). One of the fetuses with cleft palate also had subcutaneous and pulmonary edema, a distended abdomen and polyhydramnios (excess amniotic fluid). These fetal findings were not in the historical control database and were, therefore, considered treatment-related. There were no teratogenic effects or other signs of developmental toxicity at doses up to and including 100 mg/kg/day (favipiravir GD20 AUC = 190 µg•h/mL; T-705M1 AUC = 313 µg•h/mL).

5.3.4.2.5. Embryo-Fetal Development Antiviral Comparison Study

The developmental toxicity of favipiravir (30, 100 mg/kg/day) was compared to two other nucleic acid analogue antivirals, ribavirin (Rebetol®, 3 and 10 mg/kg/day) and valacyclovir (200 and 400 mg/kg/day) , administered by oral gavage to pregnant rats on GD7 to 17. Cesarean sections were performed on GD20. Treatment-related fetal malformations occurred at 100 mg/kg/day for favipiravir, ≥3 mg/kg/day for ribavirin, and ≥200 mg/kg/day for valacyclovir. Rat: human exposure ratios were calculated for each drug based on the intended (favipiravir) or recommended (ribavirin and valacyclovir) clinical exposure. Favipiravir and valacyclovir (labeled as Pregnancy Category B) had comparable rat: human clinical AUC ratios based on developmental toxicity (~2 – 5 fold multiples of clinical exposure). Conversely, ribavirin (Pregnancy Category X), which accumulates in tissues and has a long biological half-life, showed teratogenicity at exposures that were 1 to 2 orders of magnitude lower than exposures at recommended clinical doses. It was concluded that the fetal risk for favipiravir was lower than for ribavirin.

5.3.4.3. Pre/Postnatal Development Study

In a pre- and postnatal development study in rats, total doses of 0, 10, 30, or 100 mg/kg/day were administered (BID) by oral gavage from GD7 through lactation day (LD) 20. Endpoints evaluated in dams (F0) included clinical observations, body weight, food consumption, delivery and lactation parameters, gross pathology, and organ weights. In pups (F1), endpoints included body weights, developmental landmarks, behavioral tests, reproductive performance, GD20 cesarean parameters, and F2 fetal body weight, sex ratio, and external morphology.

Effects on F0 maternal animals included decreased weight gain and food consumption during gestation and lactation, and yellow colored nails at 100 mg/kg/day, and yellow colored hair at ≥30 mg/kg/day. All females were pregnant and no females exhibited total litter loss. There were no effects on delivery or lactation parameters. In offspring, there was a decrease in the number of live pups per litter, and pup viability was decreased through postnatal day (PND) 4 at 100 mg/kg/day. Pup weights were also reduced at birth and remained lower than control weights through adulthood in the 100 mg/kg/day group. No treatment-related effects were noted for postnatal development, behavioral assessments (conditioned learning, open field tests) or any reproductive or parameters for F1 offspring, or developmental parameters for F2 offspring at any

dose. Therefore, the NOAEL was 10 mg/kg/day for maternal animals and 30 mg/kg/day for pre-/postnatal development of offspring.

5.3.4.4. Reproductive Toxicity Studies with the T-705M1 Metabolite

Reproductive toxicity with the T-705M1 metabolite has been evaluated in an early embryonic development study in rats and embryo-fetal development studies in rats and rabbits. The metabolite was administered intravenously and the high dose in each study was limited by the solubility of the metabolite in the IV formulation and the maximum volume that could safely be administered intravenously. No evidence of developmental toxicity, including teratogenicity, was observed in any of these studies.

In rats, T-705M1 at doses of 0, 25, 50, or 100 mg/kg/day was administered intravenously (10 mL/kg, 3 mL/min) on GD7-17 to groups of 21 – 23 pregnant dams, and cesarean sections were performed on GD20 . No clinical signs or changes in maternal body weight or food consumption were noted. T-705M1 was not teratogenic and there were no effects on any reproductive or developmental parameters. Therefore, the NOAEL for maternal and developmental toxicity was 100 mg/kg/day, the highest dose tested.

In an early embryonic development study in rats , T-705M1 at doses of 0, 25, 50, or 100 mg/kg/day was administered intravenously (10 mL/kg, 3 mL/min) on GD0-7 to groups of 22 females, and cesarean sections were conducted on GD20. There were no clinical signs or changes in body weight or food consumption in females. T-705M1 was not teratogenic and there were no effects on any reproductive or developmental parameters. Therefore, the NOAEL for maternal and early embryonic developmental toxicity was 100 mg/kg/day, the highest dose tested. At this dose, based on data from repeated dose toxicity studies, the AUC following repeated dosing would be approximately 32 µg•hr/mL.

In rabbits, T-705M1 at doses of 0, 100, 200, and 300 mg/kg/day was administered intravenously (1 hr infusion) on GD6-19 to groups of 22 – 24 pregnant New Zealand White rabbits, and cesarean sections were performed on GD29 . There were no treatment related effects on maternal mortality, clinical signs, body weight, or food consumption. T-705M1 was not teratogenic and there were no effects on any reproductive or developmental parameters. Therefore, the NOAEL for maternal and developmental toxicity was 300 mg/kg/day, the highest dose tested. At this dose, the AUC was 394 and 423 µg•hr/mL on the first and last day of dosing, respectively.

The T-705M1 teratology studies in rabbits provided the rationale for contraception period reduction from three months to seven days after the last dose for both men and women

5.3.4.5. Testicular Toxicity

In the original IND-enabling toxicology studies, no histopathological effects were noted in the reproductive organs of male rats at doses of up to 200 mg/kg/day (BID at 100 mg/kg/dose). In the dog study, a dose of 300 mg/kg/day produced germ cell degeneration/depletion, ductal atrophy, absence of sperm in epididymis, and atrophy of the prostatic acini. The dose of 100 mg/kg/day showed no effects in these organs.

Because of this and the effects seen in males in the previously described fertility study, 13 additional animal studies were conducted to provide additional information on potential effects

on male reproduction in mice, rats, rabbits, and monkeys. In addition, these studies were independently reviewed by a Board–certified veterinary pathologist.

Two studies were conducted in mice for two weeks at doses up to 1000 mg/kg/day. The GLP study in mice was inconclusive due to the occurrence of histopathological effects in the reproductive organs of control animals on this study. The second non-GLP study with two weeks of treatment at doses up to 300 mg/kg/day showed no effects at the highest dose.

In a single dose study in rats, favipiravir was administered at a dose of 1000 mg/kg and showed no histopathological effects.

In rats, two studies were conducted where favipiravir was administered at up to 100 mg/kg/day for seven days followed by a six-week recovery period. Both studies concluded that there were no treatment-related effects in reproductive tissues at the end of the treatment period or at the end of the six-week recovery period.

Three GLP two-week studies were completed in rats. The first two-week study was conducted where favipiravir was administered at doses of 30, 100, and 300 for 3, 5, 7, 10, and 14 days (to determine the time course of potential effects) followed by a four-week recovery period. At 100 mg/kg/day, no effects were seen in the testes or sperm at the end of the treatment period. However, at the end of a four-week recovery period, delayed effects included spermatid retention, minimal degeneration of spermatids (as noted by a consulting pathologist), a trend toward decreased sperm counts and motility (eg, 78% motility vs. 100% in controls), and some abnormal sperm morphology and epididymal cell debris in rats at 100 mg/kg/day. In the treatment group at 300 mg/kg/day, overt signs of toxicity were observed including some mortality, body weight loss and decreased food consumption. After five days of treatment, tubular dilatation was seen in one rat with no degenerative change seen in the testes. Seven days of treatment produced tubular dilatation and degeneration/necrosis of germ cells and early spermatocytes. After 10 days of treatment, principal effects were tubular dilatation and necrosis of spermatocytes. After 10 days of treatment, vacuolation of Sertoli cells, hemorrhage, and neutrophil infiltration in the interstitium were also seen. After 14 days of treatment, tubular necrosis was evident along with the described sperm effects. Due to mortality at 300 mg/kg/day, evaluation of recovery was limited, but generally the effects seen at the conclusion of the treatment period were still evident. The NOAEL in this study was 30 mg/kg/day.

The second two-week GLP study was conducted at 30, 100, and 200 mg/kg/day, but with three recovery periods (4, 13, and 26 weeks). At the end of the two-week treatment period, there were no histopathological effects in the testes or epididymides at 30 and 100 mg/kg/day. At 200 mg/kg/day, some but not all rats had unilateral or bilateral tubular dilatation, tubular necrosis and minimal degeneration of spermatids with cellular debris in the epididymal ducts. At the four-week recovery point, effects were still seen in some animals at 200 mg/kg/day. One animal at 100 mg/kg/day had spermatid retention. At the 13-week and 26-week recovery points, drug related effects were not observed. Tubular dilatation was observed in one animal at 26 weeks, but the relationship to treatment was questionable. The NOAEL for testicular toxicity in this study was 30 mg/kg/day. Full recovery of effects occurred at 13 weeks following discontinuation of dosing.

The third GLP study at a dose of 60 mg/kg/day showed no histopathological effects.

Two non-GLP two-week studies were conducted in rats with doses of 100 and 200 mg/kg/day and effects were compared with those seen in animals treated with ribavirin, valacyclovir, valganciclovir and famciclovir. The effects with favipiravir were similar to those described above, and were seen with the other antivirals except ribavirin. Valganciclovir induced a much greater response than favipiravir.

A single study was conducted in rabbits wherein favipiravir was administered for two weeks at doses of 200 and 600 mg/kg/day. Although the high dose of 600 mg/kg/day caused significant toxicity including mortality, it did not adversely affect spermatogenesis or sperm parameters. The NOAEL for reproductive toxicity and testicular changes was considered to be 200 mg/kg/day.

A study was conducted in the cynomolgus monkey wherein favipiravir was administered for two weeks at doses of 100, 200 and 300 mg/kg/day followed by an eight-week recovery period. There were no histopathological effects on the testes or epididymides at any dose. Effects seen in the seminal vesicles of some but not all animals at 200 and 300 mg/kg/day (single cell necrosis and slight atrophy of the acinar cells) may be related to decreased food consumption that could have reduced testosterone levels. In a six-week monkey study, the NOAEL for testicular changes was determined to be 150 mg/kg/day.

In an additional study in monkeys, males (n = 9/group) were administered favipiravir orally at doses of 70, 100, and 150 mg/kg/day. At the end of treatment, three males per group were sacrificed, three males were sacrificed after a 4-week recovery and the remaining three males were sacrificed after a 12-week recovery. Administration of favipiravir did not adversely affect any of the parameters examined except triglycerides which were increased at 150 mg/kg/day; this resolved during recovery. Testicular and epididymal weights were decreased in the high-dose males at the end of the 4-week recovery and relative epididymal weights were decreased at 100 mg/kg/day at the end of the 4-week recovery period. However, because there were no correlating microscopic changes and because these values were within the control range of the laboratory, they were not considered to be related to favipiravir. In this study, the NOAEL for testicular toxicity was determined to be 150 mg/kg/day.

The Sponsor and the FDA agree that the NOAELs for testicular effects are 200, 100, and 150 mg/kg/day in rabbits, dogs, and monkeys, respectively.

5.3.5 Local Tolerance Studies

Two phototoxicity studies were completed as follows: in a non-GLP guinea pig study, the intensity of phototoxicity of favipiravir was similar to that of levofloxacin and weaker than that of ciprofloxacin or sparfloxacin. A phototoxicity study, conducted in mice, showed that favipiravir was phototoxic at doses of 100 and 300 mg/kg, but showed no response at 30 mg/kg.

5.3.6 Other Toxicity Studies

Favipiravir was administered to rats for four weeks at doses of 13, 32, and 80 mg/kg/day followed by a four-week recovery period. Effects on the T-cell dependent antibody response were measured. Favipiravir did not affect the T-cell dependent antibody response.

Favipiravir and T-705M1 were evaluated for the potential to produce inflammatory cytokines using lipopolysaccharide-stimulated human peripheral blood mononuclear cells. Neither agent

had any effect in the production of interleukin (IL)-1, IL-6, IL-8 and tumor necrosis factor at up to 300 µg/mL and 100µg/mL, respectively. The third standalone toxicity study involved the evaluation of the potential of favipiravir to interact with ketamine or xylazine. Six-week old rats were treated for six days at doses of 30 or 100 mg/kg one minute after intramuscular injection of ketamine or xylazine. Parameters evaluated included body weights, food consumption, duration of anesthesia, clinical pathology, and gross and microscopic pathology. Favipiravir did not enhance effects attributed to the anesthetics alone and did not affect the duration of anesthesia, and the anesthetics did not enhance effects attributed to favipiravir alone.

In an in vitro study evaluating the effect on human bone marrow CD34+ cells, where cells were cultured for 7 – 10 days, favipiravir only inhibited the proliferation of human hematopoietic progenitor cells at very high concentrations, and was a much weaker inhibitor when compared to ribavirin and zidovudine.

An in vitro mitochondrial toxicity study was conducted. The study concluded that the potential of favipiravir to induce mitochondrial toxicity is low compared with that of zidovudine and zalcitabine.

6. EFFECTS IN HUMANS

Overall, 40 clinical studies with favipiravir have been completed and analyzed. Studies designated as "US" were designed and conducted primarily in the US Studies designated as "JP" were designed and conducted in Japan. Of the 40 completed clinical studies, 33 were Phase 1 studies (17 JP studies, 16 US studies), three were Phase 2 studies (one JP study and two US studies of which one was a global study excluding Asia), and four were Phase 3 studies (two JP studies of which one was a multinational study in Asia and two US studies that were global studies excluding Asia). 3160 study subjects have received at least one dose of favipiravir.

6.1. Pharmacokinetics and Product Metabolism in Humans

In adults, favipiravir is rapidly and completely absorbed following oral administration. t_{max} occurred between 0.5 to 4.0 hours, the median time being 1.0 hour after single dose and 2.0 hours following multiple doses. In humans, the absolute bioavailability is anticipated to be lower than that observed in nonclinical studies (ie, average 97.6% in mice), however, an IV vs. oral bioavailability study has not been completed in humans. The lower bioavailability is anticipated due to higher aldehyde oxidase activity in the liver which will convert a larger proportion of favipiravir to the hydroxyl metabolite T-705M1. Aldehyde oxidase is expressed in a wide variety of tissues including the liver, lung (epithelial cells, trachea, bronchi, alveoli), gastrointestinal (GI) (epithelial cells, large and small intestines), kidney (proximal, distal, and collecting tubules), prostate and adrenal glands. The highest expression occurs in the liver and lung. (Garattini et al., 2009)

Two single-dose pharmacokinetics (PK) studies in healthy volunteers have shown that increasing oral single doses from 30 to 1200 mg resulted in a nearly proportional increase in favipiravir plasma levels (Table 3). Rapid absorption of favipiravir was observed as t_{max} occurred in less than one hour. The fraction of dose excreted unchanged as favipiravir was less than 0.20%. Therefore, renal excretion was not a major mechanism for the elimination of unchanged favipiravir. Unlike the parent compound, urinary excretion of T-705M1 was very high.

Table 3: Pharmacokinetic Parameters of Favipiravir and T-705M1 Following Single-Dose Administration

Parameter	30 mg (N=6)	90 mg (N=6)	200 mg (N=6)	400 mg (N=6)	600 mg (N=6)	1200 mg (N=6)
Favipiravir						
C_{max} (µg/mL)	0.884 (15.4)	2.72 (30.5)	6.19 (14.8)	12.2 (20.4)	20.6 (19.5)	40.3 (24.6)
t_{max} (hr)	0.75 (0.50, 0.75)	0.63 (0.50, 1.00)	0.75 (0.50, 1.00)	0.62 (0.50, 1.00)	0.75 (0.50, 1.00)	0.75 (0.50, 1.00)
AUC_{0-t} (µg·hr/mL)	1.49 (18.57)	5.86 (53.39)	12.94 (29.09)	26.68 (18.22)	45.15 (22.09)	129.39 (42.41)
$t_{1/2}$ (hr)	1.04 ± 0.08	1.27 ± 0.47	1.20 ± 0.18	1.35 ± 0.07	1.31 ± 0.14	1.84 ± 0.39
CL/F (L/hr)	19.61 ± 3.64	16.12 ± 5.12	15.82 ± 3.81	15.19 ± 3.05	13.57 ± 3.29	9.65 ± 2.79
Vd/F (L)	29.25 ± 4.42	26.85 ± 3.40	26.71 ± 3.67	29.55 ± 5.55	25.35 ± 4.68	24.41 ± 3.89
t_{max} (urine) (hr)	N/A	1.80 ± 1.10[a]	2.00 ± 1.10	1.33 ± 0.82	1.33 ± 0.82	1.67 ± 1.03
Dose excreted (%)	0.00 ± 0.00[b]	0.09 ± 0.07	0.14 ± 0.07	0.18 ± 0.11	0.17 ± 0.07	0.27 ± 0.14
T-705M1						
C_{max} (µg/mL)	0.454 (15.4)	1.36 (20.7)	3.42 (16.2)	6.39 (16.6)	9.43 (12.4)	17.5 (8.44)
t_{max} (hr)	0.75 (0.50, 1.00)	0.88 (0.50, 1.50)	1.00 (0.75, 1.50)	1.00 (0.75, 1.50)	1.00 (0.75, 1.50)	1.00 (0.75, 1.50)
AUC_{inf} (µg·hr/mL)	1.37 (14.72)	4.85 (7.87)	11.83 (15.40)	21.89 (23.29)	36.21 (16.65)	78.15 (6.56)
$t_{1/2}$ (hr)	1.74 ± 0.22	1.96 ± 0.37	2.01 ± 0.20	2.25 ± 0.59	1.97 ± 0.47	2.80 ± 0.23
t_{max} (Urine) (hr)	1.67 ± 1.03	1.33 ± 0.82	2.33 ± 1.03	1.67 ± 1.03	2.33 ± 1.03	2.33 ± 1.03
Dose Excreted (%)	75.10 ± 14.55	87.06 ± 6.81	95.94 ± 23.01	98.26 ± 11.84	91.27 ± 4.08	83.71 ± 2.53

$t_{1/2}$: Half-life
CL/F: Apparent total body clearance after extravascular administration
Note: Results for doses 30–400 mg are from US101, and results from doses 600–1200 mg are from US102.
Note: Cmax and AUC_{0-t} are presented as geometric mean (coefficient of variation [CV]); t_{max} are presented as median values (minimum, maximum); all other parameters are presented as mean ± standard deviation (SD).
[a] N=5.
[b] Drug concentration in urine was below limit of quantitation.

A repeat-dose PK study over 5 days in healthy volunteers has shown favipiravir plasma levels accumulated due to an inhibition of the major drug metabolizing enzyme, aldehyde oxidase. Increasing the total daily dose, administered in equally divided BID doses, resulted in a greater than proportional increase in favipiravir blood levels (Table 4). The average dose-adjusted Day 5 AUC ratio comparing 600 mg BID with 800 mg BID was 1.5 in one study and 1.9 in a second study of healthy volunteers.

Table 4: Pharmacokinetic Parameters of Favipiravir and T-705M1 Following Repeat-Dose Administration

	Group 1—600 mg BID		Group 2—800 mg BID	
Parameter	Day 1 N=6	Day 5 N=6	Day 1 N=6	Day 5 N=6
Favipiravir				
C_{max} (µg/mL)	22.0 (19.0)	23.9 (22.9)	28.4 (33.7)	34.5 (33.7)
t_{max} (hr)	0.50 (0.50, 1.00)	0.62 (0.50, 0.76)	0.50 (0.50, 0.88)	0.52 (0.50, 0.75)
AUC_{0-t} (µg·hr/mL)	43.84 (28.73)	72.93 (37.48)	60.97 (29.52)	140.17 (43.17)
$t_{1/2}$ (hr)	1.39 ± 0.23	1.93 ± 0.53	1.49 ± 0.12	2.50 ± 0.27
CL/F (L/hr)	14.16 ± 4.49	8.73 ± 3.41	13.48 ± 3.43	6.11 ± 2.36
Vd/F (L)	27.25 ± 5.39	22.55 ± 4.72	28.59 ± 6.26	21.40 ± 6.89
t_{max} (urine) (hr)	N/A	38.00 ± 17.66	N/A	32.00 ± 4.90
T-705M1				
C_{max} (µg/mL)	9.87 (20.9)	7.21 (20.3)	13.1 (23.8)	8.10 (25.7)
t_{max} (hr)	0.76 (0.75, 2.00)	1.01 (1.00, 2.00)	1.00 (0.50, 1.07)	1.00 (0.75, 2.22)
AUC_{0-t} (µg·hr/mL)	34.67 (6.12)	34.94 (4.05)	50.56 (13.40)	53.29 (14.36)
$t_{1/2}$ (hr)	1.96 ± 0.20	3.29 ± 0.28	2.12 ± 0.15	4.25 ± 1.78[a]
t_{max} (Urine) (hr)	N/A	22.00 ± 14.53	N/A	14.00 ± 9.80

Note: C_{max} and AUC_{0-t} are presented as geometric means (CV); t_{max} is presented as a median (minimum, maximum); all other parameters are presented as mean ± SD.
[a] N=4.

After oral administration, favipiravir concentrations in plasma were consistently higher than the major plasma metabolite, T-705M1 (Table 4). By the last collection interval on Day 6, approximately 0.2% of unchanged favipiravir was recovered. T-705M1 recovery accounted for nearly 100% of administered favipiravir after 600 mg and 76% was recovered after 800 mg.

Favipiravir and metabolites T-705M1 and T-705M2 were excreted predominately in urine and to a small extent into the feces. In healthy volunteers following administration of a single oral 400 mg dose, 86.7% of the dose was recovered in the urine as the T-705M1 metabolite, 3.6% as a glucuronide conjugate, and 0.2% as favipiravir, totaling 90.5% at 48 hours.

Serum protein binding studies indicated moderate and concentration-independent binding in humans. Serum favipiravir binding ranged between 53.4 to 54.4% over a concentration range of 0.3 to 30 µg/mL. Approximately 65% of the amount bound was bound to albumin and 6.5% bound to alpha1-acid glycoprotein.

In vitro studies in microsomes and human liver cytosol suggested the cytochrome mixed-function oxidase systems did not significantly contribute to the metabolism of favipiravir. Nor did favipiravir interact with most CYP isoforms. For example, favipiravir exhibited only weak inhibitory activity on CYP1A2, 2C9, 2C19, 2D6, 2E1, or 3A4 (IC_{50} >800 µmol/L, 126 µg/mL). Favipiravir did, however, inhibit CYP2C8 in a concentration-dependent manner with an IC_{50} value of 477 µmol/L (70 µg/mL). Similarly, T-705M1 inhibited CYP2E1 to 72.6% of control at 270 µmol/L (43 µg/mL). Lastly, favipiravir did not induce CYP1A2, CYP2C9, CYP2C19, or CYP3A4 activities after incubation with 8, 80, or 800 µmol/L of favipiravir.

Renal transporters did not influence the excretion of favipiravir or T-705M1. In vitro studies in S2 cells demonstrated both compounds are not substrates to hOAT1, hOAT2, hOAT3, hOAT4, human organic cation transporter (hOCT) 1, hOCT2, or hOCT3 transporters. Similar studies in HEK293 cells have shown hOATP2 and hURAT1 were also not involved in the renal excretion of T-705M1 or favipiravir. Favipiravir and T-705M1 moderately inhibited hOAT1, hOAT3, and hURAT1 (30.9 to 65.7% of control). Additionally, hURAT1-mediated uric acid uptake was increased by T-705M1, suggesting T-705M1 may stimulate the reabsorption of uric acid in human renal proximal tubules.

6.1.1 Drug Interactions

Food interaction studies have shown favipiravir absorption from the 200 mg tablet formulation was not altered when taken with a high fat meal. The extent of absorption of favipiravir plasma concentrations over time, as determined by AUC, was 316.3 µg•hr/mL vs. 299.8 µg•hr/mL following tablet administration alone and with food, respectively. The rate of favipiravir absorption, however was slightly delayed. Time to t_{max} was increased from 1.4 to 2.0 hours, and C_{max} was decreased from 45.51 to 40.88 µg/mL when taken with food. The observed C_{max} and AUC differences, however, were within the 0.8 to 1.25 90% CI test for bioequivalence.

A series of healthy volunteer studies have been completed to investigate possible favipiravir interactions with drugs that are either frequently administered to influenza patients or are eliminated by pathways common to favipiravir. To date, studies that have been completed include acetaminophen, hydrazine, norethindrone-ethinyl estradiol contraceptive (Ortho-Novum®), oseltamivir, pyrazinamine, and raloxifene. Except as noted, favipiravir co-

administration was well tolerated and did not significantly alter the PK of either agent or in a clinically important manner.

- Acetaminophen: Favipiravir in combination with acetaminophen increased acetaminophen blood levels 14 to 17% based on plasma AUC comparisons.
- Hydralazine: Co-administration of favipiravir and hydralazine resulted in a 13% reduction in hydralazine AUC. No changes in favipiravir PK were observed.
- Ortho Novum® 1/35 (norethindrone and ethinyl estradiol): Favipiravir co-administration increased both norethindrone and ethinyl estradiol blood levels. Norethindrone plasma AUC increased 47% and ethinyl estradiol plasma AUC increased 43%. One subject discontinued the study due to transient, mildly elevated ALT (2.8 × normal) and AST (1.7 × normal).
- Oseltamivir: Favipiravir did not alter the PK of oseltamivir nor did oseltamivir alter favipiravir PK.
- Raloxifene: Co-administration of favipiravir with raloxifene, a potent aldehyde oxidase inhibitor, did not appreciably alter favipiravir PK. Favipiravir plasma AUC was reduced 15% when administered in combination with raloxifene.
- Repaglinide: Favipiravir administration with repaglinide, an anti-diabetic agent that is extensively metabolized by CYP2C8 and CYP3A4, increased repaglinide plasma AUC 30 to 50% due to inhibition of CYP2C8.
- Pyrazinamide: Pyrazinamide administration with favipiravir examined possible renal urate transporter interactions. Pyrazinamide increased blood uric acid levels 2 to 9 mg/dL over baseline. The addition of favipiravir increased blood uric acid levels 4 to 11 mg/dL over baseline, indicating a moderate additive effect. One subject developed headache and fever in association with elevated liver function tests (AST, ALT, gamma-glutamyl transferase, and lactate dehydrogenase) following pyrazinamide and favipiravir co-administration, which was determined to be an serious adverse event (SAE) and resolved upon discontinuation.

6.2. Safety and Efficacy

6.2.1 Phase 1 Single-Dose and Multiple-Dose Studies

Total 33 Phase 1 studies have been conducted in the US or Japan (Table 5).

Table 5: Phase 1 Clinical Studies

Study ID/ Phase/Status/Country	Study Design	Dose Regimen	Study Population	Efficacy/Safety Outcomes Summary
JP101 Phase 1 Completed Japan	Randomized, single-center, double-blind, ascending, single dose study to evaluate safety, tolerability and PK	Oral favipiravir 30 mg, 90 mg, 200 mg, 400 mg, 800 mg, or 1600 mg Or matching placebo	Healthy males 20-39 years N=48 (n=36 favipiravir; n=12 placebo)	PK: • Favipiravir and T-705M1 reached peak levels in plasma within an hour of administration (median t_{max} 0.5 – 0.8 hours and 0.8 – 1.1 hours, respectively), with complete elimination within 48 hours ($t_{1/2}$ 1.3 – 3.9 hours and 1.8 – 5.1 hours, respectively). Safety: • No SAEs, including death, or study discontinuations were reported. • Eleven treatment-emergent AEs (TEAE) were reported by 5 of 36 (13.9%) subjects treated with favipiravir and two TEAEs were reported by 2 of 12 (16.7%) subjects treated with placebo. All AEs were assessed as mild in severity. • AEs assessed to be related to favipiravir were ALT and AST increase. Both events resolved without treatment.
JP102 Phase 1 Completed Japan	Randomized, single-center, 2-period, 2-treatment (fed and fasted state), crossover study to evaluate food effect	Oral favipiravir 400 mg	Healthy males 20-39 years N=12	PK: • Favipiravir and T-705M1 reached peak levels in plasma within 0.5 and 1 hour, respectively, in the fasted state and 2 and 3 hours in the fed state, respectively. Concentrations of both were below the LLOQ at 36 hours. • The food effect on the PK was not predicted to markedly affect any antiviral effect of favipiravir. Safety: • No SAEs, including death, or study discontinuations were reported. • Only one AE, an increase in total bilirubin, was observed in a patient who fasted. Event was considered mild in severity and assessed as remotely related to favipiravir.
JP103 Phase 1 Completed Japan	Randomized, double-blind, placebo-controlled, ascending multiple dose study to evaluate safety, tolerability and PK	Oral favipiravir: Group 1: 400 mg TID for 7 days Group 2: 400 mg TID Days 1-2, 400 mg QD Days 3 to 7 Group 3: 600 mg BID Days 1-2, 600 mg QD Days 3 to 7 Or matching placebo	Healthy males 20-39 years N=24 (n=18 favipiravir, n=6 placebo)	PK: • Mean plasma favipiravir concentrations increased cumulatively (on Days 1, 4, 8 C_{max} were 17.24 µg/mL (10.3%), 36.15 µg/mL (28.8%), and 43.83 µg/mL (35.5%), respectively and AUC were 50.02 µg·hr/mL (31.9%), 381.57 µg·hr/mL (96.1%), and 460.49 µg·hr/mL (74.3%), respectively) and rapidly reached a peak after dosing on each day. • Concentrations decreased rapidly on Day 1 but more slowly on Day 4, and cumulative urinary excretion rate was low being similar to a single dose. • Results suggested that the regimen could be adjusted to achieve a target therapeutic level. Safety: • No SAEs, including death, were reported, and no subject discontinued because of an AE. • Four TEAEs were reported by 3 of 18 (16.7%) subjects treated with favipiravir and one TEAE was reported by one of six subjects in the placebo treatment group. • Two subjects treated with favipiravir had increases in blood uric acid which were reported as mild in severity. The events were considered probably related to the study drug.
JP104 Phase 1 Completed Japan	Randomized, double-blinded, placebo-controlled, ascending, single dose study to evaluate safety, tolerability and PK	Oral favipiravir 400 mg or 800 mg Or matching placebo	Healthy subjects 65 years or older N=16 (n=12 favipiravir, n=4	PK: • Mean plasma favipiravir concentration reached 22.63 and 47.60 µg/mL 0.5 hours after the administration of 400 and 800 mg favipiravir, respectively, and decreased rapidly thereafter. • Mean plasma T-705M1 concentration reached peak values of 6.20 µg/mL one

Study ID/ Phase/Status/Country	Study Design	Dose Regimen	Study Population	Efficacy/Safety Outcomes Summary
			placebo)	hour after administration of 400 mg favipiravir and 13.56 μg/mL 0.75 hours after administration of 800 mg favipiravir, and rapidly decreased thereafter. • No pharmacokinetic difference affected safety, making dose adjustment based on age unnecessary in the absence of marked renal impairment. Safety: • No SAEs, including death, or study discontinuations were reported. • One patient reported an increase in urinary beta 2 microglobulin (400-mg group) and another an increase in beta-N acetyl-D-glucosaminidase (800-mg group). Both AEs were mild and were considered remotely related or possibly related to the study drug.
JP106 Phase 1 Completed Japan	Randomized, double-blind, placebo-controlled, multiple dose study to evaluate PK and testicular safety	Oral favipiravir: Group 1: 600 mg BID Day 1, QD Days 2 to 5 Group 2: 400 mg BID Days 1 to 4, QD Day 5. Or matching placebo	Healthy males 45-64 years N=16 (n=12 favipiravir, n=4 placebo)	PK: • Favipiravir concentrations increased rapidly following administration and were eliminated without delay. • No abnormalities were detected in the reproductive (testicular) endocrine measures (inhibin B, follicle stimulating hormone, free testosterone, luteinizing hormone and prolactin). Safety: • No SAEs, including death, were reported, and no subject discontinued because of an AE. • All 12 subjects receiving favipiravir reported at least one AE, and 24 AEs were reported. • AEs considered related to favipiravir were diarrhea, headache, feeling hot, and an increase in blood uric acid level. All events were considered mild in severity.
JP107 Phase 1 Completed Japan	Multiple dose study to evaluate the safety, tolerability and PK in healthy elderly	Oral favipiravir: Group 1: 600 mg BID Day 1, QD Days 2 to 5 Group 2: 400 mg BID Days 1 to 4, QD Day 5 Or matching placebo	Healthy subjects 65 years or older N=16 (n=12 favipiravir, n=4 placebo)	PK: • Mean plasma concentrations of favipiravir increased rapidly following administration and were eliminated without delay. • No dose adjustment is needed for elderly subjects. Safety: • No SAEs, including death, were reported. • One subject in Group 1 discontinued as per a request for discontinuation. • Three AEs were reported in 2 subjects (2/6 subjects) in Group 2, 1 event was reported in 1 subject (1/4 subjects) in the placebo group, and no AEs were reported in Group 1. All AEs were mild in severity. • AEs related to study drug in favipiravir-treated subjects were reported in 16.7% (1/6 subjects, 2 events) in Group 2. These events were increased blood fibrinogen level and an increased level of C-reactive protein.
JP108 Phase 1 Completed Japan	Drug-drug interaction (DDI): Theophylline	Oral favipiravir 600 mg BID Day 6, QD Days 7 to 10, BID Day 24, QD Day 25 Oral theophylline 200 mg BID Days 1 to 9, QD on Day 10	Healthy males 45-64 years N=10	PK: • It was noted that the amount of favipiravir exposure to the body increased under concomitant administration with theophylline, but the increase was mild. • No clinical signs or symptoms were observed and no adjustment of favipiravir dosage was necessary. Safety: • No SAEs, including death, or study discontinuations were reported. • Twenty-one TEAEs were reported by 8 subjects (80.0%) and all were mild, and subjects recovered without treatment. • 12 AEs had a causal relationship to favipiravir: increases in blood uric acid levels and decreases in urine uric acid levels.

Study ID/ Phase/Status/Country	Study Design	Dose Regimen	Study Population	Efficacy/Safety Outcomes Summary
				• Blood uric acid levels increased after administration of theophylline and significantly increased after co-administration of favipiravir and theophylline. Blood uric acid levels decreased to normal after the washout period and increased again after a single administration of favipiravir. On the third day of co-administration of favipiravir and theophylline, urinary uric acid levels decreased in 4 of 6 subjects who had reported increases in blood uric acid levels. • Careful monitoring of uric acid is recommended during concomitant administration with theophylline.
JP109 Phase 1 Completed Japan	DDI: Oseltamivir	Oral favipiravir 600 mg BID Day 1 and Day 16, QD Days 2 and 17 Oral oseltamivir 75 mg BID Day 12 to 16, QD Day 17	Healthy males 45-64 years N=10	PK: • The 90% CI for the geometric mean ratios of log-transformed AUC_{0-t} and C_{max} fell within the pre-determined range and the concomitant use of favipiravir and oseltamivir phosphate was deemed to have no effect on the PK of either drug. Safety: • No SAEs, including death, or study discontinuations were reported. • Only 1 AE (an increase in blood fibrinogen level) was reported. • The event was assessed as "unrelated", mild in severity, and resolved without treatment.
JP110 Phase 1 Completed Japan	Bioequivalence of 100 mg tablet and 200 mg tablet	Oral favipiravir 400 mg (four 100 mg tablet) or 400mg (two 200 mg tablet) on Day 1 and Day 15	Healthy males 20-40 years N=24	PK: • The 90% CI of the geometric mean ratios of 200 mg tablet group to 100 mg tablet group were 0.933 to 1.108 for C_{max} and 0.942 to 1.053 for AUC_{0-t}. They were contained within the bioequivalence limits of 0.80 to 1.25 and are considered bioequivalent. Safety: • No SAEs, including deaths, were reported. • One subject in the 100 mg tablet group discontinued due to pyrexia which was assessed as mild in severity and considered unrelated. • In all, 37.5% of subjects (9/24) reported TEAEs; 25% (6/24, 9 events) in the 100 mg tablet group, and 13% (3/23, 4 events) in the 200 mg tablet group. • All events were mild in severity. • Events considered possibly related to the study drug were increased blood bilirubin level (4 subjects) and single cases of dysphonia, fall in blood pressure, and activated prolonged partial thromboplastin time measures.
JP111 Phase 1 Completed Japan	Multiple, high-dose study to evaluate safety, tolerability, and PK of favipiravir	Oral favipiravir: Group 1: 1200 mg + 400 mg Day 1, 400 mg BID Days 2 to 6, 400 mg QD Day 7 Group 2: 1200 mg + 600 mg Day 1, 600 mg BID Days 2 to 6, 600 mg QD Day 7 Or matching placebo	Healthy males 20–39 years N=16 (n=6 Group 1, n=6 Group 2, n=4 placebo)	PK: • Peak and trough concentrations did not increase with multiple doses of 400 mg following the Day 1 second dose in Group 1, however, Group 2 peak and trough concentrations increased with multiple doses following the Day 1 second dose. • Urinary excretion rates of favipiravir until 48 hours after the last administration were 0.8% in both groups, but those of T- 705M1 for group 1 were 53.1% and for group 2 were 60.3%. No significant differences in PK parameters of favipiravir between Day 1 and Day 7 were reported in group 1. Safety: • No SAEs, including deaths, were reported. • One subject was discontinued because of a rash, which was considered probably related to the study drug. • Drug-related TEAEs were reported by 4 subjects (66.7%) in Group 1 (n=3 increases in blood uric acid levels, n=1 diarrhea), 5 subjects (83.3%) in Group 2 (n=5 increases in blood uric acid levels and n=1 rash), and 2 subjects (50%) in the

Study ID/ Phase/Status/Country	Study Design	Dose Regimen	Study Population	Efficacy/Safety Outcomes Summary
				placebo group (n=1 increase in blood bilirubin level, n=1 syncope).
JP114 Phase 1 Completed Japan	Randomized, 2-period, 2-treatment cross-over, food-effect study on PK of favipiravir	Oral favipiravir at fasting or after a meal: 1200 mg Day 1 1200 mg Day 15	Healthy males 20-40 years N=16	PK: • The ratios (90% CI) of the geometric means for the C_{max}, AUC, AUC_{0-t} and AUC_{0-12} for favipiravir during post-prandial dosing in relation to the values during dosing under fasting conditions were 0.908 (0.826 - 0.998), 0.963 (0.888 - 1.044), 0.963 (0.888 - 1.045) and 0.949 (0.887 - 1.016), respectively. • The 90% CI for the ratio of the geometric mean for each parameter was within the predefined range of 0.8 - 1.25. Food had no significant effect on the PKs of favipiravir, and investigators concluded that favipiravir could be administered whether patients were fasting or not. Safety: • No SAEs, including deaths, were reported. • One subject (not fasting) discontinued the study after experiencing rash and pruritus, which were mild in severity and considered possibly related to favipiravir. • In fasting group, no TEAEs were considered related to favipiravir.
JP115 Phase 1 Completed Japan	Randomized, cross-over, 2-part QT/QTc evaluation study of favipiravir Part A, Single blind study Part B, Blinded and randomized crossover study	Part A: oral favipiravir at fasting Group A-1: 2000 mg Group A-2: 2400mg Part B: 4 groups, 4 periods favipiravir 1200 mg or 2400 mg, matching placebo, or moxifloxacin hydrochloride 400 mg given orally to each group at periods 1 to 4 at fasting. The washout period was at least 14 days	Healthy subjects 20-39 years N=68 (n=12 Part A; n=56 Part B)	PK: • The maximum estimated values for ΔΔQTc (Fridericia) with single administration of favipiravir 1200 and 2400 mg were 0.83 msec (3 hours after administration) and 0.50 msec (6 hours after administration), respectively. The maximum values of the upper limit of the one-sided 95% CI with favipiravir 1200 and 2400 mg were 3.17 msec (6 hours after administration) and 2.88 msec (6 hours after administration), respectively. • At any timepoint, the upper limit of the one-sided 95% CI of ΔΔQTc (Fridericia) estimate was less than 4 msec, which satisfied previously defined criteria (<10 msec) that indicates no prolongation effect on QT/QTc interval. • Measures of Bazett and Fridericia yielded the same results. Safety: • No SAEs, including deaths, were reported. • One subject who received moxifloxacin discontinued the study due to rash. • All AEs were mild in severity, and hard feces was a common AE in all treatment groups. • AEs for which a causal relationship with test drug could not be ruled out included: 1200-mg group—headache (n=4), APTT prolongation (n=3), and feces hard (n=2); 2400-mg group—blood uric acid increased (n=6), diarrhea (n=4), and feces hard (n=2); moxifloxacin group—diarrhea (n=5), headache (n=3), QT prolongation (n=3), abdominal discomfort (n=2), feces hard (n=2), and vomiting (n=2).
JP116 Phase 1 Completed Japan	DDI: Hydralazine hydrochloride Randomized crossover, open label study with two groups over two periods:	Oral hydralazine chloride: Single oral dose of 10% Apresoline® 50 mg (5 mg as hydralazine chloride) for 3 days (Days 1, 3, 7 in Group A, Days 1, 21, 25 in Group B) Oral favipiravir 1200 mg +	Healthy males 20–39 years N=14	PK: • A 90% CI for the geometric mean ratio of C_{max} and AUC_{0-12} of favipiravir in concomitant administration with hydralazine hydrochloride compared with that of favipiravir single administration fell within the predetermined range of 0.80 to 1.25 for both the first and last doses. The PK of favipiravir were considered unaffected by concomitant administration with hydralazine hydrochloride. • A 90% CI for the geometric mean ratio of C_{max} and AUC_{0-12} of hydralazine in concomitant administration with favipiravir compared with that in hydralazine single administration did not fall within the predetermined range of 0.80 to 1.25

Study ID/ Phase/Status/Country	Study Design	Dose Regimen	Study Population	Efficacy/Safety Outcomes Summary
		400 mg Day 3 and 21, 400 mg BID Days 4 to 6 and 22 to 24, 400 mg QD Day 7 and 25. Wash-out period: Days 8 to 20		except for AUC_{0-12} obtained after the last dose and the lower value was slightly lower than 0.80. As such, the PK of hydralazine hydrochloride was considered mildly affected by concomitant administration with favipiravir. • Blood pressure levels should be monitored carefully when favipiravir is given concomitantly to hypertension patients receiving hydralazine hydrochloride Safety: • No SAEs, including death, or study discontinuations were reported. • The incidence of AEs that were regarded related to the study drug was 35.7% (n=5; ALT increased [1], blood uric acid increased [4]) when favipiravir was administered alone and 28.6% (n=4 blood uric acid increased) when favipiravir and hydralazine hydrochloride were coadministered. • All reported AEs were mild in intensity except for the moderate hordeolum which occurred with hydralazine administration alone.
JP117 Phase 1 Completed Japan	DDI: Pyrazinamide	Oral pyrazinamide: 1.5 g QD Day 1 to Day 15 Oral favipiravir: 1200 mg + 400 mg on Day 11, followed by 400 mg BID Days 12 to 14, 400 mg QD Day 15	Healthy males and females 20–39 years N=14	PK: • Peak plasma concentration of favipiravir was reached 2 hours after the first dose of concomitant administration (Day 11). Trough levels did not increase after multiple administrations that followed. • The plasma concentration at 4 hours after administration and the trough level of pyrazinamide increased slightly compared with those after pyrazinamide single administration. These values were comparable between Day 1 and Day 5 of concomitant administration (Day 11 and Day 15, respectively). • Favipiravir is unlikely to synergistically increase blood uric acid levels even when it is concomitantly administered with drugs that are classified into the type that cause uric acid excretion decrease. Special attention should be paid to patients with gout or history of gout and patients with high blood uric acid levels. Safety: • No deaths or study discontinuations were reported. • One SAE with prolonged hospitalization was reported in one subject (hepatic function abnormal) and was assessed as "definitely related". • Blood uric acid increased and hepatic function abnormal were frequently reported with an incidence of 100% (14/14 subjects, 14 events) and 64.3% (9/14 subjects, 9 events), respectively, and were assessed as "definitely related" to the study drug. • All blood uric acid increased were reported during pyrazinamide single administration. Three events of hepatic function abnormal were reported during pyrazinamide single administration and 6 events of hepatic function abnormal were reported during concomitant administration. Two events of hepatic function abnormal, which were reported during concomitant administration, were moderate. • All other events were assessed as mild.
JP118 Phase 1 Completed Japan	Randomized, placebo-controlled, double-blind study to evaluate the safety, tolerability and PK of favipiravir in consideration of the dosage and administration in the US	Oral favipiravir: Group 1: 1600 mg BID Day 1, 400 mg BID Days 2 to 5, and 400 mg QD Day 6 Group 2: 1200 mg BID Day 1, 600 mg BID Days 2 to 5,	Healthy males 20-39 years N=32 (Group 1, n=6, Group 2, n=6, Group 3, n=6, Group 4, n=6,	PK: • Group 1 mean peak plasma concentration was the highest at the time of the second dose on Day 1. Mean minimum plasma concentration (C_{min}) reached a maximum value of 45.07 µg/mL after the second dosing on Day 1, and the value gradually dropped thereafter. • Group 2 mean peak value was highest at the time of the dosing on Day 6. The mean C_{min} was 24.34 µg/mL at the time of the second dose on Day 1, and the value was mostly constant.

Study ID/ Phase/Status/Country	Study Design	Dose Regimen	Study Population	Efficacy/Safety Outcomes Summary
		and 600 mg QD Day 6 Group 3: 1600 mg + twice 400 mg Day 1, 400 mg TID Days 2 to 5, and 400 mg QD Day 6 Group 4: 2000 mg + twice 400 mg Day 1, 400 mg TID Days 2 to 5, and 400 mg QD Day 6 Or matching placebo	placebo, n=8)	• Group 3 mean peak value was highest at the time of the initial dosing on Day 1. The mean C_{min} was 22.28 µg/mL at the time of the second dosing on Day 1 and it was 14.72 µg/mL at the time of the third dosing on Day 1, and the value remained mostly constant thereafter. • Group 4 mean peak value was highest at the time of the initial dosing on Day 1. The mean C_{min} was 38.05 µg/mL at the time of the second dosing on Day 1 and it was 26.32 µg/mL at the time of the third dosing on Day 1, with the value remaining mostly constant thereafter. • The number of subjects that maintained a plasma concentration for favipiravir on Day 2 of dosing that was at least 20 µg/mL was 5 subjects in Group 1, 3 subjects in Group 2, 2 subjects in Group 3, and 4 subjects in Group 4. Safety: • No SAEs, including death, or study discontinuations were reported. • Uric acid increased was frequently observed amongst all favipiravir treatment groups, and the levels returned to normal after completion of the study. • Excluding uric acid increase, AEs occurred in: Group 1, n=1, 1 instance – ALT increased; Group 2, n=3, 3 instances – diarrhea, ALT increased, AST increased; Group 3, n=2, 2 instances – diarrhea, medical device failure; Group 4, n=1, 1 instance – wound; and placebo n=1, 1 instance – blood triglycerides increased. • All AEs reported were assessed as mild in severity and, excluding medical device failure and wound, were not possible to rule out a causal relationship to the study drug.
JP119 Phase 1 Completed Japan	Randomized, placebo-controlled, double-blind study to assess the PK, safety, and tolerability	Oral favipiravir 1600 mg BID Day 1, 600 mg BID Days 2 to 5, 600 mg QD on Day 6 Or matching placebo	Healthy males 20 to 39 years N=10 (n=8 favipiravir, n=2 placebo)	PK: • Mean plasma concentration of favipiravir was mostly constant at 57.51 ~ 66.58 µg/mL when looking at the mean for the peak values at the time of the initial dosing on Day 1, at the time of the second dosing on Day 1, at the time of the first dosing on Day 3 and at the time of dosing on Day 6. • Mean C_{min} was 12.79 µg/mL after the initial dosing on Day 1, 52.63 µg/mL after the second dosing on Day 1, and remained at a level that was at least 30 µg/mL after the second dosing on Day 1. • The C_{max} and AUC for favipiravir showed no major changes between the time of the initial dosing on Day 1 and the time of dosing on Day 6. • The results of the simulation that was conducted using the PK model that incorporates mechanism-based inhibition were mostly the same as the results obtained from a simulation of the changes in the plasma concentration of favipiravir during administration of 1600/600 mg BID to healthy Japanese adults and during the administration of 1800/800 mg BID to healthy American adults, and the C_{max}, C_{min} and daily AUC values were also similar. Safety: • No SAEs, including death, or study discontinuations were reported. • AEs that occurred included blood uric acid increased (87.5%, 7/8 cases, 7 instances), diarrhea, WBC count increased and ALT increased (12.5% each, 1/8 cases, 1 instance). • All AEs reported were assessed as mild in severity. • The causal relationship with the blood uric acid increased was judged to be "definite" in all of the instances, while the causal relationship with the diarrhea and ALT increased was judged to be "probable", and the causal relationship with

Study ID/ Phase/Status/Country	Study Design	Dose Regimen	Study Population	Efficacy/Safety Outcomes Summary
				the WBC count increased was judged to be "unrelated". • No AEs occurred with the placebo treatment.
JP120 Phase 1 Completed Japan	Randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and PK of multiple oral doses of favipiravir administered for 22 days.	Oral favipiravir 1800 mg BID on Day 1, 800 mg BID on Days 2 to 21, and 800 mg QD on Day 22 Or matching placebo	Healthy males 20 to 39 years N=10 (n=8 favipiravir, n=2 placebo)	PK: • Mean peak plasma concentration of favipiravir was 64.39 µg/mL after the initial dosing on Day 1, after which the value ranged from 87.37 ~ 103.79 µg/mL during the period from the initial dosing on Day 5 ~ after the dosing on Day 22. • C_{min} for the mean plasma concentration was 21.60 µg/mL after the initial dosing on Day 1, after which the value ranged from 55.74 ~ 75.00 µg/mL during the period from the second dosing on Day 1 ~ after the second dosing on Day 21. • No major differences were observed for either the peak value for the mean plasma concentration of favipiravir or the C_{min} after Day 5. Safety: • No SAEs, including death, were reported, and no subject discontinued because of an AE. • Incidence of AEs with favipiravir was 100% (8/8 cases, 8 instances) for blood uric acid increased, 25.0% (2/8 cases, 2 instances) each for ALT increased, AST increased and WBC urine positive, and 12.5% (1/8 cases, 1 instance) each for upper abdominal pain and exanthema, and with placebo was 1/2 (1/2 cases, 1 instance) for protein urine positive. • Excluding the WBC urine positive that occurred with favipiravir, all AEs that occurred in this study were judged to be AEs for which it was not possible to rule out a causal relationship with the study drug. • All AEs were assessed as mild in severity.
US101 Phase 1 Completed US	Randomized, double blind, single-dose, placebo controlled, ascending dose study to evaluate the safety, tolerability, and PK	Oral favipiravir: Group 1: 30 mg Group 2: 90 mg Group 3: 200 mg Group 4: 400 mg	Healthy subjects 19–39 years N=32 (n=6 Group A, n=6 Group B, n=6 Group C, n=6 Group D, n=8 placebo)	PK: • The increases in favipiravir exposure within the 30 through 400 mg favipiravir dose range investigated were dose proportional. • The T-705M1 metabolite exhibited a similar PK profile to favipiravir. Unlike favipiravir, renal excretion played a significant role in elimination of the T-705M1 metabolite (<0.20% versus 75.10% to 98.26%). Safety: • No SAEs, deaths, or study discontinuations were reported. • AE incidence for the study overall and for the initial 6 days was highest following 200- and 400-mg favipiravir administration. • 64 TEAEs reported were generally mild and considered remotely related or unrelated to favipiravir. • Frequent AEs reported included headache (7 subjects, 22%), fatigue (4 subjects, 13%), and pharyngolaryngeal pain (4 subjects, 13%). • Single oral doses of favipiravir up to 400 mg appeared to be generally safe and well tolerated by the healthy male subjects and the female subject in this study.
US102 Phase 1 Completed US	Randomized, double blind, placebo controlled, ascending single-dose study to evaluate the safety, tolerability, and PK of higher doses	Oral favipiravir: Group 1: 600 mg Group 2: 1200 mg Or matching placebo	Healthy subjects 19–64 years N=16 (n=6 Group A, n=6 Group B, n=4 placebo)	PK: • Renal excretion was not considered a major mechanism for eliminating unchanged favipiravir. The fraction of favipiravir excreted was <0.30%. • Values of C_{max} (t_{max}) < 1 hr (median time) and $t_{1/2}$ was ~ 1–2 hr. • Mean Vd/F was similar following favipiravir administration up to the 1200 mg dose. Safety: • No SAEs, including death, were reported, and no subject discontinued because of

Study ID/ Phase/Status/Country	Study Design	Dose Regimen	Study Population	Efficacy/Safety Outcomes Summary
				an AE. • 23 TEAEs reported in 38% (n=6/16) of subjects and no treatment- or dose-related AE trends were observed. • Of the 23 TEAEs, 21 were reported as mild in severity and two were reported as moderate. • Frequent AEs included headache (two subjects, 13%) and pyrexia (two subjects, 13%). • Eight of the TEAEs were considered possibly related to the study drug and included erythematous rash and pruritus (four events each) occurring in one subject (600 mg).
US103 Phase 1 Completed US	Randomized, double-blind, placebo-controlled, multiple oral dose study to evaluate the safety, tolerability, and PK of favipiravir	Oral favipiravir: Group 1: 600 mg BID Days 1-2, QD Days 3-5 Group 2: 800 mg BID Days 1-2, QD Days 3-5 Or matching placebo	Healthy subjects 20–64 years N=16 (n=6 Group 1, n=6 Group 2, n=4 placebo)	PK: • Value of t_{max} for favipiravir for both dose groups was ~ 0.5 hr on Days 1 and 5. • C_{max} and AUC values increased in a dose dependent manner. • The $t_{1/2}$ value was 1.39 and 1.49 hr on Day 1 and 1.93 and 2.50 hr on Day 5. • CL/F and Vd/F were comparable between dose groups. • Plasma concentrations after the 800-mg regimen were greater than those observed after the 600-mg regimen. Safety: • No SAEs, including death, were reported, and no subject discontinued because of an AE. • Eighteen TEAEs were reported in 69% (n=11/16) of subjects dosed and all were considered mild in severity. • Of these 18 TEAEs, nine were assessed as possibly related (favipiravir: diarrhea, headache (n=2), pain (n=2); placebo: abnormal dreams, fatigue, headache, poor quality sleep), six to be remotely related (favipiravir: abnormal feces, mucous stools, pruritus and urine odor abnormal; placebo: pruritus and rash erythematous), and three to be unrelated (favipiravir: dizziness, lower extremity mass and panic attack) to the study drug. • Frequent TEAEs reported in this study were headache, pain, and pruritis.
US103b Phase 1 Completed US	Randomized, double-blind, placebocontrolled, multiple oral dose study to evaluate the safety, tolerability, and PK of higher doses of favipiravir	Oral favipiravir: Group 1: 1200 mg BID Day 1, 600 mg BID Days 2 to 5 Group 2: 1200 mg BID Day 1, 800 mg BID Days 2 to 5 Or matching placebo	Healthy males (vasectomized) and females and elderly subjects 20–80 years N=32 (n=6 adult subjects and n=6 elderly subjects for each Group; n=8 placebo)	PK: • Age did not have a significant impact on the PK of favipiravir, though considerable inter-subject differences were observed. • Following a 1200 mg dose of favipiravir on Day 1, AUC_{0-12}, AUC_{inf}, AUC_{0-t}, and C_{max} were similar for all 4 groups. However, these parameters were slightly higher in the elderly group that received 1200/800 mg BID. Between the adult and elderly age groups, the weight-adjusted parameters, AUC_{0-12}/70 kg and C_{max}/70 kg were closer in magnitude. Across all groups, K_{el}, $t_{1/2}$, t_{max}, and Vd/F were similar. CL/F was slightly higher in the adult group that received 1200/800 mg BID. • On Day 5, AUC_{0-12}, AUC_{0-t}, and C_{max} were slightly higher in the elderly group that received 1200/800 mg BID than in the adult group that received 1200/800 mg BID. In comparison to Day 1, K_{el} and $t_{1/2}$ was lower and longer on Day 5. As such, elimination rates were not age dependent. The differences of T-705M1 to favipiravir AUC_{0-12} ratio among all groups were not significant. CL/F was slightly lower in the 1200/800 mg BID groups but was not age dependent. CL/F/70 kg was similar among all groups on Day 1 but was slightly lower on Day 5 in the 1200/800 mg BID groups. On Day 5, t_{max} was similar across all groups. Safety:

Study ID/ Phase/Status/Country	Study Design	Dose Regimen	Study Population	Efficacy/Safety Outcomes Summary
				• No SAEs, including death, were reported, and no subject discontinued due to an AE. • Twenty-seven TEAEs were reported by 16 of 32 (50%) subjects overall, with similar incidence across all dose groups, including placebo. Three TEAEs were moderate in severity (arthralgia, headache, and insomnia) while other TEAEs were mild. • Most frequent TEAEs were headache (9 events in adult subjects only) and constipation (4 events in elderly subjects only). • Eighteen TEAEs were considered possibly related to the study drug and the remaining 9 to be remotely related or unrelated. • Uric acid increases from baseline were larger in the active treatment with the elderly dose group (1200/800 BID) displaying the largest increase. Serum uric acid levels returned to near baseline by Day 13.
US103c Phase 1 Completed US	Randomized, double-blind, placebo controlled, study to evaluate the safety, tolerability, and PK of higher doses of favipiravir	Oral favipiravir: Group 1: 1600 mg BID Day1, 800 mg BID Days 2 to 5 Group 2: 1800 mg BID Day 1, 600 mg BID Days 2 to 5 Or matching placebo	Healthy males 19–39 years N=16 (n=6 in each Group, n=4 placebo)	PK: • On Day 1, favipiravir 1600/800 mg BID and 1800/600 BID produced similar peak exposures. However, favipiravir 1600/800 mg BID resulted in a 1.6-fold higher overall exposure during the treatment period. • No differences reported between dose regimens in T-705M1 exposure or urine recovery. Safety: • No SAEs, including death, were reported, and no subject discontinued due to an AE. • Overall, ten TEAEs were reported by 6 of 16 (38%) subjects, occurring in 1 (17%) subject in Group 1, 3 (50%) subjects in Group 2, and 2 (50%) subjects who received placebo. • All TEAEs were experienced 1 time by 1 subject each, with the exception of back pain (placebo) and procedural dizziness (Group 2) which were reported twice by the same subjects. • TEAEs were mild in severity, and three TEAEs were possibly related (dyspepsia, GI pain, pollakiuria), while the remaining seven were unrelated (vessel puncture site hematoma, procedural dizziness, back pain, dizziness postural, peripheral coldness). • Asymptomatic elevations in uric acid were observed in the active treatment groups and was reversible.
US105 Phase 1 Completed US	Randomized, double-blind, placebo-controlled, non-inferiority study to evaluate the reproductive safety and PK	Oral favipiravir 1200 mg BID Day 1, 800 mg BID Days 2 to 5 Or matching placebo	Healthy males 19–45 years N=116 (n=58 favipiravir, n=58 placebo)	PK: • PK concentrations and parameters (AUC_{0-12}/70 kg was 123 µg*hr/mL and 535 µg*hr/mL, after the first dose and last dose, respectively) confirmed that favipiravir exposure was within the expected range for the dosing regimen used. Reproductive Safety: • The upper 95% CI for the difference in proportions of favipiravir and placebo subjects with a ≥ 50% reduction in sperm concentration, sperm motility, and sperm morphology on Day 95 was 6.66%, 6.66%, and 8.74%, respectively, significantly less than the prespecified non-inferiority margin of 0.2 (20%); therefore, it was concluded that favipiravir was not inferior to placebo. • Three subjects (n=1 placebo and n=2 favipiravir) had mild treatment-emergent semen parameter AEs considered possibly related to study drug ▪ Placebo: Subject had decreased sperm motility at Day 95.

Study ID/ Phase/Status/Country	Study Design	Dose Regimen	Study Population	Efficacy/Safety Outcomes Summary
				▪ Favipiravir: Subject had decreased sperm concentration, decreased sperm count, and decreased total motile sperm count at Day 65, and all parameters returned to normal on Day 95. ▪ Favipiravir: Subject had decreased sperm motility (Day 65), decreased semen volume (Day 95), and decreased normal sperm morphology/dcreased sperm concentration (Day 125), and all parameters returned to normal about two months after Day 125. • There were no statistically significant differences between the favipiravir and placebo groups with regard to the other semen parameters and reproductive endocrine tests evaluated. Overall Safety: • No SAEs, including death, were reported, and no subject discontinued due to an AE. • Total of 152 TEAEs were reported by 55 of 116 subjects (47%), and this incidence was similar across active and placebo groups. • Majority of TEAEs were mild, 15 TEAEs were moderate in severity. • Headache was the most frequently reported TEAE (7 favipiravir subjects [12%] and 18 placebo subjects [31%]). • Uric acid increased for the favipiravir group and returned to a near-baseline level by Day 13.
US106 Phase 1 Completed US	DDI – acetaminophen Single-center, open-label	Oral acetaminophen 650 mg QD Day 1, 2, 6 Oral favipiravir 1200 mg BID Day 2, 800 mg BID Days 3 to 5, 800 mg QD Day 6	Healthy subjects 19–50 years N=28	PK: • Based on the bioequivalence criteria of 0.80-1.25, acetaminophen C_{max} was not altered by favipiravir to a clinically significant degree. Acetaminophen-favipiravir interaction is unlikely to be clinically important. • Point estimates for acetaminophen AUC ranged approximately 14–17% higher with co-administration of favipiravir. • The upper 90% confidence limits on the geometric mean ratios of acetaminophen in combination with favipiravir on Days 2 and 6 vs. acetaminophen alone slightly exceeded the 1.25 cut-off to establish bioequivalence (in each case >1.25, but <1.26). • Favipiravir was absorbed rapidly, observable 0.25 hours after dosing, and found to peak approximately 1 hour after dosing. Safety: • No SAEs including deaths, were reported, and no subject discontinued due to an AE. • Four of 28 (14.3%) subjects experienced a single mild TEAE, and only 1 (headache) was considered possibly related to study drug. • Asymptomatic elevations in uric acid were observed and mean serum uric acid levels returned to near baseline by Day 14.
US107 Phase 1 Completed US	Single-center, open-label study to evaluate the distribution into semen	Oral favipiravir 1200 mg BID Day 1, 800 mg BID Days 2 to 5	Healthy males 19–45 years N=20	PK: • When compared to plasma concentrations, favipiravir was observed at relatively low concentrations in semen on Days 3 (20.049 ± 7.690 µg/mL) and 7 (0.057 ± 0.074 µg/mL). The semen favipiravir concentrations were below lower limit of quantitation (BLQ) by Day 12 (or 7 days after the last dose). • High concentrations of T-705 M1 metabolite were observed in semen, as compared to plasma concentrations at the respective times, following administration of favipiravir (Day 3, 7, 12, and 19: 83.545 ± 36.544 µg/mL,

Study ID/ Phase/Status/Country	Study Design	Dose Regimen	Study Population	Efficacy/Safety Outcomes Summary
				86.625 ± 43.625 µg/mL, 14.676 ± 11.897 µg/mL, and 3.142 ± 4.551 µg/mL, respectively). After approximately 14 days after the last dose on Day 5, individual T-705M1 metabolite concentrations were BLQ in 2 subjects. • Results support shortening the recommended period of contraception and condom use to 7 days after favipiravir treatment of five days. Safety: • No SAEs including deaths, were reported, and no subject discontinued due to an AE. • Only 2 TEAEs (headache and constipation) were reported, and both were unrelated to study drug. • Asymptomatic minor elevations in serum uric acid were observed, and levels returned within the reference range (3.7 – 7.7 mg/dL) by Day 12.
US108 Phase 1 Completed US	DDI – Raloxifene hydrochloride Non-randomized, one-sequence, open-label study	Oral Treatment A followed by B Treatment A: favipiravir 1200 mg BID Day 1, 800 mg BID Day 2, 800 mg QD Day 3 Treatment B: raloxifene hydrochloric acid 60 mg tablet QD on Days 10 to 25, favipiravir 1200 mg BID on Day 23, 800 mg BID on Day 24 and 800 mg QD on Day 25	Healthy adult postmenopausal females N=18	PK: • Favipiravir and T-705M1 exposure were similar after the first favipiravir dose with or without raloxifene. • Raloxifene lowered overall favipiravir exposure following the last dose of favipiravir on Day 3 by 15% to 19%, but did not affect overall exposure of T-705M1. • Although a DDI with raloxifene hydrochloride was detected following the last doses of both drugs with 90% CI not contained within 80 to 125%, since mean ratios for AUC were 81 to 85%, this interaction may not be clinically meaningful. • Favipiravir can be used without dosage and administration adjustment when co-administered with aldehyde oxidase inhibitors. Safety: • No SAEs including death were reported. • One subject discontinued the study on Day 9 due to hepatic enzyme level increase considered possibly related to study drug. • Fourteen subjects (78%) experienced a total of 46 AEs (most mild), 33 of which were considered probably, possibly or remotely related to favipiravir. • The most frequently reported AEs were mild back pain (n= 5, 28%), mild constipation (n=4, 22%), vomiting (n=3, 17%, 1 event was considered moderate in severity and 2 events were considered mild in severity), mild myalgia (n=3, 17%), mild abdominal discomfort (n=2, 11%), mild lower abdominal pain (n=2, 11%). • Five subjects experienced asymptomatic increases in uric acid levels that were at or near baseline at the end of the study.
US109 Phase 1 Completed US	Open-label, parallel-group, multiple-dose study to determine the PK of favipiravir in adult subjects with hepatic impairment and in healthy adult subjects	Oral favipiravir: Group 1: Part 1: Matched to Group 2 and 3: 1200 mg BID Day 1, 800 mg BID Days 2 to 5 Part 2: Matched to Group 4: 800 mg BID Day 1, 400 mg BID Days 2 and 3 Group 2: 1200 mg BID Day 1, 800	Subjects 19–69 years Group 1 (n=18): healthy subjects Group 2 (n=6): subjects with mild hepatic impairment (Child-Pugh Grade A, Score 5-6)	PK: • Mild and moderate hepatic impairment resulted in 2.13- and 2.03-fold increases in favipiravir exposures, respectively, following single doses on Day 1, with approximately 2.2-fold lower CL/F. Severe hepatic impairment resulted in 3.7-fold increase in total systemic exposure on Day 1, and 6.3- and 2.1-fold increases in AUC_{0-12} and peak exposure, respectively, following multiple oral doses on Day 3 with lower CL/F compared to healthy matches. • Mean $t_{1/2}$ values of favipiravir were generally longer in subjects with mild, moderate, and severe hepatic impairment than that of healthy matches. • The free fractions of favipiravir trended slightly higher in subjects with mild, moderate, and severe hepatic impairment than for healthy matches but were unlikely to influence the PK of favipiravir.

Study ID/ Phase/Status/Country	Study Design	Dose Regimen	Study Population	Efficacy/Safety Outcomes Summary
		mg BID Days 2 to 5 Group 3: 1200 mg BID Day 1, 800 mg BID Days 2 to 5 Group 4: 800 mg Day 1 or 800 mg BID Day 1, 400 mg BID for Days 2 and 3	Group 3 (n=6): subjects with moderate hepatic impairment (Child-Pugh Grade B, Score 7-9) Group 4 (n=6): subjects with severe hepatic impairment (Child-Pugh Grade C, Score 10-15)	• Approximately 0.65% of the total favipiravir dose was recovered as unchanged drug in urine in subjects with mild and moderate hepatic impairment after multiple doses, while approximately 0.31% and 0.47% were recovered from their respective healthy matches, respectively. • For the metabolite (T-705M1), no significant decreases (ie, < 2-fold) in the total and peak T-705M1 exposures were observed in subjects with mild and moderate hepatic impairment relative to their respective matches after single and multiple doses. For subjects with severe hepatic impairment, AUCs of T-705M1 were comparable to those of healthy matches, while peak exposure was not (ie, decreases > 2-fold) observed in C_{max} compared to healthy matches. • Approximately 45.4% and 44.1% of the total favipiravir dose were recovered as T-705M1 in urine in subjects with mild and moderate hepatic impairment, respectively, after 1200 mg BID for 1 day and then 800 mg BID for 4 days, while approximately 58.3% and 63.2% were recovered from their respective healthy matches, respectively. Approximately 45.8% and 75.1% of the total favipiravir dose were recovered as T-705M1 in urine in subjects with severe hepatic impairment and healthy matches, respectively. • Dosage adjustment should be considered in hepatic impairment. Safety: • No SAEs, including deaths were reported, and no subject discontinued from the study due to an AE. • Eighteen subjects (50%) experienced 21 AEs of which 11 subjects experienced increased blood uric acid levels. • Twenty events were assessed as mild in severity and one event was moderate (headache/moderate impaired). • Subjects in Group 4 and in Group 1 reported non-clinically significant elevations in bilirubin, AST, glucose fibrinogen, and hemoglobin. These elevations occurred without trend on Day 2 to Day 6 and were resolved at the end of the study. • Asymptomatic blood uric acid and liver function test elevations were observed in both hepatically impaired and healthy subjects.
US110 Phase I Completed US	DDI – Ortho-Novum® 1/35, norethindrone 1 mg/ethinyl estradiol 0.035 mg Non-randomized, one-sequence, multiple dose, open-label study	Oral Treatment A followed by oral Treatment B with no washout period Treatment A: Ortho-Novum® 1/35 tablet QD on Days 1 to 7 Treatment B: Ortho-Novum 1/35 tablet QD on Days 8 to 12, and favipiravir 1200 mg BID on Days 9 to 11 and favipiravir 800 mg QD on Day 12	Healthy premenopausal women 19–45 years N=26	PK: • Norethindrone C_{max} and AUC_{0-24} were approximately 23% and 47% higher, respectively, when favipiravir was co-administered with Ortho-Novum® compared to Ortho-Novum® alone. Co-administration did not affect the norethindrone median t_{max} and mean $t_{1/2}$. • Ethinyl estradiol C_{max} and AUC_{0-24} were approximately 48% and 43% higher, respectively, when favipiravir was co-administered with Ortho-Novum® compared to Ortho-Novum® alone. Co-administration did not affect the ethinyl estradiol median t_{max} values for ethinyl estradiol but mean $t_{1/2}$ values for ethinyl estradiol were shorter (by approximately 2.5 hr) compared to Ortho-Novum alone. • Mean plasma favipiravir and T-705M1 exposure was comparable to expected levels, based on previous studies • A relatively weak DDI with Ortho-Novum® was concluded despite the slight increase in norethindrone/ethinyl estradiol exposure following co-administration with favipiravir. No change in efficacy for norethindrone/ethinyl estradiol oral contraceptives is expected. Safety:

Study ID/ Phase/Status/Country	Study Design	Dose Regimen	Study Population	Efficacy/Safety Outcomes Summary
				• No SAEs including death were reported. • One subject discontinued the study due to increased ALT that was mild in severity and assessed as possibly related to study drug. • In all, 23 (88%) subjects reported 102 AEs (96, mild in severity; 6, moderate): 12 (46%) reported 25 events following Ortho-Novum alone and 20 (77%) reported 77 events following Ortho-Novum plus favipiravir. • Nausea, a documented side effect of norethindrone and ethinyl estradiol contraceptives, was the most frequently reported AE (13 events, n=12, 46%). (USPI http://www.janssen.com/us/sites/www_janssen_com_usa/files/products-documents/039811-160323_ortho-novum_modiconuspi-feb2016_0.pdf) Other common AEs were mild headache (9 events, n=9, 35%), mild constipation (7 events, n=7, 27%), mild feeling hot (5 events, n=5, 19%), dizziness (4 events [3 events mild in severity and 1 was moderate], n=4, 15%), mild hyperhidrosis (4 events, n=4, 15%), mild back pain (4 events, n=3, 12%), mild vomiting (3 events, n=3, 12%), dysmenorrhea (3 events, n=3, 12%), and n=5 (19%) of subjects experienced abdominal pain, upper abdominal pain, lower abdominal pain, abdominal discomfort, and/or abdominal tenderness. • Asymptomatic elevations in serum uric acid were observed starting at Day 10 and returned within the reference range by Day 20.
US111 Phase I Completed US	DDI – repaglinide One-sequence (Treatment A followed by B), non-randomized, multiple-dose, open-label study	Treatment A: oral repaglinide 0.5 mg QD Day 1 Washout Days 2 to 8 Treatment B: oral favipiravir 1200 mg BID Day 9, 800 mg BID Days 10 to 12, and 800 mg QD Day 13 with repaglinide 0.5 mg QD	Healthy subjects 19–55 years N=18	PK: • CYP2C8 substrate repaglinide and favipiravir co-administration resulted in a 30% to 50% increase in C_{max} and AUC repaglinide exposure. • Median t_{max} and mean $t_{1/2}$ values for repaglinide did not appear to be affected by favipiravir co-administration. • Mean plasma favipiravir and T-705M1 exposure was comparable to expected levels, based on previous studies. Safety: • No SAEs, including death, were reported in the study. • One subject discontinued the study due to viral pharyngitis which was assessed as unrelated to study drug. • A total of 13 AEs were reported by 7/18 subjects (39%) overall. Three subjects (17%) reported 3 events following repaglinide alone and 5 subjects (28%) reported 10 events following favipiravir alone. No subjects reported AEs following repaglinide plus favipiravir treatment. • Eleven AEs were mild in severity and 2 were moderate. The principal investigator considered 4 AEs to be possibly related to study drug, 2 remotely related, and 7 unrelated. • The most commonly reported AE was constipation in a subject receiving repaglinide alone and in a subject receiving favipiravir alone. • Asymptomatic elevations in serum uric acid were observed with favipiravir administration and the values were within reference range by Day 21. • Mean finger-stick blood glucose values varied considerably from baseline values following both treatments. No difference was noted in the magnitude of the blood glucose decreases between groups receiving repaglinide alone and repaglinide with favipiravir.
US112 Phase I	Randomized, open-label, two-way crossover study to	Oral favipiravir with 14-day wash-out period between	Healthy subjects 18 years or older	PK: • The mean (SD) C_{max} of favipiravir and T-705M1 for both 1 x 400-mg tablet and 2

Study ID/ Phase/Status/Country	Study Design	Dose Regimen	Study Population	Efficacy/Safety Outcomes Summary
Completed US	assess the bioequivalence of favipiravir 400 mg tablets versus 200 mg tablets	doses Sequence 1: 2 x 200 mg tablets on Day 1 and 1 x 400 mg tablet on Day 14 Sequence 2: 1 x 400 mg tablet on Day 1 and 2 x 200 mg tablets on Day 14	N=26	x 200-mg tablets were comparable (favipiravir: 15.06 [3.845] µg/mL and 13.60 [3.402] µg/mL; T-705M1: 7.19 [1.388] µg/mL and 7.52 [1.635] µg/mL, respectively). • The 400- and 200-mg tablets were considered bioequivalent as the 90% CI of the ratio of the geometric least squares (LS) means fell within the pre-specified range (80% to 125%) for favipiravir and T-705M1 AUC_{0-t}, AUC_{0-inf}, and C_{max}. • There was no significant difference in t_{max} (P >0.05) between the 400- and 200-mg tablets for favipiravir or T-705M1. Safety: • No SAEs, including death, were reported, and no subject discontinued from the study due to an AE. • A total of 5 subjects (19.2%) had at least 1 TEAE during the study, of which four were assessed as mild in severity and one was moderate in severity. • In the 400 mg tablet dose, the most common TEAEs were hyperoxaluria and proteinuria, both in a single subject. • In the 2 x 200 mg tablet dose, two subjects had nausea, one subject had hyperoxaluria, and another subject had proteinuria. • Overall, two subjects had 1 or more TEAEs considered possibly related to a single 400-mg dose of favipiravir in this study: mild tension headache (1 x 400-mg tablets), mild AST increased (2 x 200-mg tablets), and mild hyperoxaluria (2 x 200-mg tablets).

US119
Phase 1
Completed
US
	Open-label study to evaluate the PK and metabolism of favipiravir in a subject who previously exhibited an unusual favipiravir PK profile (in US213 Part A)	Oral favipiravir 2400 mg + 600 mg + 600 mg on Day 1, 600 mg TID on Days 2 to 5	52-year-old healthy female
			
			N=1
				PK:
				• In Study 213 Part A, subject achieved a favipiravir C_{min} value of 34.90 µg/mL at Day 1/PM which then dropped to near zero by Day 5, with morning and evening C_{min} at 0.27 µg/mL.
				• Subject's results in Study 119 were consistent with results seen in other subjects who received the same favipiravir TID regimen in Study US213.
				  • Peak plasma concentration of 119 µg/mL was reached by 1 hour after the first dose, and concentrations remained above 20 µg/mL throughout the dosing period.
				  • C_{max} and C_{min} of favipiravir were 85.60 and 57.10 µg/mL at Day 1/PM, respectively, and 57.10 and 35.90 µg/mL at Day 5/PM. C_{max} and C_{min} of favipiravir were 81.30 and 51.20 µg/mL, respectively at Day 5/AM.
				Safety:
				• Subject did not experience any AEs.
				• No clinically significant abnormal laboratory results, physical examinations, ECG, nor vital signs were noted.
				• No elevations in uric acid were noted.

US120 Phase 1 Completed US	Open-label, multi-center, non-randomized, parallel-group, single dose study to determine the PK of favipiravir and T-705M1 in subjects with renal impairment	Oral favipiravir single dose Estimated creatinine clearance (ClCr) based on Cockroft-Gault equation <u>Normal renal function</u> (Chronic kidney disease [CKD] Stage 0, ClCr ≥ 90	Subjects 18 to 79 years of age N=27 <u>Normal:</u> N=9 6 males 3 females	PK: • Dose-normalized AUC_{inf} for plasma favipiravir for subjects with severe renal impairment when compared to normal renal function was 1.3-fold higher. The 90% CIs of the geometric LS mean ratio for AUC_{inf}/Dose were (80.41, 214.69) for severe impairment and were within the predefined no-effect limits (50.00, 200.00) for subjects with mild and moderate impairment when compared to subjects with normal renal function. • The 90% CIs of the geometric LS mean ratio for C_{max}/Dose for plasma favipiravir for subjects with mild, moderate, and severe renal impairment were within the

Study ID/ Phase/Status/Country	Study Design	Dose Regimen	Study Population	Efficacy/Safety Outcomes Summary
		mL/min): 1800 mg Mild impairment (CKD Stage 2, ClCr 60-89 mL/min): first 2 subjects 1200 mg, next 4 subjects 1800 mg Moderate impairment (CKD Stage 3, ClCr 30 to 59 mL/min): first 2 subjects 1200 mg, next 4 subjects 1800 mg Severe impairment (CKD Stage 4, CrCl <30, not on dialysis): first 2 subjects 1200 mg, next 4 subjects 1800 mg No subjects had end stage renal disease or received dialysis.	Mild: N=6 4 males 2 females Moderate: N=6 3 males 3 females Severe: N=6 2 males 4 females	predefined no-effect limits (50.00, 200.00) when compared to subjects with normal renal function. • Dose-normalized AUC_{inf} for plasma T-705M1 for subjects with moderate renal and severe renal impairment was 1.9-fold and 5.3-fold higher, respectively, compared to subjects with normal renal function. The 90% CIs of the geometric LS mean ratio for AUC_{inf}/Dose were (152.60, 236.55) and (427.45, 662.62) for moderate and severe impairment treatment comparisons, respectively and were within the predefined no-effect limits (50.00, 200.00) for mild impairment when compared to subjects with normal renal function. • Dose-normalized C_{max} for plasma T-705M1 for subjects with severe renal impairment was 2.4-fold higher and the 90% CI of the geometric LS mean ratio for C_{max}/Dose was (195.62, 285.33) when compared to subjects with normal renal function. The 90% CIs of the geometric LS mean ratio for C_{max}/Dose for plasma T-705M1 for subjects with mild renal impairment and moderate renal impairment were within the predefined no-effect limits (50.00, 200.00) when compared to subjects with normal renal function. Safety: • No SAEs including death were reported and no subject discontinued the study. • Overall, nine TEAEs were reported by 3 of 27 subjects (11.1%). One subject reported 1 event (mild headache) in Group B, one subject reported 6 events (mild tachycardia, mild hyperhidrosis, moderate dizziness, moderate headache, mild tremor, mild ecchymosis) in Group C and one subject reported 2 events (mild ecchymosis, mild thrombophlebitis superficial) in Group D. • No event was related to study drug. • No uric acid elevations were observed. • Alternative influenza dose regimen of favipiravir in patients with impaired renal function does not appear to be necessary.
US121 Phase 1 Discontinued US	Randomized, single-blind, 10-Day ascending multiple-dose safety study with the primary goal of determining the safety and tolerability of escalating doses of favipiravir in healthy subjects.	Oral favipiravir: Cohort 1a and 1 Exp: 1800 mg BID Day 1, 800 mg BID Days 2 to 10 Cohort 2: 1800 mg BID Day 1,1000 mg BID Days 2 to 10 Or matching placebo	Healthy subjects aged 18 to 65 years N=up to 80 subjects	See Section 6.2.1.1
US213 Part A (US213a) Phase1 Completed US (US213 Part B [US213b] is a Phase 2 study and can be found in Table 6)	Phase 1/2, randomized, double-blind, placebo-controlled, multicenter study	Oral favipiravir: Part A Regimen 1: 1200 mg TID on Day 1, 600 mg TID Days 2 to 5 Regimen 2: 2400 mg, 600 mg, 600 mg Day 1, 600 mg TID Days 2 to 5 Or matching placebo	Part A Healthy subjects 30–65 years N=16	PK: • On Day 1 of favipiravir administration with Regimen 2, the mean plasma concentration was greater than the set target C_{min} of 20 µg/mL by 1 hour after the AM dose, and remained above 20 µg/mL until the time of PM dose. Subjects treated with Regimen 1 also achieved a C_{min} > 20 µg/mL by 1 hour after the AM dose. However, by 4 hours after dosing the mean concentration decreased below 20 µg/mL and was approximately 2.43 µg/mL at the time of the PM dose. • Treatment with Regimen 2 achieved the target mean favipiravir level immediately after the first dose on Day 1, and maintained it throughout the study. Safety: • No SAEs, including death, were reported in Part A of the study.

Study ID/ Phase/Status/Country	Study Design	Dose Regimen	Study Population	Efficacy/Safety Outcomes Summary
				• Five subjects reported TEAEs: 3 in the active arm of Regimen 2, 1 in the placebo arm of Regimen 2, and 1 in the placebo arm of Regimen 1. • None of the TEAEs were considered related to study drug. • All events were mild and resolved without sequelae.

6.2.1.1. Completed Phase 1 Studies

In the phase 1 studies, favipiravir's safety profile appeared similar to that of placebo and comparator agents with the exception of elevations in uric acid levels. Favipiravir was associated with asymptomatic elevations in uric acid. Elevations in blood uric acid trended towards baseline or within normal ranges after favipiravir study dosing completed and, therefore, were not considered clinically significant. No other clinically notable shifts in serum chemistry, hematology/coagulation, urinalysis, or other special laboratory parameters were observed. To date, favipiravir has not been shown to have any clinically significant effect on QT prolongation, DDI, or in special populations such as the elderly or patients with renal impairment. Dosage adjustment of favipiravir should be considered for subjects with hepatic impairment. Overall, favipiravir may be considered a well-tolerated therapy for adult subjects with suspected uncomplicated influenza.

US121 was a Phase 1 study with the primary goal of determining the safety and tolerability of escalating doses of favipiravir in healthy subjects. The study's secondary objectives are: 1) to characterize favipiravir PK for escalating dose regimens; 2) to characterize the plasma, urine, and semen PK of favipiravir and its primary metabolite, M1, over the dose ranges studied; 3) to characterize changes in aldehyde oxidase activity over the dose ranges studied and the relationship to favipiravir plasma concentrations; 4) to evaluate parameters of male reproduction related to the safety of favipiravir for dose regimens that exceed the total daily dose and duration currently proposed for the treatment of influenza (1800 mg BID Day 1, 800 mg BID Days 2-5).

The study had also the exploratory objective of identifying and characterizing new favipiravir metabolites, if any, at higher favipiravir doses in plasma and urine.

The study was terminated early, after subjects were enrolled and treated in two out of the five planned cohorts. The active portion of the study concluded on 05 August 2016, the date of the last visit of the last subject in Cohort 2, while close-out activities were completed on 30 September 2016, date of the database lock. MDVI decided to terminate the study after determining that although there were no safety findings that would preclude continued development, and the study results provided an additional margin of safety supporting the influenza dosing schedule, further dose escalation under this protocol was not helpful to the current uncomplicated influenza indication.

6.2.2 Phase 2 Studies

Three Phase 2 studies in subjects with uncomplicated influenza have been completed (Table 6).

Table 6: Phase 2 Clinical Studies

Study ID/Phase/Status/Country	Study Design	Dose Regimen	Study Population	Efficacy/Safety Outcomes
JP205 Phase 2 Completed Japan	Randomized, multicenter, double-blind study	Oral favipiravir: High dose group: 600 mg BID Day 1, 600 mg QD Days 2 to 5 Low dose group: 400 mg BID Days 1 to 2, 400 mg QD Days 3 to 5 Oral oseltamivir control group: 75 mg BID Days 1 to 5	Subjects with influenza 45 – 64 years N=160 (n=55 high-dose, n=52 low-dose, n=53 OC)	Primary endpoint: • Time to afebrile state: No significant difference was detected between oseltamivir and high-dose favipiravir (P = 0.083) but there was a significant difference between oseltamivir and low-dose favipiravir (P = 0.015). The time to afebrile state was longer by 6.6 and 13.2 hours in high and low doses, respectively, than it was for oseltamivir. Selected secondary endpoints: • Time to symptom alleviation: No significant difference was detected between oseltamivir and high-dose favipiravir (P = 0.473) but there was a significant difference between oseltamivir and low-dose favipiravir (P = 0.027). The time to symptom alleviation was longer by 6.9 hours and 18.0 hours, respectively, than it was for oseltamivir. • Viral titer: Viral titers decreased in all groups from baseline to less than 1 on Day 3 (mean ± SD at baseline (enrollment), Days 3 and 6 were 2.94 ± 1.82, 0.55 ± 1.07 and 0.04 ± 0.25 in the high-dose favipiravir group, 3.28 ± 1.99, 0.83 ± 1.35 and 0.00 ± 0.00 in the low-dose group, and 2.85 ± 1.35, 0.53 ± 1.19 and 0.00 ± 0.00 in the oseltamivir control group). Safety: • Two subjects developed SAEs: hospitalization for haematochezia in the high-dose favipiravir group which was assessed "possibly related" and pneumonia in the low-dose favipiravir group assessed as unrelated. No deaths occurred. • Six significant AEs were reported: One event in one patient in the high dose favipiravir group, two events in two subjects in the low-dose group, and three events in three subjects in the oseltamivir control group. Of these events, three subjects discontinued due to vertigo (in the high-dose group) and gastroenteritis and urticaria (in the oseltamivir control group). • AE incidence was 40.0% (22/55 patients, 34 events) in the high-dose group, 38.5% (20/52 patients, 35 events) in the low-dose group and 43.4% (23/53 patients, 44 events) in the oseltamivir control group. Most frequent AE was diarrhoea was reported at an incidence of 14.5% (8/55) in the high-dose group, 7.7% (4/52) in the low-dose group and 11.3% (6/53) in the oseltamivir control group. The incidence of blood uric acid increased was 1.8% (1/55) in the high-dose group and 0% in the low-dose and oseltamivir control groups.
US204 Phase 2 Completed US South Africa Australia New Zealand Latin America	Randomized, double-blind, placebo-controlled, multicenter study	Oral favipiravir: Low dose: 1000 mg BID on Day 1, 400 mg BID on Days 2-5 High dose: 1200 mg BID on Day 1, 800 mg BID on Days 2-5 Or matching placebo	Subjects with uncomplicated influenza 20–80 years N=530 (n= 201 placebo, n=134 low-dose, n=195 high-dose)	Primary endpoint (preplanned): • Time to alleviation (of the 6 primary influenza symptoms and resolution of fever) was similar between the treatment groups. Median time to alleviation was 91.9 hours (95% CI, 70.3-105.4) for the placebo group, 100.4 hours (95% CI, 82.4-119.8) for the low-dose favipiravir group, and 86.5 hours (95% CI, 79.2-102.1) in the high-dose favipiravir group. • Median times to alleviation between patients receiving placebo and favipiravir were similar by subgroups for age, smoking history, prior influenza vaccine, baseline body temperature, time from symptom onset to first visit, virus type/subtype, virus load at enrollment, region, total score of the 6 primary influenza symptoms at enrollment, and time to afebrile state. Post hoc analysis: • $TCID_{50}$ mean values were lower for the higher exposure group compared with

Study ID/Phase/Status/Country	Study Design	Dose Regimen	Study Population	Efficacy/Safety Outcomes
				the placebo and low or moderate exposure groups on Days 2 through 5, with statistically significant differences on Day 2 (P = 0.002), Day 3 (P < 0.001), Day 4 (P = 0.015), and Day 5 (P = 0.018). • Log_{10} transformed viral load (copies of viral RNA per mL by quantitative polymerase chain reaction [qPCR]) mean values were lower for the higher exposure group compared with the placebo and low or moderate exposure groups on Days 2 through 5, with statistically significant differences compared with placebo on Day 2 (P = 0.026), Day 3 (P = 0.038), Day 4 (P < 0.001), and Day 5 (P = 0.001). • The cessation rate of viral shedding was greater in the higher exposure group than in the placebo group at Days 2 through 5, with statistically significant differences at Day 3 (P < 0.001), Day 4 (P = 0.007), and Day 5 (P = 0.022). Safety: • Four patients experienced SAEs. Three of the SAEs were treatment emergent (1 patient in the placebo group, and 2 patients in the low-dose favipiravir group). None of the SAEs were considered related to study drug, and no deaths were reported. • Six patients (1.2%) had AEs leading to discontinuation from the study, and 8 patients (1.5%) had an AE leading to discontinuation from study drug. • The most commonly reported TEAEs in the placebo group were diarrhea (10 of 197 patients, 5.1%), headache (9 of 197 patients, 4.6%), and nausea (9 of 197 patients, 4.6%). The most commonly reported TEAEs in the low-dose favipiravir group were blood fibrinogen increased (4 of 132 patients, 3.0%) and headache, cough, diarrhea, rash, and blood uric acid increased (each with 3 of 132 patients, 2.3%). The most commonly reported TEAEs in the high-dose favipiravir group were diarrhea (9 of 189 patients, 4.8%), blood uric acid increased (7 of 189 patients, 3.7%), and bronchitis (5 of 189 patients, 2.6%). • TEAEs considered related to study drug were reported by 41 of 197 patients (20.8%) in the placebo group, 25 of 132 patients (18.9%) in the low-dose favipiravir group, and 37 of 189 patients (19.6%) in the high-dose favipiravir group.
US213 Part B (US213b) Phase 2 Completed US (US213 Part A [US213a] is a Phase 1 study and can be found in Table 5)	Randomized, double-blind, placebo-controlled, multicenter study	Part B (comparison TID and BID regimens) Oral favipiravir: Regimen 2: 2400 mg, 600 mg, 600 mg Day 1, 600 mg TID Days 2 to 5 Regimen 3: 1800 mg BID Day 1, 800 mg BID Days 2 to 5 Or matching placebo	Part B Subjects with uncomplicated influenza 18–80 years N=545	Primary endpoint: • By $TCID_{50}$ analysis, the mean changes from baseline (Day 1 prior to dosing) observed in viral load were greater on Days 2 through 5 for the BID and TID favipiravir regimens compared with placebo, and statistically significant differences were demonstrated on Day 3 (BID P = 0.0005, TID P = 0.0061) and Day 4 (BID P = 0.0035, TID P = 0.0110). Significant reductions in $TCID_{50}$ AUC were determined for BID (P = 0.0035) and TID (P = 0.0037) compared with placebo. The time to undetectable virus (by $TCID_{50}$ analysis) in 75% of subjects was 91.2 hours for placebo, 65.7 hours for the BID favipiravir regimen (P = 0.035), and 66.2 hours for the TID favipiravir regimen (P = 0.030). • By qPCR analysis, the mean changes from baseline observed in log10 viral load were greater on Days 3, 4, and 5 for the BID and TID favipiravir regimens compared with placebo, and significant differences between the BID favipiravir regimen and placebo were demonstrated on Day 3 (P = 0.0159), Day 4 (P = 0.0426), and Day 5 (P = 0.0040). There was a significant difference between TID favipiravir and placebo in mean change by log10 qPCR analysis on Day 3 only

Study ID/Phase/Status/Country	Study Design	Dose Regimen	Study Population	Efficacy/Safety Outcomes
				(P = 0.0104). There was no significant difference in the time to undetectable virus (log scale) by qPCR analysis for either favipiravir regimen compared with placebo. • There were significant differences in treatment effects in subjects infected with influenza virus subtype H3N2. Mean changes from baseline observed in viral load by $TCID_{50}$ analysis were greater on Days 2 through 5 for the BID and TID favipiravir regimens compared with placebo, and statistically significant differences were demonstrated on Day 3 (BID P = 0.0004; TID P = 0.0171), Day 4 (BID P = 0.0018; TID P = 0.0197), and Day 5 (BID P = 0.0030; TID P = 0.0058). The $TCID_{50}$ time to undetectable virus (in 75% of subjects) was 72.3 hours for placebo, 48.4 hours for the BID favipiravir regimen (P = 0.013), and 48.5 hours for the TID favipiravir regimen (P = 0.023). For influenza virus subtype H3N2, mean changes from baseline observed in log10 viral load by qPCR analysis were greater on Days 2 through 5 for the BID favipiravir regimen compared with placebo and greater on Days 3 through 5 for the TID favipiravir regimen compared with placebo. Statistically significant differences were demonstrated for the BID and TID regimens compared with placebo on Day 3 (BID P = 0.0133; TID P = 0.0108), Day 4 (BID P = 0.0062; TID P = 0.0639), and Day 5 (BID P = 0.0022; TID P = 0.2455). • The median time to alleviation (of the 6 influenza symptoms and resolution of fever) was 97.3 hours for placebo-treated subjects compared with 82.3 hours (P = 0.010) for favipiravir BID-treated subjects. The TID favipiravir regimen median time to alleviation was 95.2 hours. The distributions of time to alleviation (TID favipiravir versus placebo) were not significantly different (P = 0.414). • The BID favipiravir regimen demonstrated a significantly shorter time to alleviation of individual influenza symptoms compared with placebo (treatment differences followed by p-value: cough 26.5 hours, P = 0.034; fatigue 27.7 hours, P = 0.005; headache 27.1 hours, P < 0.001; nasal congestion 27.2 hours, P = 0.012; pain 34.8 hours, P < 0.001; and sore throat 23.3 hours, P = 0.048), while fever was not reduced (0.2 hour treatment difference, P = 0.594). Safety: • No SAEs or deaths were reported in Part B of the study. • TEAEs were reported in 25 subjects (13.6%) in the placebo group, 34 subjects (18.6%) in the BID favipiravir regimen, and 33 subjects (18.2%) in the TID favipiravir regimen. There was no dose/regimen effect identified with regard to the overall frequency or severity of TEAEs between the BID and TID regimens. Diarrhea (2.2% placebo, 1.6% favipiravir BID, 2.2% favipiravir TID), sinusitis (1.1% placebo, 0.5% favipiravir BID, 2.2% favipiravir TID) and headache (0.5% placebo, 0.5% favipiravir BID, 2.2% favipiravir TID) were reported in ≥2% of subjects. There were no severe AEs in favipiravir-treated subjects. There was 1 severe AE reported in the placebo group. • One subject in the TID favipiravir regimen discontinued study medication due to moderate bronchitis that was considered unrelated to study drug. The TID regimen exhibited an increased frequency and/or severity of abdominal pain, headache, and sinusitis. • Mean values and changes from baseline in chemistry results were similar across

Study ID/Phase/Status/Country	Study Design	Dose Regimen	Study Population	Efficacy/Safety Outcomes
				treatment groups. Asymptomatic elevations in uric acid were observed in favipiravir-treated subjects (both BID and TID regimens) compared with placebo-treated subjects.

In the phase 2 studies, favipiravir's safety profile appeared similar to that of placebo with the exception of elevations in uric acid. Changes in blood uric acid were not accompanied by clinical symptoms and, therefore, were not considered clinically significant. In US213b, Investigators were blinded to uric acid levels in order to avoid unintentional study unblinding. Therefore, elevations in uric acid were reported separately and not included as an AE.

6.2.3 Phase 3 Studies

Four Phase 3 studies in subjects with uncomplicated influenza have been completed (Table 7).

Table 7: Phase 3 Clinical Studies

Study ID/Phase/Status/Country	Study Design	Dose Regimen	Study Population	Efficacy/Safety Outcomes
JP312 Phase 3 Completed Taiwan South Korea Japan	Double-blind, non-inferiority, multi-center, parallel-group	Oral favipiravir: 1200 mg + 400 mg Day 1, 400 mg BID Days 2 to 5 Oral oseltamivir: 75 mg capsules BID Days 1 to 5	Subjects with influenza 20-74 years N=762 (379 favipiravir, 383 oseltamivir)	Efficacy: • Median time (95% CI) to primary symptoms alleviation: 55.4 (50.4, 62.5) hours favipiravir vs. 47.8 (44.4, 55.8) hours oseltamivir; median difference 7.7 (−2.2, 15.3) • Viral titers decreased on Day 3 in both treatments. • Cessation rate of viral shedding (% of subjects with viral titers below the lower limit of measurement [1.5 $\log_{10}TCID_{50}$]): 68.7% favipiravir vs. 64.4% oseltamivir on Day 3; 85.7% vs. 77.1% on Day 4, respectively. A Fisher's exact test showed that the cessation rate of viral shedding by Day 3 in patients with viral titer ≥6.0 at enrollment was significantly higher for favipiravir than for oseltamivir (P = .013). Safety: • SAEs: cellulitis in favipiravir and spontaneous abortion in oseltamivir. Both events were considered unrelated. • Discontinuation due to an AE: n=2 favipiravir (eczema and enteritis infectious), n=4 oseltamivir (eczema, gastroenteritis, vomiting, pruritus, rash, and herpes simplex). • AE incidence: 31.7% (n=120/378, 163 events) favipiravir vs. 25.3% (n=96/380, 135 events) in oseltamivir. • Most frequently reported AEs included diarrhea and blood uric acid increased in favipiravir and diarrhea, vomiting, nausea, and blood triglycerides increased in oseltamivir.
JP313 Phase 3 Completed Japan	Open-label, multicenter, multiple-dose	Oral favipiravir: 1200 mg + 400 mg Day 1, 400 mg BID Days 2 to 5	Subjects with influenza 20-74 years N=16	Efficacy: • Median time (95% CI) to alleviation of 7 major symptoms (cough, sore throat, headache, nasal congestion, feeling feverish, body aches and pains, fatigue [tiredness]) and the time to alleviation of all the symptoms (major symptoms plus neck pain, interrupted sleep, and loss of appetite) was 48.5 (20.3 to 89.1) and 48.5 (20.8 to 89.1) hours, respectively. • Viral titers fell below the detection limit ($TCID_{50}$: < 1.5) on Day 3. Mean (± SD) change in viral titer on Day 2, Day 3 and Day 8 were −2.94 (± 2.12), −5.08 (± 1.83) and −5.49 (± 1.52) $\log_{10}TCID_{50}$, respectively. Safety: • AE incidence: 25.0% (n= 4/16, 5 events) • AEs with causal relationship: hyperuricemia, blood uric acid increase, ALT increase, AST increase
US316 Phase 3 Completed Australia, Belgium, Bulgaria, Hungary, New Zealand, Poland, Russia, South Africa, Spain, Sweden, The Netherlands, Turkey, Ukraine, US	Randomized, double-blind, placebo-controlled, multicenter study	Oral favipiravir 1800 mg (1st loading dose) + 1800 mg (2nd loading dose) on Day 1 followed by 800 mg BID for Days 2 to 5. Or matching placebo	Subjects with onset of uncomplicated influenza within 48 hours before 1st dose 18 to 80 years N=855	Select Primary and Secondary Endpoints: • Median time to alleviation (of six influenza symptoms [body aches and pains, cough, fatigue, headache, nasal congestion, and sore throat] and resolution of fever): 84.2 hours for favipiravir vs. 98.6 hours for placebo; mean difference 14.4 hours (p=0.004). • Greater benefit for favipiravir compared to placebo in subjects who took longer to resolve (9.4 hour and 36.3 hour differences, respectively). • Mean viral titers (as measured by $TCID_{50}$) decreased more rapidly in subjects on favipiravir than in those on placebo. This difference was statistically significant from the first on-treatment assessment time point (24 hours after first dose),

Study ID/Phase/Status/Country	Study Design	Dose Regimen	Study Population	Efficacy/Safety Outcomes
				falling below the LLOQ 48 hours after treatment was initiated and remained significant at all subsequent time points for subjects in the ITTI population, the primary efficacy population. Safety: • SAEs: n=2 placebo (breast cancer and malignant melanoma), n=1 favipiravir (pneumonia). None were related to study drug. • Discontinuation due to an AE: n=8 favipiravir and n=8 placebo. • AE incidence: 25.9% favipiravir vs. 30.7% placebo; predominately mild or moderate in severity (2.1% of events were severe). • Most commonly reported AEs: diarrhea, nausea, and urinary tract infection; all reported more frequently in placebo subjects than favipiravir subjects. • Subjects in the favipiravir group showed mild, asymptomatic increases from baseline in mean uric acid levels on Day 5. Mean uric acid levels either improved or resolved by the first post-treatment time point analyzed (Day 15). There were no other clinically important changes in laboratory values.
US317 Phase 3 Completed Argentina, Brazil, Canada, Colombia, The Dominican Republic, El Salvador, Guatemala, Mexico, Peru, Puerto Rico, US	Randomized, double-blind, placebo-controlled, multicenter study	Oral favipiravir: 1800 mg (1st loading dose) + 1800 mg (2nd loading dose) on Day 1 followed by 800 mg BID for Days 2 to 5. Or matching placebo	Subjects with onset of uncomplicated influenza within 48 hours before 1st dose 18 to 80 years N=1144	Select Primary and Secondary Endpoints: • Median time to alleviation (of six influenza symptoms [body aches and pains, cough, fatigue, headache, nasal congestion, and sore throat] and resolution of fever): 77.8 hours for favipiravir vs. 83.9 hours for placebo; mean difference 6.1 hours (p=0.303). • Mean viral titers decreased significantly more rapidly from baseline in subjects on favipiravir than in those on placebo beginning at the time of the first nasopharyngeal swab taken 24 hours after start of treatment (Day 2) through Day 5. The mean viral titer for subjects in the favipiravir group fell to near the LLOQ by the $TCID_{50}$ assay (0.7852, LLOQ=0.75 $TCID_{50}$/mL) on Day 3 compared to Day 5 for subjects in the placebo group. Safety: • AE incidence: 28.0% favipiravir vs. 25.1% placebo; predominately mild or moderate in severity (1.0% of events were severe). • Most commonly reported AEs: diarrhea, nausea, and urinary tract infection; all reported more frequently in favipiravir subjects than placebo subjects. • SAEs: n=2 placebo (hypertensive crisis, pyelonephritis), n=4, 5 events favipiravir group (thyroid cancer, asthma, lobar pneumonia, colitis, staphylococcal bacteraemia). None were assessed as related to study drug by the Investigator, however, the Sponsor considered colitis as possibly related. • Subjects in the favipiravir group showed mild, asymptomatic increases from baseline in mean uric acid levels on Day 5. Mean uric acid levels either improved or resolved by the first post-treatment time point analyzed (Day 15). There were no other clinically important changes in laboratory values. • Discontinuation due to an AE: n=10 favipiravir and n=1 placebo.

6.2.4 Clinical and Virologic Efficacy from Three Key Studies (US213b, US316, and 317) in Subjects with Acute Uncomplicated Influenza

Three key studies support the efficacy of favipiravir in uncomplicated influenza: 2 adequate and well-controlled phase 3 studies (US316 and US317) and a supportive well-controlled phase 2 study (US213b) (Table 8). Part A of US213 was a phase 1 safety and PK study (Table 5) and part B included two favipiravir treatment arms including a BID and TID regimen (213b BID and 213b TID, Table 6).

The three key studies shared consistency of conduct, a similar study design (common endpoints, common visit schedule, large sample sizes, randomized, double-blind, and placebo-controlled) permitting a comparison of the results. Subtle differences in the eligibility criteria due to regional variation (such as more restrictive age criteria in certain countries) are not considered to affect the comparability of the study populations.

The dose regimens used in these studies differed from that used in the Japanese phase 2 and 3 studies since US subjects had consistently lower AUC and C_{max} values compared with Japanese subjects who received the same single doses of favipiravir. For studies 316, 317, and 213b BID, favipiravir was administered as 1800 mg BID on Day 1 followed by 800 mg BID on Days 2 to 5. For 213b TID, favipiravir was administered as 2400 mg plus 600 mg plus 600 mg on Day 1 followed by 600 mg TID on Days 2 to 5.

Table 8: Summary of Key Studies Conducted in Adults with Influenza Symptoms with Suspected Influenza A or B

Study	Number of Sites/Regions	Randomization/ Subjects Treated	Medication Dose/Day	Endpoints
US213b	68 sites/1 region US	2:1:2:1 Total N=545 favipiravir BID N=183 favipiravir TID N=179 pooled placebo N=183	Day 1: Studies 316, 317, 213b BID = 1800 mg BID Study 213b TID = 2400 mg + 600 mg + 600 mg Total daily dose = 3600 mg Days 2 to 5: Studies 316, 317, 213b BID = 800 mg BID Total daily dose = 1600 mg Study 213b TID = 600 mg TID Total daily dose = 1800 mg Or matching placebo	1°Safety and PK 2°Virologic response and alleviation
US316	122 sites/14 regions Australia, Belgium, Bulgaria, Hungary, New Zealand, Poland, Russia, South Africa, Spain, Sweden, The Netherlands, Turkey, Ukraine, US	1:1 Total N=855 favipiravir N=426 placebo N=429		1°Alleviation 2°Virologic response
US317	128 sites/10 regions Argentina, Brazil, Canada, Colombia, The Dominican Republic, El Salvador, Guatemala, Mexico, Peru, Puerto Rico, US	3:1 Total N=1144 favipiravir N=863 placebo N=281		1°Alleviation 2°Virologic response

Age, sex, body mass index, and weight were similar for the favipiravir and placebo groups within each study, and across studies. Mean age ranged from 39.6 to 41.3 years, and with the exception of the favipiravir group in the US213b study, both groups in all studies had a slightly higher proportion of women than men. Race and ethnicity varied by study as would be expected based on the countries/regions in which the studies were conducted. US317, with investigational sites in South and Central America, had a higher proportion of Hispanics (approximately 50%) than the other studies. This study also had a lower proportion of White subjects, and a higher proportion of subjects who described their race as Other (16%). The majority of subjects in all 3

studies had not been vaccinated against influenza within the current season. The mean time from influenza symptom onset to first dose of study drug was similar for both treatment groups and all studies, ranging from 28.75 to 32.2 hours.

The intent-to-treat (ITT) population was defined as all subjects who were randomized and received any amount of study drug and represents the population likely to be treated presumptively during an influenza outbreak. The ITTI population was defined in studies US316 and US317 as subjects who were randomized, received any amount of study drug, and who were subsequently confirmed as having influenza by reverse transcriptase polymerase chain reaction (PCR) on nasopharyngeal swab samples collected predose on Day 1. The ITTI population in US213b used the same definition with 2 slight differences: subjects were required to have post-baseline efficacy data to be included, and influenza could be confirmed by either positive PCR or culture tests on Day 1 or positive results on Day 2 if the Day 1 results were negative.

6.2.4.1. Clinical Efficacy from Three Key Studies (213b, 316, and 317)

The primary endpoint of Studies 316 and 317 was median time to alleviation of symptoms and resolution of fever in the ITTI population; this was a secondary endpoint for Study 213b. The ITTI population was defined as subjects in the ITT population who were confirmed as being infected with influenza by qPCR. Subjects were considered to have experienced alleviation when all of the 6 influenza symptoms (body aches and pains, cough, fatigue, headache, nasal congestion, and sore throat) had been rated as either 0 (none/absent) or 1 (mild) and fever had resolved, with both maintained for at least 21.5 hours. The majority of subjects in the favipiravir treatment groups in all studies were able to achieve alleviation more rapidly than subjects in the placebo groups (Table 9).

Table 9: Time to Alleviation of Six Influenza Symptoms and Resolution of Fever (ITTI Population)

	Phase2			Phase3			
	US213b			US316		US317	
	Placebo (N=88)	Favipiravir BID (N=101)	Favipiravir TID (N=82)	Placebo (N=322)	Favipiravir BID (N=301)	Placebo (N=169)	Favipiravir BID (N=526)
Number of Subjects Who Alleviated	83	98	75	306	288	163	505
Number of Subjects Who Were Censored	5	3	7	16	13	6	20
Time When 25% of Subjects Had Alleviated (hours)	72.8	46.1	59.3	63.0	53.6	55.7	54.0
95% CI	(52.7, 80.0)	(35.4, 56.3)	(47.5, 68.3)	(58.4, 71.8)	(47.8, 56.8)	(53.1, 60.9)	(48.2, 55.5)
Median Time to Alleviation (hours)	97.3	82.3	95.2	98.6	84.2	83.9	77.8
95% CI	(88.8, 110.9)	(69.1, 93.3)	(73.4, 115.3)	(94.6, 107.1)	(77.1, 95.7)	(76.0, 95.5)	(72.3, 82.5)
Time When 75% of Subjects Had Alleviated (hours)	153.2	120.2	143.8	177.8	141.5	119.7	119.5
95% CI	(126.9, 187.3)	(101.1, 147.2)	(120.1, 210.0)	(146.0, 194.3)	(124.7, 163.6)	(105.9, 174.5)	(113.8, 137.7)
Mean Time to Alleviation (hours)	119.8	98.4	113.9	145.0	120.8	125.5	114.5
p-value		0.0101	0.4142		0.0036		0.3033

In study US213b, p-value was assessed using Wilcoxon Gehan test. In study US316 and US317, time to event analysis was assessed using Kaplan-Meier estimates while the between group comparisons were assessed using a two-sided Peto-Peto-Prentice test.

Median time to alleviation (of six influenza symptoms [body aches and pains, cough, fatigue, headache, nasal congestion, and sore throat] and resolution of fever) in favipiravir subjects was statistically significant, comparing to placebo subjects, in the primary analysis population (ITTI population) in US213b BID (15 hours, 82.3 hours for favipiravir versus 97.3 hours for placebo, p=0.010), and in US316 (14.4 hours, 84.2 hours for favipiravir versus 98.6 hours for placebo, p=0.004). Although the difference in time to alleviation was not statistically significant in US213b TID and US317 (2.1 hours, 95.2 hours for favipiravir versus 97.3 hours for placebo, p=0.414; and 6.1 hours, 77.8 hours for favipiravir versus 83.9 hours for placebo, p=0.303, respectively) the trend was consistent with the results of Studies US213b BID and US316. The median time to alleviation results from US213b BID and TID treatment arms led to the selection of the BID favipiravir regimen for further development.

For US316, analysis of the 25th and 75th percentiles for time to alleviation (by treatment group) suggests a greater benefit in those subjects whose symptoms took longer to resolve (differences in favipiravir minus placebo of 9.4 hours in the 25th percentile versus 36.3 hours in the 75th percentile).

The results in the ITT population aligned fairly closely with those in the ITTI populations. In US316, the median time to alleviation was 84.5 hours for favipiravir versus 95.9 hours for placebo (difference of 11.4 hours, p=0.007). In US213b BID and US213b TID, the median time to alleviation was 83.7 hours and 79.6 hours, respectively, for favipiravir versus 95.8 hours for placebo (difference of 12.1 hours, p=0.025 and 16.2 hours, p=0.042, respectively). In US317, the median time to alleviation was 78.3 hours for favipiravir vs 84.2 hours for placebo (difference of 5.9 hours, p=0.134).

6.2.4.1.1. Accelerated Failure Time Model

Table 10 presents time to alleviation using an accelerated failure time (AFT) model for analysis to assess the magnitude of clinical effect. The AFT model, which has been utilized in uncomplicated influenza studies, provides an estimate of the acceleration factor (or time ratio) indicating the percentage reduction in alleviation time for active treatment vs placebo. (Dobson, et al., 2015; Kay & Kinnersely, 2002)

In US316, the time ratio for favipiravir versus placebo was estimated to be 0.83, indicating a 17% anticipated reduction in time to alleviation favoring favipiravir over placebo (with parametric estimates of the median time to alleviation of 87.2 hours and 104.9 hours, respectively, a difference of 17.7 hours). In US213b, the time ratio was 0.76 for BID treatment and 0.92 for TID treatment, corresponding to a 24% and 8% reduction, respectively, in time to alleviation for favipiravir compared to placebo.

Consistent with the results of the primary analysis, there was no meaningful reduction in the time ratio for favipiravir versus placebo in US317 (0.94, corresponding to a 6% anticipated reduction in time to alleviation for favipiravir compared to placebo, with parametric estimates of the median time to alleviation of 82.0 hours and 86.9 hours, respectively, a difference of 4.9 hours).

Table 10: Time to Alleviation of Six Primary Influenza Symptoms and Resolution of Fever, AFT Model, ITTI Population

	Phase2			Phase3			
	US213b			US316		US317	
	Placebo (N=88)	Favipiravir BID (N=101)	Favipiravir TID (N=82)	Placebo (N=322)	Favipiravir BID (N=301)	Placebo (N=169)	Favipiravir BID (N=526)
AFT Model Estimated Median Time to Alleviation (hr)	101.2	76.6	92.7	104.9	87.2	86.9	82.0
Time Ratio (favipiravir/placebo)		0.76	0.92		0.83		0.94
p-value[a]		0.0102	0.4422		0.0033		0.3663

[a] AFT Model with Log-logistic distribution.

6.2.4.1.2. Mean Time to Alleviation

To facilitate a comparison with published studies of the neuraminidase inhibitors that reported mean rather than median times to alleviation of symptoms, a post-hoc analysis of the mean time to alleviation was undertaken. The estimated benefit in mean time to alleviation was 24.2 hours in US316 and 21.4 hours in US213b BID. Although there was no significant difference in the mean times to alleviation in US317 (11 hours) or US213b TID (5.9 hours), as with medians, favipiravir tended to show a benefit over placebo.

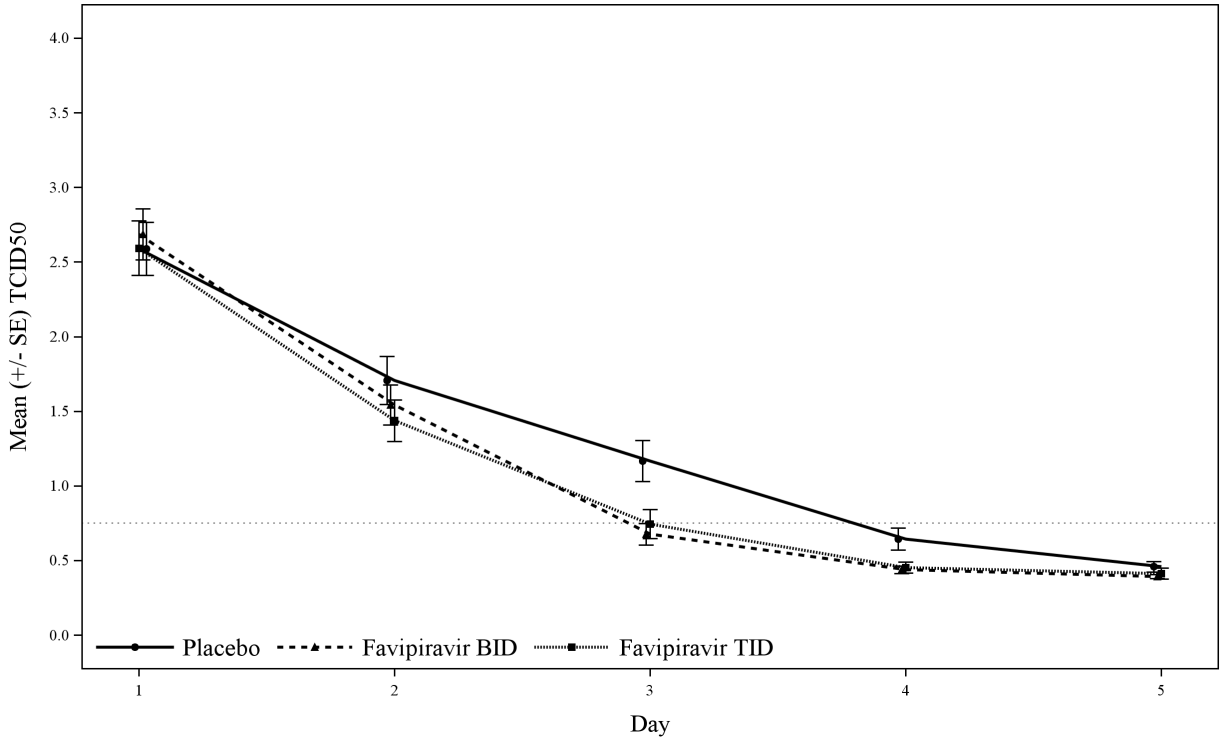
6.2.4.2. Virologic Efficacy from Three Key Studies (213b, 316, and 317)

6.2.4.2.1. Changes in Log-Transformed Viral Load: Determination of the $TCID_{50}$

Figure 2, Figure 3, Figure 4, and Table 11 present mean viral load over time for each of the individual studies, US213b, US316, and US317, respectively. All figures demonstrate the greater reduction in mean viral load in subjects treated with favipiravir compared with placebo subjects.

In US213b BID and TID (Figure 2), the decrease in viral load in favipiravir subjects was greater than in placebo subjects, with the difference achieving statistical significance on Day 3 (48 hours after dosing started). Favipiravir subjects' mean viral load dropped below LLOQ on Day 3, compared to Day 4 for placebo subjects.

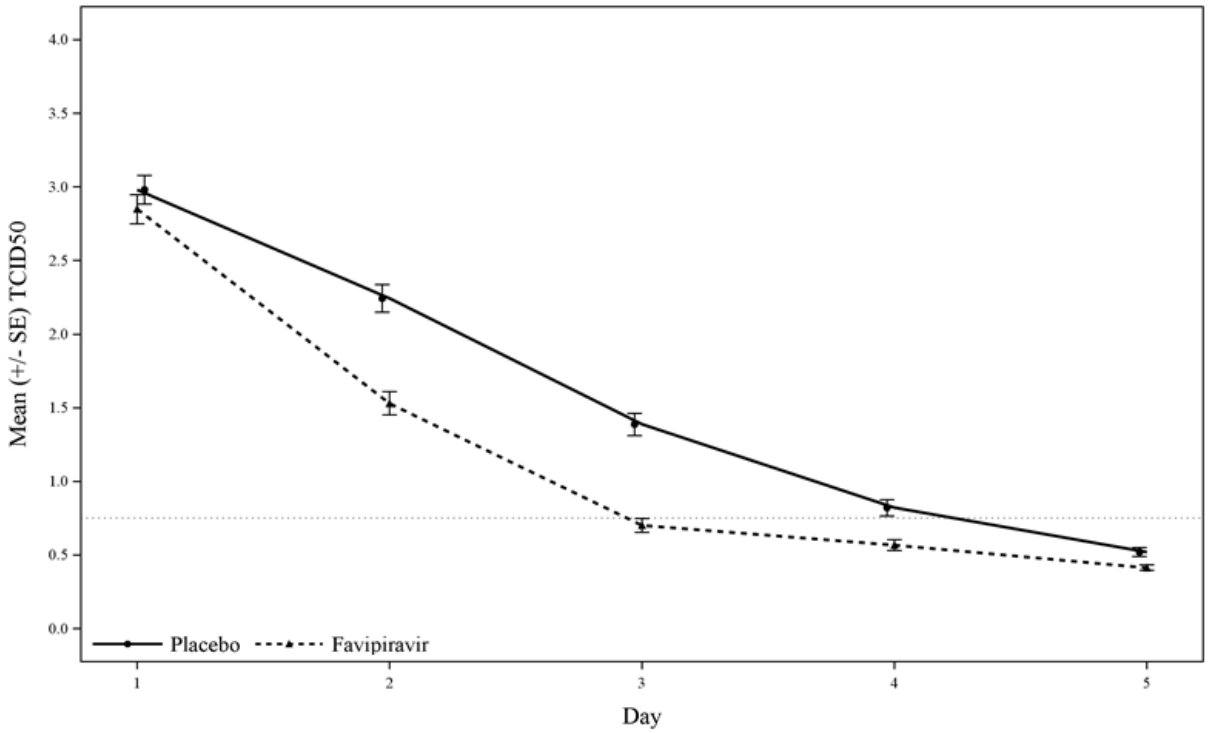
Figure 2: Viral Load by Log Transformed $TCID_{50}$ in Subjects with Influenza (US213b), ITTI Population



Placebo includes placebo BID and TID.

In US316 (Figure 3), the decrease in mean viral load was significantly greater in favipiravir subjects than in placebo subjects from the first assessed time point (Day 2, 24 hours after dosing started) until the titers dropped to the LLOQ. Titers dropped below the LLOQ in the favipiravir group on Day 3 compared with Day 5 for the placebo group.

Figure 3: Viral Load by Log Transformed $TCID_{50}$ in Subjects with Influenza (US316), ITTI Population



In US317 (Figure 4), the decrease in mean viral load in favipiravir subjects was significantly greater than in placebo subjects from the first assessed time point (Day 2, 24 hours after dosing started) until the titers dropped to near the LLOQ. Titers dropped to near the LLOQ in the favipiravir group after Day 3, compared with after Day 5 for the placebo group.

Figure 4: Viral Load by Log Transformed $TCID_{50}$ in Subjects with Influenza (US317), ITTI Population

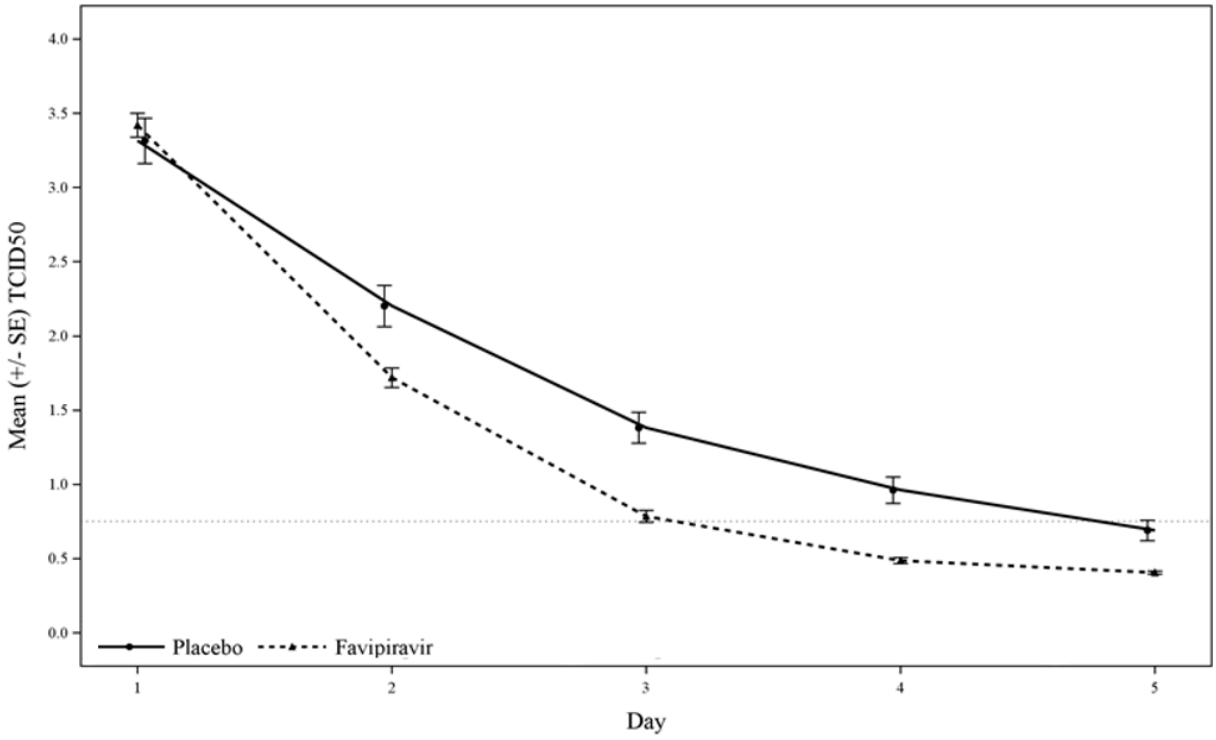


Table 11: Summary of Viral Load Over Time in Log_{10} $TCID_{50}$/mL, ITTI Population

		Phase 2			Phase 3			
		US213b			US316		US317	
Visit Day		Placebo (N=88)	Favipiravir BID (N=101)	Favipiravir TID (N=82)	Placebo (N=322)	Favipiravir BID (N=301)	Placebo (N=169)	Favipiravir BID (N=526)
Screening/Baseline /Day 1 - Observed	n	87	101	82	321	301	169	526
	Mean (SD)	2.6 (1.65)	2.7 (1.72)	2.6 (1.66)	3.0 (1.75)	2.8 (1.71)	3.3 (1.98)	3.4 (1.85)
	Median	2.75	2.75	3.00	3.25	3.00	3.50	3.75
	Min, Max	0.4,5.5	0.4,5.8	0.4,6.0	0.4,7.0	0.4,7.0	0.4,7.3	0.4,7.0
Day 2 - Observed	n	85	100	82	314	293	161	505
	Mean (SD)	1.7 (1.49)	1.5 (1.34)	1.4 (1.27)	2.2 (1.66)	1.5 (1.37)	2.2 (1.77)	1.7 (1.47)
	Median	1.25	1.00	0.88	2.00	1.00	1.75	1.25
	Min, Max	0.4,4.8	0.4,5.5	0.4,5.3	0.4,6.8	0.4,6.3	0.4,6.3	0.4,6.3
Day 2 - Change From Baseline	n	84	100	82	314	293	161	505
	Mean (SD)	-0.9 (1.57)	-1.2 (1.65)	-1.2 (1.65)	-0.8 (1.67)	-1.3 (1.68)	-1.1 (1.65)	-1.7 (1.75)
	Median	-0.6	-1.0	-1.3	-0.6	-1.4	-1.3	-2.0
	Min, Max	-4.6,3.8	-4.1,4.1	-3.9,3.9	-4.9,4.5	-5.4,4.6	-4.6,4.9	-5.5,5.6
	LS Mean	-0.9	-1.1	-1.2	-0.7	-1.4	-1.1	-1.7
	95% CI	(-1.2, -0.7)	(-1.3, -0.9)	(-1.4, -0.9)	(-0.9, -0.6)	(-1.5, -1.2)	(-1.3, -0.9)	(-1.8, -1.6)
	p-value[a]		0.3176	0.1914		<.0001		<.0001
Day 3 - Observed	n	88	100	79	311	291	162	504
	Mean (SD)	1.2 (1.29)	0.7 (0.73)	0.7 (0.86)	1.4 (1.31)	0.7 (0.80)	1.4 (1.32)	0.8 (0.90)
	Median	0.38	0.38	0.38	0.75	0.38	0.38	0.38
	Min, Max	0.4,5.5	0.4,4.0	0.4,4.0	0.4,5.5	0.4,5.0	0.4,5.0	0.4,4.5

		Phase 2			Phase 3			
		US213b			US316		US317	
Visit Day		Placebo (N=88)	Favipiravir BID (N=101)	Favipiravir TID (N=82)	Placebo (N=322)	Favipiravir BID (N=301)	Placebo (N=169)	Favipiravir BID (N=526)
Day 3 - Change From Baseline	n	87	100	79	311	291	162	504
	Mean (SD)	-1.4 (1.76)	-2.0 (1.71)	-1.8 (1.78)	-1.6 (1.97)	-2.1 (1.73)	-1.9 (1.98)	-2.6 (1.95)
	Median	-1.4	-1.9	-2.4	-1.8	-2.3	-2.1	-2.9
	Min, Max	-4.6,3.6	-5.1,1.3	-5.6,3.4	-5.5,4.4	-5.6,3.9	-6.1,4.0	-6.6,3.9
	LS Mean	-1.5	-1.9	-1.9	-1.5	-2.2	-2.0	-2.6
	95% CI	(-1.7, -1.3)	(-2.1, -1.8)	(-2.1, -1.7)	(-1.7, -1.4)	(-2.3, -2.1)	(-2.1, -1.8)	(-2.7, -2.5)
	p-value[a]		0.0005	0.0061		<.0001		<.0001
Day 4 - Observed	n	87	98	79	308	287	161	494
	Mean (SD)	0.6 (0.68)	0.4 (0.25)	0.5 (0.33)	0.8 (0.97)	0.6 (0.62)	1.0 (1.12)	0.5 (0.45)
	Median	0.38	0.38	0.38	0.38	0.38	0.38	0.38
	Min, Max	0.4,3.8	0.4,1.8	0.4,2.8	0.4,5.8	0.4,4.5	0.4,5.3	0.4,3.5
Day 4 - Change From Baseline	n	86	98	79	308	287	161	494
	Mean (SD)	-1.9 (1.62)	-2.2 (1.68)	-2.1 (1.74)	-2.2 (1.88)	-2.3 (1.74)	-2.3 (2.07)	-2.9 (1.84)
	Median	-2.1	-2.1	-2.6	-2.5	-2.4	-2.4	-3.1
	Min, Max	-4.9,1.6	-5.4,0.0	-5.6,2.4	-6.1,3.6	-5.9,2.4	-6.9,4.9	-6.6,2.1
	LS Mean	-2.0	-2.2	-2.2	-2.1	-2.3	-2.4	-2.9
	95% CI	(-2.1, -1.9)	(-2.3, -2.1)	(-2.3, -2.1)	(-2.2, -2.0)	(-2.4, -2.2)	(-2.5, -2.3)	(-3.0, -2.8)
	p-value[a]		0.0035	0.0110		0.0003		<.0001
Day 5 - Observed	n	87	99	76	306	289	160	497
	Mean (SD)	0.5 (0.33)	0.4 (0.14)	0.4 (0.33)	0.5 (0.53)	0.4 (0.30)	0.7 (0.86)	0.4 (0.21)
	Median	0.38	0.38	0.38	0.38	0.38	0.38	0.38
	Min, Max	0.4,2.8	0.4,1.8	0.4,3.3	0.4,4.3	0.4,4.8	0.4,4.3	0.4,3.5

		Phase 2			Phase 3			
		US213b			US316		US317	
Visit Day		Placebo (N=88)	Favipiravir BID (N=101)	Favipiravir TID (N=82)	Placebo (N=322)	Favipiravir BID (N=301)	Placebo (N=169)	Favipiravir BID (N=526)
Day 5 - Change From Baseline	n	86	99	76	306	289	160	497
	Mean (SD)	-2.1 (1.60)	-2.3 (1.70)	-2.2 (1.73)	-2.5 (1.78)	-2.4 (1.72)	-2.6 (2.13)	-3.0 (1.85)
	Median	-2.1	-2.1	-2.6	-2.6	-2.6	-2.9	-3.1
	Min, Max	-5.1,0.4	-5.4,0.0	-5.6,2.9	-6.1,2.6	-6.4,1.1	-6.9,3.9	-6.6,0.4
	LS Mean	-2.2	-2.2	-2.2	-2.4	-2.5	-2.7	-3.0
	95% CI	(-2.2, -2.1)	(-2.3, -2.2)	(-2.3, -2.1)	(-2.4, -2.3)	(-2.5, -2.4)	(-2.8, -2.6)	(-3.0, -2.9)
	p-value[a]		0.1342	0.3514		0.0025		<.0001

[a] Analysis of covariance (ANCOVA) model using PROC GLM, treatment as class variable, baseline value as a covariate, Type III SS.
LLOQ was 0.75 $TCID_{50}$/mL. To calculate the mean for subjects whose titer was below the LLOQ, a value of half the LLOQ was assigned (0.375).

6.2.4.2.2. AUC as Measured by $TCID_{50}$

AUC as measured by $TCID_{50}$ is an alternative antiviral analysis to assess changes in viral titer over the course of the study. Significantly greater reductions in mean viral load in nasopharyngeal swabs of favipiravir subjects compared with placebo subjects were observed across the three key studies as assessed by $TCID_{50}$ AUC (US213b BID group difference of 20.3 $TCID_{50}$*hr/mL [placebo = 116.6 and BID group = 96.3], p=0.0035, TID group difference of 21.4 $TCID_{50}$*hr/mL [placebo = 116.6 and TID group = 95.2], p=0.0037; US316 difference 39.7 $TCID_{50}$*hr/mL [placebo = 143.8 and favipiravir = 104.1], p<0.0001; US317 difference 37.0 $TCID_{50}$*hr/mL [placebo = 152.5 and favipiravir = 115.5], p<0.0001, Table 12).

Table 12: AUC of Log_{10} $TCID_{50}$/mL, ITTI Population

	Phase2			Phase3			
	US213b			US316		US317	
	Placebo (N= 88)	Favipiravir BID (N= 101)	Favipiravir TID (N= 82)	Placebo (N= 322)	Favipiravir BID (N= 301)	Placebo (N= 169)	Favipiravir BID (N= 526)
N	86	98	76	318	296	165	509
Mean (SD)	116.6 (78.93)	96.3 (56.09)	95.2 (56.60)	143.8 (88.99)	104.1 (64.56)	152.5 (101.58)	115.5 (65.92)
Median	88.4	81.8	76.3	126.8	89.4	139.6	98.9
Min, Max	33.3 , 351.9	34.2 , 276.8	33.9 , 269.2	33.3 , 510.4	15.8 , 373.2	8.9 , 442.0	34.0 , 378.4
LS Mean	117.8	95.8	94.5	143.8	104.1	152.5	115.5
95%CI	(107.1, 128.6)	(85.7, 105.8)	(83.1, 105.9)	(135.2, 152.4)	(95.1, 113.0)	(140.9, 164.2)	(108.8, 122.1)
p-value[a]		0.0035	0.0037		<.0001		<.0001

[a] Analysis of variance model using treatments for US316 and US317. ANCOVA model using treatment and baseline $TCID_{50}$ for US213b. AUC was calculated using the trapezoidal method.
AUC was not calculated for a subject if they were missing a baseline value or had no post-baseline planned assessment.
Lower limit of quantification (LLOQ) was 0.75 $TCID_{50}$/mL. To calculate the mean for subjects whose titer was below the LLOQ, a value of half the LLOQ was assigned (0.375).

6.2.4.2.3. Time to Undetectable Virus as Measured by Log_{10} $TCID_{50}$

Neither treatment group completely eliminated virus from all subjects during the five days of treatment, however, favipiravir was able to clear virus (ie, shortened the duration of viral shedding) significantly more rapidly than placebo overall. In 213b, the time when 75% of subjects had undetectable virus was 91.2 hours for placebo, 65.7 hours for the BID favipiravir regimen (p=0.035), and 66.2 hours for the TID favipiravir regimen (p=0.030) as assessed by $TCID_{50}$.

Similarly in studies US316 and US317, subjects receiving favipiravir reached the point at which 75% of the subjects had undetectable virus significantly sooner than the placebo group (US316, 71.6 hours vs. 94.2 hours and US317, 70.0 hours vs. 95.8 hours, respectively, p<0.001).

6.2.5 Overall Summary of Safety from Key Clinical Studies

Safety in the population of subjects with confirmed or suspected influenza treated with a 5 day regimen of favipiravir at the proposed dose (or a broadly similar exposure given TID) was assessed using data from the three key studies (US213b, 316 and 317).

The safety population was defined as subjects who had received any amount of study drug. The majority of all TEAEs in these studies have been mild in severity and assessed as unrelated to study drug and resolved without sequelae.

6.2.5.1. Most Frequent Adverse Events from the Three Key Clinical Studies

Table 13 presents TEAEs (by PT) in the safety population of the three key studies that occurred in at least 0.5% of the subjects in either treatment group.

Table 13: Number of Subjects with TEAE by System Organ Class (SOC) and PT with at Least 0.5% Occurrence (US213b, US316, US317), Safety Population

SOC PT	Pooled Placebo (N = 894) n (%)	Pooled Favipiravir (N =1653) n (%)
Number of Subjects With Adverse Event(s)	227 (25.4)	419 (25.3)
Gastrointestinal disorders	75 (8.4)	122 (7.4)
Diarrhoea	39 (4.4)	38 (2.3)
Nausea	16 (1.8)	34 (2.1)
Vomiting	8 (0.9)	16 (1.0)
Abdominal pain upper	5 (0.6)	8 (0.5)
Dyspepsia	5 (0.6)	6 (0.4)
Abdominal pain	7 (0.8)	4 (0.2)
Infections and infestations	59 (6.6)	82 (5.0)
Urinary tract infection	16 (1.8)	24 (1.5)
Sinusitis	6 (0.7)	6 (0.4)
Oral herpes	5 (0.6)	2 (0.1)
Pneumonia	5 (0.6)	2 (0.1)

SOC PT	Pooled Placebo (N = 894) n (%)	Pooled Favipiravir (N =1653) n (%)
Investigations	39 (4.4)	86 (5.2)
Blood triglycerides increased	11 (1.2)	32 (1.9)
Alanine aminotransferase increased	11 (1.2)	31 (1.9)
Aspartate aminotransferase increased	11 (1.2)	21 (1.3)
Blood cholesterol increased	6 (0.7)	5 (0.3)
Nervous system disorders	23 (2.6)	39 (2.4)
Headache	8 (0.9)	18 (1.1)
Dizziness	5 (0.6)	8 (0.5)
Respiratory, thoracic and mediastinal disorders	48 (5.4)	55 (3.3)
Bronchitis	11 (1.2)	6 (0.4)
Epistaxis	8 (0.9)	8 (0.5)
Vascular disorders	5 (0.6)	23 (1.4)
Dizziness	2 (0.2)	14 (0.8)

Note: AEs are classified according to SOC and PT of MedDRA Version 15.0. Subjects are counted once within each SOC or PT.
Note: US213b BID and TID, US316 and US317 are pooled for analysis. In US213b, TEAE if an AE started within 15 days of first dose. In US316 and US317, TEAE if an AE occurred within 22 days of first dose.

A similar proportion of subjects in the placebo (25.4%) and favipiravir (25.3%) groups experienced at least 1 TEAE, defined as an AE with onset within 15 days of first dose (for Study US213b) or within 22 days of first dose (US316 and US317) (Table 14). The AE profile of favipiravir was broadly similar to placebo and there was no pattern in the TEAEs to suggest any safety issue. The slight imbalances in TEAEs for laboratory results (eg, blood triglycerides increased, ALT increased, AST increased) were not supported by the safety laboratory results, thus they seem to reflect inconsistencies in the designation of laboratory abnormalities as AEs rather than any differences in the occurrence of the laboratory abnormalities themselves.

Table 14: Summary of TEAE (US213b, US316, US317), Safety Population

Safety Population	Pooled Placebo (N = 894) n (%)	Pooled Favipiravir (N = 1653) n (%)
Number of Subjects with at least One		
Adverse Event (AE)	227 (25.4)	419 (25.3)
Related AE	83 (9.3)	155 (9.4)
Serious AE (SAE)		
Related SAE	--	--
Unrelated SAE	4 (0.4)	5 (0.3)
AE Leading to Discontinuation	10 (1.1)	18 (1.1)
AE Leading to Death	--	--

Note: US213b BID and TID, US316 and US317 are pooled for analysis. In US213b, TEAE if an AE started within 15 days of first dose. In US316 and US317, TEAE if an AE occurred within 22 days of first dose.
Note: Relatedness, as assessed by the Investigator, includes definitely, possibly, and probably related, missing and unknown relationship. Not related includes unrelated and remotely related.

6.2.5.2. Serious or Clinically Significant Adverse Events from All Clinical Studies

When viewed collectively across the favipiravir clinical development program, the SAEs do not suggest any pattern of AEs (Table 15). Eighteen treatment-emergent SAEs have been observed during the favipiravir clinical development program: 12 occurred in the favipiravir group, one in the comparator (oseltamivir) group, and five in the placebo group. Two SAEs that were observed in the favipiravir group, hepatic function abnormal and haematochezia, were considered to be related to study drug and were moderate in intensity. Other SAEs were considered by the Investigator to be unrelated to favipiravir. No deaths were reported in the favipiravir development program.

Table 15: Listing of Serious TEAE in the Favipiravir Clinical Development Program (Safety Population)

Treatment	Dose Regimen (Study)	Preferred Term (PT)	Severity	Relatedness[a]	Action Taken
Favipiravir (N=2677)	Pyrazinamide: 1.5 g QD Day 1 to Day 15, Favipiravir: 1200 mg + 400 mg on Day 11, followed by 400 mg BID Days 12-14, 400 mg QD Day 15 (JP117)	Hepatic function abnormal	Moderate	Definite	No dose change
	600 mg BID Day 1, 600 mg QD Days 2 to 5 (JP205)	Haematochezia	Moderate	Possible	Drug withdrawn
		Pneumonia	Moderate	Unrelated	Drug withdrawn
	1200 mg first dose + 400 mg second dose on Day 1, 400 mg BID Days 2-5 (JP312)	Cellulitis	Mild	Unrelated	No dose change
	1000 mg BID Day 1, 400 mg BID Days 2 to 5 (US204)	Vulval abscess	Severe	Unrelated	No dose change
		Hepatic encephalopathy	Mild	Unrelated	No dose change
	1800 mg BID Day 1, 800 mg BID Days 2 to 5 (US316)	Pneumonia	Mild	Unrelated	Drug withdrawn
	1800 mg BID Day 1, 800 mg BID Days 2 to 5 (US317)	Thyroid cancer	Severe	Unrelated	No dose change
		Asthma	Severe	Unrelated	No dose change
		Lobar pneumonia	Severe	Unrelated	No dose change
		Colitis	Moderate	Unrelated	Drug withdrawn
		Staphylococcal bacteraemia	Severe	Unrelated	No dose change
Active comparator (oseltamivir) (N=433)	75 mg BID Days 1 to 5 (JP317)	Spontaneous abortion	Moderate	Unrelated	No dose change
Placebo (N=1008)	N/a (US204)	Bronchial obstruction	Mild	Unrelated	No dose change
	N/a (US316)	Breast cancer	Severe	Unrelated	No dose change
		Malignant melanoma	Moderate	Unrelated	No dose change
	N/a (US317)	Hypertensive crisis	Mild	Unrelated	No dose change
		Pyelonephritis	Severe	Unrelated	No dose change

[a] Relatedness as assessed by the Investigator

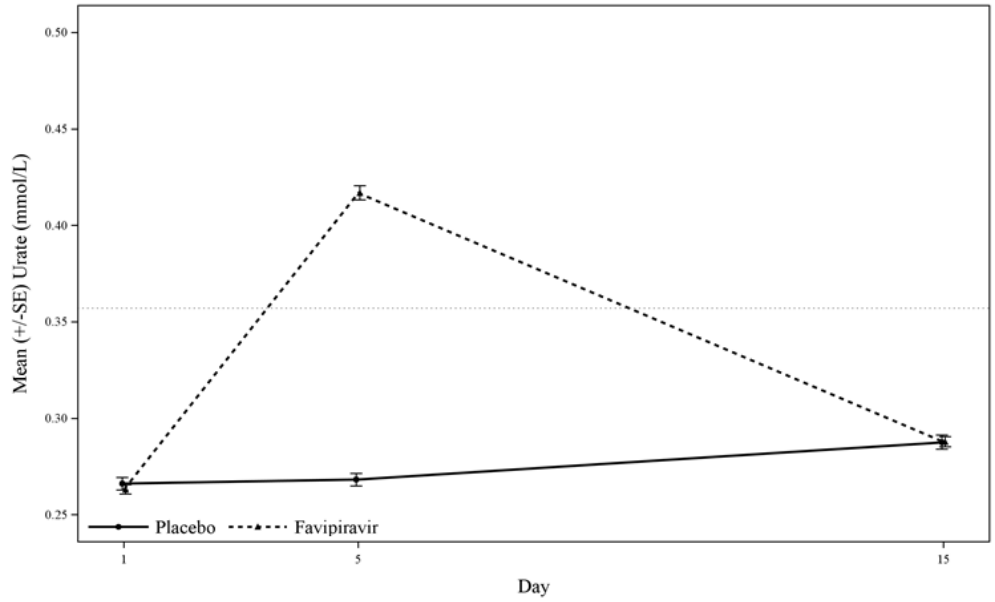
6.2.5.3. Effects on Uric Acid

As was noted in earlier phase studies, favipiravir administration was associated with asymptomatic elevations in uric acid. Consequently, Investigators were blinded to the uric acid results to prevent inadvertent unblinding of subject treatment assignments. Thus elevations in serum uric acid were identified from the safety laboratory assessments but were not captured as AEs.

Uric acid elevations were noted at Day 5 and resolved or trended towards baseline by the first post-dosing assessment time point on Day 15. At baseline, the mean uric acid level for the favipiravir group was 0.263 mmol/L for females and 0.342 mmol/L for males (Figure 5, Figure 6, Table 16, Table 17). At Day 5, the mean uric acid level for the favipiravir group was 0.417 mmol/L for females and 0.448 mmol/L for males. At Day 15 (the first post-tratment time point analyzed), the mean uric acid level had fallen to 0.288 mmol/L for females and 0.368 mmol/L for males. The elevations in uric acid were not associated with any clinically identifiable AE known to be associated with acute or chronic elevations of uric acid (eg, gout, urate

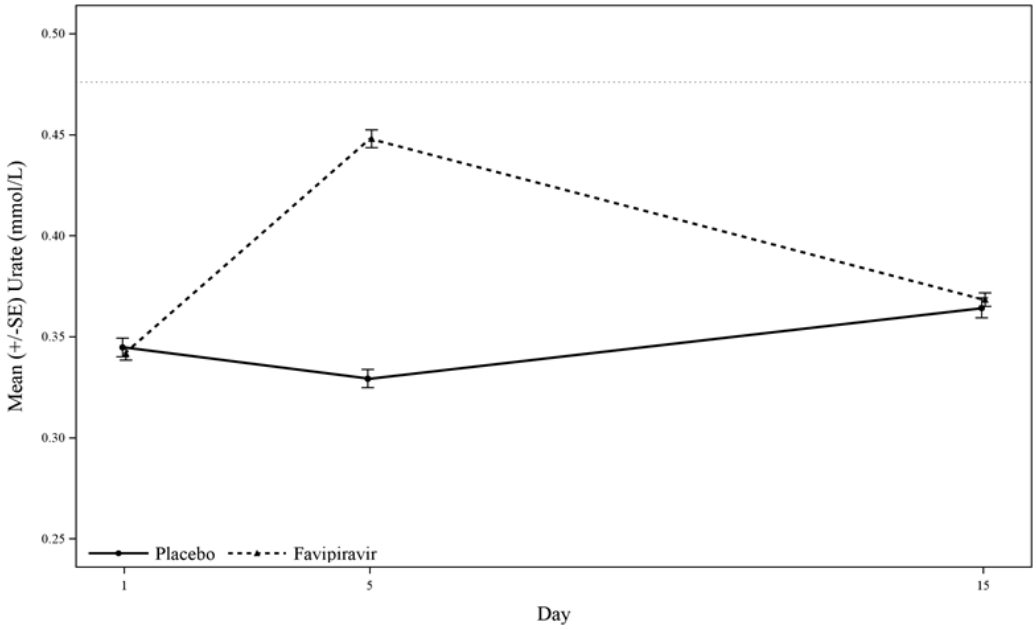
nephropathy). Such AEs are known to develop after notably higher uric acid elevations over considerably longer periods of time. (Sloan, 1982)

Figure 5: Uric Acid Over Time (US213b, US316, US317) Female, Safety Population



Note: US213b BID and TID, US316 and US317 are pooled for analysis.
Note: Female ULN = 0.357.

Figure 6: Uric Acid Over Time (US213b, US316, US317) Male, Safety Population



Note: US213b BID and TID, US316 and US317 are pooled for analysis.
Note: Male ULN = 0.476

Table 16: Summary of Uric Acid Over Time (US213b, US316, US317) Female, Safety Population

Visit Day		Pooled Placebo (N = 527)	Pooled Favipiravir (N = 971)
Baseline - Observed	n	519	957
	Mean (SD)	0.266 (0.0740)	0.263 (0.0732)
	Median	0.256	0.256
	Min, Max	0.089,0.577	0.089,0.595
Day 5 - Observed	n	471	836
	Mean (SD)	0.268 (0.0711)	0.417 (0.1066)
	Median	0.262	0.416
	Min, Max	0.113,0.595	0.137,0.827
Day 5 - Change From Baseline	n	466	825
	Mean (SD)	0.002 (0.0453)	0.153 (0.0961)
	Median	0.006	0.155
	Min, Max	-0.256,0.167	-0.315,0.499
Day 15 - Observed	n	439	784
	Mean (SD)	0.288 (0.0762)	0.288 (0.0749)
	Median	0.280	0.280
	Min, Max	0.119,0.654	0.095,0.636
Day 15 - Change From Baseline	n	434	773
	Mean (SD)	0.018 (0.0536)	0.024 (0.0492)
	Median	0.018	0.024
	Min, Max	-0.256,0.274	-0.184,0.267

Note: US213b BID and TID, US316 and US317 are pooled for analysis.
Note: Female ULN = 0.357.
Note: Unit for uric acid is mmol/L.

Table 17: Summary of Uric Acid Over Time (US213b, US316, US317) Male, Safety Population

Visit Day		Pooled Placebo (N = 367)	Pooled Favipiravir (N = 682)
Baseline - Observed	n	359	677
	Mean (SD)	0.345 (0.0873)	0.342 (0.0825)
	Median	0.339	0.333
	Min, Max	0.161,0.726	0.149,0.964
Day 5 - Observed	n	326	596
	Mean (SD)	0.329 (0.0816)	0.448 (0.1062)
	Median	0.321	0.446
	Min, Max	0.143,0.654	0.161,0.940
Day 5 - Change From Baseline	n	319	592
	Mean (SD)	-0.015 (0.0559)	0.106 (0.0857)
	Median	-0.012	0.101
	Min, Max	-0.262,0.125	-0.166,0.428
Day 15 - Observed	n	309	564
	Mean (SD)	0.364 (0.0863)	0.368 (0.0807)
	Median	0.363	0.369
	Min, Max	0.172,0.785	0.149,0.648
Day 15 - Change From Baseline	n	303	559
	Mean (SD)	0.017 (0.0586)	0.024 (0.0602)
	Median	0.018	0.024
	Min, Max	-0.250,0.190	-0.316,0.238

Note: US213b BID and TID, US316 and US317 are pooled for analysis.
Note: Male ULN = 0.476.
Note: Unit for uric acid is mmol/L.

6.2.5.4. Effects on QT/QTc Interval

In a two-part, blinded study (JP115), the effects of favipiravir on the QT/QTc interval in healthy volunteers were evaluated. Part A (n=12) of the study assessed the tolerability, safety, and PK of a single 2000 mg or 2400 mg dose of favipiravir. Part B (n=56) assessed the QT/QTc intervals of 1200 mg favipiravir, 2400 mg favipiravir, placebo, or moxifloxacin 400 mg as the positive control in a cross-over design with at least a 14-day washout period.

Plasma favipiravir concentration reached peak value two to three hours after administration. The maximum estimated values for ΔΔQTc (Fridericia) with favipiravir 1200 and 2400 mg were 0.83 msec (3 hours after administration) and 0.50 msec (6 hours after administration), respectively. The maximum values of the upper limit of the one-sided 95% CI with favipiravir 1200 and 2400 mg were 3.17 msec (6 hours after administration) and 2.88 msec (6 hours after administration), respectively. At any time point, the upper limit of the one-sided 95% CI of ΔΔQTc (Fridericia) estimate was less than 4 msec, which satisfied previously defined criteria that indicates no

prolongation effect on QT/QTc interval (upper limit of the one-sided 95% CI of ΔΔQTc is below 10 msec). A single dose of favipiravir at 1200 or 2400 mg had no prolongation effect on QT/QTc interval.

There were no SAEs, including deaths in the study. One subject discontinued the study due to rash after moxifloxacin administration. All AEs were mild in severity. Hard feces were a common AE in all groups. Other reported common AEs included headache and APTT prolongation in the favipiravir 1200 mg group, blood uric acid increases and diarrhea in the favipiravir 2400 mg group, and headache, QT prolongation, abdominal discomfort, and vomiting in the moxifloxacin group.

6.2.5.5. Effects on Testicular Toxicity

In US105, the effects of favipiravir 1200 mg BID on Day 1 followed by 800 mg BID for Days 2-5 versus placebo on testicular safety was assessed in healthy male subjects. Favipiravir exposure in this reproductive safety study were within the expected range for the dosing regimen. Results showed that favipiravir does not affect human testicular function. Mean values for all semen parameters, as well as for testicular endocrine parameters, were within reference range at the Day 65 and 95 time points for both arms, and no statistically significant differences between favipiravir and placebo for changes from baseline were observed. No safety concerns were identified from AE, clinical laboratory, ECG, or vital sign results. Two subjects (one from each group) had mild treatment-emergent semen parameter AEs considered possibly related to study drug. By Day 95, parameters were normal for favipiravir-treated subject.

6.2.5.6. Effects of Higher Doses and Longer Durations

In study JP120, healthy subjects received repeated administration of favipiravir for 22 days (1800 mg BID on Day 1, followed by 800 mg BID from Day 2 to Day 21, and a single dose of 800 mg on Day 22). All eight subjects who received favipiravir experienced blood uric acid increase, however, the values trended towards normalization after study completion. Other AEs reported included ALT increase and AST increase in the same two subjects, white blood cells urine positive (n=2), upper abdominal pain (n=1), and exanthema (n=1). One of the two placebo subjects experienced protein urine positive. All events reported were mild in severity, and all events except white blood cells urine positive were judged to be AEs for which it was not possible to rule out a causal relationship. Similar to uric acid levels, AST and ALT trended towards normalization after study discontinuation. No other clinically significant findings were observed.

In US121, two cohorts of healthy subjects received oral favipiravir for ten days. The first cohort received 1800mg BID on Day 1, followed by 800 mg BID Days 2-10. This was identical to the dose regimen used in the US pivotal influenza trials, but extended from five to 10 days. The second cohort were given the same loading dose (1800 mg BID Day 1) followed by 1000 mg BID Days 2-10. The adverse effect profile was similar to that seen in the influenza studies.

A Japanese investigator-conducted program in patients with Severe Fever with Thrombocytopenia Syndrome virus administered 1800 mg BID Day 1 followed by 800 mg BID Days 2-10. Patients appeared to tolerate this well.

Inserm has conducted an open label clinical trial in Ebola patients in West Africa (the JIKI trial) and the doses of 2400 mg, 2400 mg and 1200 mg on Day 1 (given every eight hours) followed by 1200 mg BID for up to an additional nine days, appeared to be well tolerated. (Sissoko et al., 2016)

A small number of patients with a variety of RNA viral diseases (rabies, Lassa fever, norovirus) have been treated at different dose regimens under compassionate use. None of these regimens exceeded the doses given in the JIKI trial, nor exceeded the 21 days given in JP120.

6.3. Marketing Experience

Favipiravir is approved as anti-influenza drug in Japan, and the Japanese Government stockpiled 2 million courses of the drug as a countermeasure against Pandemic. In addition, favipiravir is used as a paid investigational drug and/or a compassionate use drug in the US, several European and Asian countries.

7. SUMMARY OF DATA AND GUIDANCE FOR THE INVESTIGATOR

7.1. Usage

Favipiravir is a selective nucleic acid (purine) analog that is converted to T-705RMP and T-705RTP by cellular kinases. Favipiravir is being developed for the treatment of acute, uncomplicated illness due to influenza infection in patients 18 years of age or older who have been symptomatic for no more than 2 days. Favipiravir inhibits growth in cells from ten different RNA virus families and has been shown to be effective in animal models for RNA viruses including new and old world arenaviruses, Chikungunya virus, rabies virus, as well as Ebola virus. It has been used in compassionate use cases to treat people with Jamestown Canyon virus, Lassa fever, Ebola, norovirus and rabies.

7.2. Dosage and Administration

Favipiravir is supplied as 200 mg tablets to be administered orally. Favipiravir is not approved for any indication. The proposed dosing regimen used in the Phase 3 studies for uncomplicated influenza was:

- Day 1: 1800 mg (9 tablets) BID, total daily dose 3600 mg
- Days 2 to 5: 800 mg (4 tablets) BID, total daily dose 1600 mg

7.3. Contraindications

Favipiravir is contraindicated in subjects with a known hypersensitivity to the drug substance or to any of the excipients. Favipiravir should be administered to subjects according to the exclusion and inclusion criteria specified in the clinical study protocol.

7.4. Warnings and Precautions

Favipiravir is intended for investigational use only by selected investigators familiar with the information in this brochure and experienced in conducting clinical studies.

Favipiravir may only be administered to human subjects participating in clinical studies sponsored and approved by MDVI who have provided formal written informed consent.

Based on nonclinical and clinical studies, the following events may occur. Patients or subjects should be advised of these potential events and how to avoid them.

Effects in subjects with renal impairment. Clinical studies of subjects with renal impairment have shown higher exposure levels and reduced urinary excretion compared to subjects with normal renal function. No alternative dosing is recommended. No data are available in patients with end stage renal disease or renal failure.

Phototoxicity. Nonclinical studies have shown mild phototoxicity. One study subject experienced mild photosensitivity (rash) following a tanning bed session. All subjects should avoid excessive exposure to sunlight or artificial ultraviolet light.

Laboratory Values. Mild to moderate, asymptomatic elevations in serum uric acid have been observed in healthy volunteers and subjects with influenza treated with favipiravir in clinical studies. The changes have been reversible upon favipiravir discontinuation. Laboratory values and potential AEs related to increases in uric acid levels should be monitored.

Mutagenesis. Favipiravir proved mildly positive under some conditions studied in the mammalian chromosomal aberration test and mouse lymphoma assay at high concentrations. Although the potential for genotoxicity at high exposures cannot be ruled out, evidence indicates that this risk is minimal at the exposures planned in influenza clinical studies.

GI Tract Lesions. In two proof-of-concept studies of orally administered favipiravir against lethal Ebola virus infection in cynomolgus macaques, GI tract lesions were observed that were not consistent with the known natural history of Ebola nor with previous animal and clinical studies of favipiravir. The contributing factors responsible for these lesions cannot be determined with certainty. However, evidence suggests that bacterial infections and pre-existing enterocolitis in the treated macaques may have been responsible for the confounding results, and an ongoing risk to patients may not exist.

7.5. Adverse Reactions

Safety data from the three key studies in subjects with confirmed or suspected influenza infection are presented in Table 13. The AE profile of favipiravir was broadly comparable to placebo when favipiravir was given for 5 days at the dose intended for influenza (1800 mg BID on Day 1 day followed by 800 mg BID on Days 2 to 5).

For the purposes of regulatory reporting, the PTs listed in Table 18 are considered expected with favipiravir treatment. The events occurring at an incidence of at least 0.5% in the three key studies comprise this table, and the incidence of some of the events listed occurred at a slightly higher or similar incidence as in the placebo group (Table 13).

Please note, favipiravir was associated with asymptomatic elevations in uric acid in most Phase 2 and 3 studies, therefore, Investigators were blinded to the uric acid results to prevent inadvertent unblinding of subject treatment assignments. Thus, elevations in serum uric acid were identified from the safety laboratory assessments but were not captured as AEs. Asymptomatic elevations in uric acid were observed on Day 5 (the first on-study assessment) and had resolved or declined towards baseline by the first post-treatment assessment on Day 15.

Table 18: Expected Adverse Drug Reactions by PT (US213b, US316, US317)

PT	Pooled Favipiravir N = 1653 n (%)
Diarrhoea	38 (2.3)
Nausea	34 (2.1)
Blood triglycerides increased	32 (1.9)
ALT increased	31 (1.9)
Urinary tract infection	24 (1.5)
AST increased	21 (1.3)
Headache	18 (1.1)
Vomiting	16 (1.0)

Note: AEs are classified according to PT of MedDRA Version 15.0. Subjects are counted once within PT.
Note: US213b BID and TID, US316 and US317 are pooled for analysis. In US213b, TEAE if an AE started within 15 days of first dose. In US316 and US317, TEAE if an AE occurred within 22 days of first dose.

7.6. Pharmacokinetics

PK studies have shown favipiravir plasma protein binding averages 53 to 54%. Of the portion bound to protein, 65% is to albumin, and 6.5% to alpha1-acid glycoprotein.

Favipiravir is extensively metabolized with less than 1% recovered unchanged in urine. The major metabolite, T-705M1, is formed by aldehyde oxidase in human liver cytosol.

The cytochrome mixed function oxidase systems do not significantly contribute to the metabolism of favipiravir. Favipiravir exhibits only weak inhibitory effects on CYP1A2, 2C9, 2C19, 2D6, 2E1, or 3A4 (IC_{50} >800 µmol/L, 126 µg/mL). Favipiravir does inhibit CYP2C8 in human liver microsomes. Favipiravir showed little or no induction of CYP1A2, CYP2C9, CYP2C19 and CYP3A4 in human hepatocytes. In human liver microsomes, favipiravir was not metabolized, suggesting little contribution of human CYP isozymes to the metabolism of favipiravir. The majority of favipiravir was metabolized to T-705M1 by aldehyde oxidase in human liver cytosol.

Favipiravir inhibited the CYP2C8 activity in human liver microsomes with an IC_{50} value of 477 µmol/L and acetaminophen sulfation in human liver S9 fraction with an IC_{50} value of 150 µmol/L. Favipiravir showed little or no induction of CYP1A2, CYP2C9, CYP2C19, and CYP3A4 activities in primary cultures of freshly isolated human hepatocytes. In vitro CYP inhibition study in liver microsomes showed T-705 has little or no potential to cause metabolic DDIs in vivo.

7.7. Drug-Drug Interactions

A DDI study with healthy volunteers (Study US106) showed favipiravir in combination with acetaminophen increased acetaminophen blood levels 14% to 17% based on plasma AUC comparisons. Restrictions to acetaminophen use (limiting daily use in adults to no more than 3000 mg/day) have been incorporated into all clinical study protocols and associated informed consent forms.

Favipiravir co-administration increased both norethindrone (47%) and ethinyl estradiol (43%) blood levels, however, no change in efficacy for norethindrone/ethinyl estradiol oral contraceptives is expected.

Favipiravir administration with repaglinide, an anti-diabetic agent that is extensively metabolized by CYP2C8 and CYP3A4, increased repaglinide plasma AUC 30% to 50% due to inhibition of CYP2C8. Mean finger-stick blood glucose values varied considerably from baseline values following both groups receiving repaglinide alone and repaglinide with favipiravir. No difference was noted in the magnitude of the blood glucose decreases between the two groups.

7.8. Use in Specific Populations

Reproductive Toxicity. Women who might be pregnant or who intend to become pregnant should not use favipiravir. Women who do become pregnant while taking favipiravir should discontinue treatment immediately and be monitored. The outcome of the pregnancy should be recorded.

Nursing Mothers. One study in rats showed that favipiravir was excreted in breast milk. No studies in lactating humans have been performed. It is not known if favipiravir is excreted in human breast milk. Favipiravir should not be administered to women who are lactating or nursing.

Geriatric Use. Age difference does not have significant impact on the PK of favipiravir. Favipiravir appeared to be equally well tolerated by the healthy adult and elderly subjects.

Pediatric Use. The safety and effectiveness in pediatric populations has not been investigated.

7.9. Potential for Abuse and Dependence

There is no evidence to suggest that favipiravir would have the potential for abuse or dependence. No specific study, however, has been conducted to assess the potential for abuse or dependence.

7.10. Overdosage

The effects of an overdose of favipiravir are unknown. In the event of overdose, subjects should be hospitalized for observation and appropriate supportive treatment should be given. There is no known specific treatment in case of overdose.

7.11. Description

Favipiravir is supplied as slightly yellow, film coated tablets containing 200 mg of favipiravir plus compendial grade excipients commonly used in oral tablet formulations, and are intended to be administered orally.

7.12. How Supplied/Storage and Handling

Favipiravir is supplied as a slightly yellow, film coated tablet containing 200 mg of favipiravir. Favipiravir tablets are to be kept in a dry area, stored at 15° C to 30° C (59° F to 86° F) and shielded from direct light. A record of the minimum and maximum daily temperatures during storage is to be maintained at depots and sites prior to dispensing.

7.13. Reference Safety Information

No serious adverse reactions are considered expected by the sponsor for the purpose of expedited reporting of suspected unexpected serious adverse reactions (SUSAR) and identification of SUSARs in the "cumulative summary tabulation of serious adverse reactions" in the development safety update report for T-705.

REFERENCES

Baranovich T, Wong S, Armstrong J, Marjuki H, Webby R, Webster R, and Govorkova E, 2013. Vaccines and antiviral agents: T-705 (favipiravir) induces lethal mutagenesis in influenza A H1N1 viruses in vitro. J. Virol. 87, 3741-3751.

Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, Liao X, Gu Y, Cai Q, Yang Y, Shen C, Li X, Peng L, Huang D, Zhang J, Zhang S, Wang F, Liu J, Chen L, Chen S, Wang Z, Zhang Z, Cao R, Zhong W, Liu Y, Liu L, 2020. Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. Engineering (pre-proof)

Dobson J, Whitley R, Pocock S, Monto A, 2015. Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials. Lancet 385, 1729-37.

Furuta, Y, Gowen, B, Takahashi, K, Shiraki, K, Smee D, Barnard, D, 2013. Favipiravir (T-705) a Novel viral RNA Polymerase Inhibitor. Antiviral Res. 100, 446-54.

Furuta Y, Takahashi K, Fukuda Y, Kuno M, Kamiyama T, Kozaki K, Nomura N, Egawa H, Minami S, Watanabe Y, Narita H, and Shiraki K., 2002. In vitro and in vivo activities of anti-influenza virus compound T-705. Antimicrob. Agents Chemother. 46, 977-981.

Furuta Y, Takahashi K, Kuno-Maikawa M, Sangawa H, Uehara S, Kozaki K, Nomura N, Egawa H, Shiraki K., 2005. Mechanism of action of T-705 against influenza virus. Antimicrob. Agents Chemother. 49, 981-986.

Garattini E, Fratelli M, Terao M, 2009. The mammalian aldehyde oxidase gene family. Human Genomics 4, 119–130.

Gowen B, Wong M, Jung K, Sanders A, Mendenhall M, Bailey K, Furuta Y, Sidwell R, 2007. In vitro and in vivo activities of T-705 against arenavirus and bunyavirus infections. Antimicrob. Agents Chemother. 51, 3168–3176.

Jácome R, Becerra A, Ponce de León S, Lazcano A, 2015. Structural Analysis of Monomeric RNA-Dependent Polymerases: Evolutionary and Therapeutic Implications. PLoS One 10, e0139001

Jin Z, Smith L, Rajwanshi V, Kim B, Deval J, 2013. The ambiguous base-pairing and high substrate efficiency of T-705 (favipiravir) ribofuranosyl 5'- triphosphate towards influenza A virus polymerase. PLoS ONE 8, e68347.

Jochmans D, Segura Guerrero N, Delang L, Pastorino B, Querat G, Dallmeier K, Bello F, Tas A, Snijder E, de Lamballe X, Martina B, Froeyen M, Neyts J, van Hemert M, Leyssen P, 2013. Inhibition of Chikungunya virus replication by T-705 (favipiravir) and identification of resistance associated mutations in the RNA-dependent RNA polymerase. Poster presentation at the 26th International Conference on Antiviral Research.

Kay R, Kinnersley N, 2002. On the Use of the Accelerated Failure Time Model as an Alternative to the Proportional Hazards Model in the Treatment of Time to Event Data: A Case Study in Influenza. Therap. Interven. Reg. Sci. 36, 571-9.

Oestereich L, Lüdtke A, Wurr S, Rieger T, Muñoz-Fontela C, Günther S, 2014. Successful treatment of advanced Ebola virus infection with T-705 (favipiravir) in a small animal model. Antiviral Res. 105, 17-21.

Oestereich L, Rieger T, Lüdtke A, Ruibal P, Wurr S, Pallasch E, Bockholt S, Krasemann S, Muñoz-Fontela C, Günther S, 2016. Efficacy of Favipiravir Alone and in Combination With Ribavirin in a Lethal, Immunocompetent Mouse Model of Lassa Fever. J Infect Dis. 213,934-8.

Safronetz D, Falzarano D, Scott D, Furuta Y, Feldmann H, Gowen B, 2013. Antiviral efficacy of favipiravir against two prominent etiological agents of hantavirus pulmonary syndrome. Antimicrob. Agents Chemother. 57, 4673-80.

Sangawa H, Komeno T, Nishikawa H, Yoshida A, Takahashi K, Nomura N, Furuta Y., 2013. Mechanism of action of T-705 Ribosyl Triphosphate against Influenza Virus RNA Polymerase. Antimicrob. Agents Chemother. 57, 5202-8.

Sissoko D, Laouenan C, Folkesson E, M'Lebing AB, Beavogui AH, Baize S, Camara AM, Maes P, Shepherd S, Danel C, Carazo S, Conde MN, Gala JL, Colin G, Savini H, Bore JA, Le Marcis F, Koundouno FR, Petitjean F, Lamah MC, Diederich S, Tounkara A, Poelart G, Berbain E, Dindart JM, Duraffour S, Lefevre A, Leno T, Peyrouset O, Irenge L, Bangoura N, Palich R, Hinzmann J, Kraus A, Barry TS, Berette S, Bongono A, Camara MS, Chanfreau Munoz V, Doumbouya L, Souley Harouna, Kighoma PM, Koundouno FR, Réné Lolamou, Loua CM, Massala V, Moumouni K, Provost C, Samake N, Sekou C, Soumah A, Arnould I, Komano MS, Gustin L, Berutto C, Camara D, Camara FS, Colpaert J, Delamou L, Jansson L, Kourouma E, Loua M, Malme K, Manfrin E, Maomou A, Milinouno A, Ombelet S, Sidiboun AY, Verreckt I, Yombouno P, Bocquin A, Carbonnelle C, Carmoi T, Frange P, Mely S, Nguyen VK, Pannetier D, Taburet AM, Treluyer JM, Kolie J, Moh R, Gonzalez MC, Kuisma E, Liedigk B, Ngabo D, Rudolf M, Thom R, Kerber R, Gabriel M, Di Caro A, Wölfel R, Badir J, Bentahir M, Deccache Y, Dumont C, Durant JF, El Bakkouri K, Gasasira Uwamahoro M, Smits B, Toufik N, Van Cauwenberghe S, Ezzedine K, D'Ortenzio E, Pizarro L, Etienne A, Guedj J, Fizet A, Barte de Sainte Fare E, Murgue B, Tran-Minh T, Rapp C, Piguet P, Poncin M, Draguez B, Allaford Duverger T, Barbe S, Baret G, Defourny I, Carroll M, Raoul H, Augier A, Eholie SP, Yazdanpanah Y, Levy-Marchal C, Antierrens A, Van Herp M, Günther S, de Lamballerie X, Keïta S, Mentre F, Anglaret X, Malvy D; JIKI Study Group. 2016. Experimental Treatment with Favipiravir for Ebola Virus Disease (the JIKI Trial): A Historically Controlled, Single-Arm Proof-of-Concept Trial in Guinea. PLoS Med. 13, e1001967.

Sleeman K, Mishi, V, Deyde V, Furuta Y, Klimov A, Gubareva L, 2010. In vitro antiviral activity of favipiravir (T-705) against drug-resistant influenza and 2009 A(H1N1) viruses. Antimicrob. Agents Chemother. 54, 2517–24.

Sloan R, 1982. Hyperuricemia and gout. J Fam Pract. 14, 923-6.

Smither S, Eastaugh L, Steward J, Nelson M, Lenk R, Lever M, 2014. Post-exposure efficacy of oral T-705 (Favipiravir) against inhalational Ebola virus infection in a mouse model. Antiviral Res. 104, 153-5.

Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, Shi Z, Hu Z, Zhong W, and Xiao G. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. 2020 Cell Research 0:1–3.

Wang Y, Fan G, Salam A, Horby P, Hayden FG, Chen C, Pan J, Zheng J, Lu B, Guo L, Wang C, Cao B and CAP-China Network. 2019. Comparative effectiveness of combined favipiravir and oseltamivir therapy versus oseltamivir monotherapy in critically ill patients with influenza virus infection. J Infect Dis. pii: jiz656

Watanabe T, Kiso M, Fukuyama S, Nakajima N, Imai M, Yamada S, Murakami S, Yamayoshi S, Iwatsuki-Horimoto K, Sakoda Y, Takashita E, McBride R, Noda T, Hatta M, Imai H, Zhao D, Kishida N, Shirakura M, de Vries R, Shichinohe S, Okamatsu M, Tamura T, Tomita Y, Fujimoto N, Goto K, Katsura H, Kawakami E, Ishikawa I, Watanabe S, Ito M, Sakai-Tagawa Y, Sugita Y, Uraki R, Yamaji R, Eisfeld A, Zhong G, Fan S, Ping J, Maher E, Hanson A, Uchida Y, Saito T, Ozawa, M., Neumann, G., Kida, H., Odagiri, T., Paulson, J.C., Hasegawa, H., Tashiro, M., Kawaoka Y, 2013. Characterization of H7N9 influenza A viruses isolated from humans. Nature 501, 551-5.