Report on the Deliberation Results

December 11, 2024
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	Tepoxx Capsules 200 mg
Non-proprietary Name	Tecovirimat Hydrate (JAN*)
Applicant	Japan Biotechno Pharma Co., Ltd.
Date of Application	April 10, 2024

Results of Deliberation

In its meeting held on December 6, 2024, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product. The re-examination period is 8 years. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to conduct a post-marketing use-results survey involving all patients treated with the product wherever possible until data are obtained from a specified number of patients.

**Japanese Accepted Name (modified INN)*

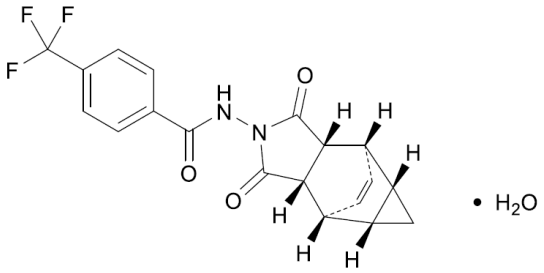
Review Report

November 26, 2024
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Tepoxx Capsules 200 mg
Non-proprietary Name	Tecovirimat Hydrate
Applicant	Japan Biotechno Pharma Co., Ltd.
Date of Application	April 10, 2024
Dosage Form/Strength	Capsules, each containing tecovirimat hydrate, equivalent to 200 mg of tecovirimat
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{19}H_{15}F_3N_2O_3 \cdot H_2O$
Molecular weight: 394.34
Chemical name: *N*-[(3a*R*,4*R*,4a*R*,5a*S*,6*S*,6a*S*)-1,3-Dioxo-3,3a,4,4a,5,5a,6,6a-octahydro-4,6-ethenocyclopropa[*f*]isoindol-2(1*H*)-yl]-4-(trifluoromethyl)benzamide monohydrate

Items Warranting Special Mention Application and expedited review in accordance with "Handling of application for marketing approval of Tepoxx Capsules 200 mg" (Joint PHB/IDPCD/ IDPCD Notification No. 0416-3 and PSB/PED Notification No.0416-5, by the Director of Infectious Disease Prevention and Control Division, Infectious Disease Prevention and Control Department, Public Health Bureau, and by the Director of Pharmaceutical

Evaluation Division, Pharmaceutical Safey Bureau, Ministry of Health, Labour and Welfare, dated April 16, 2024)

Reviewing Office Office of New Drug IV

Results of Review

On the basis of the data attached, the product's efficacy still remains to be proven because of no study conducted on efficacy in humans against smallpox, mpox, and cowpox, and complications due to replication of vaccinia virus following smallpox vaccination. However, based on non-clinical study data that demonstrated its antiviral effect, the product has promising efficacy with acceptable safety in light of its benefits expected (see Attachment). Therefore, it is significant to approve the product as a drug that is assumed to be used primarily in a public health crisis or in preparation for a crisis anticipated. As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following approval conditions.

Indication

Treatment of smallpox, mpox, and cowpox, and complications due to replication of vaccinia virus following smallpox vaccination

Dosage and Administration

The usual dosages for adults and children are as follows, administered orally after a meal for 14 days:
Patients weighing 13 kg to <25 kg:
Tecovirimat 200 mg twice daily (every 12 hours)
25 kg to <40 kg:
Tecovirimat 400 mg twice daily (every 12 hours)
40 kg to <120 kg:
Tecovirimat 600 mg twice daily (every 12 hours)
≥120 kg:
Tecovirimat 600 mg 3 times daily (every 8 hours)

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to conduct a post-marketing use-results survey involving all patients treated with the product wherever possible until data are obtained from a specified number of patients.

Attachment

Review Report (1)

October 4, 2024

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Tepoxx Capsules 200 mg
Non-proprietary Name	Tecovirimat Hydrate
Applicant	Japan Biotechno Pharma Co., Ltd.
Date of Application	April 10, 2024
Dosage Form/Strength	Capsules, each containing tecovirimat hydrate equivalent to 200 mg of tecovirimat

Proposed Indication

Treatment of the following viral infections in adult and pediatric patients weighing ≥13 kg:
Smallpox, mpox, and cowpox
Treatment of complications due to replication of vaccinia virus following smallpox vaccination

Proposed Dosage and Administration

Patients weighing 13 kg to <25 kg:
Tecovirimat 200 mg orally twice daily (every 12 hours) for 14 days, within 30 minutes after a meal
25 kg to <40 kg:
Tecovirimat 400 mg orally twice daily (every 12 hours) for 14 days, within 30 minutes after a meal
40 kg to <120 kg:
Tecovirimat 600 mg orally twice daily (every 12 hours) for 14 days, within 30 minutes after a meal
≥120 kg:
Tecovirimat 600 mg orally 3 times daily (every 8 hours) for 14 days, within 30 minutes after a meal

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Smallpox, mpox, cowpox, and the complications due to replication of vaccinia virus following smallpox vaccination are illnesses caused by infection with or replication of *Orthopoxvirus* genus of deoxyribonucleic acid (DNA) viruses (variola virus [VARV], monkeypox virus [MPXV], cowpox virus [CPXV], and vaccinia virus [VACV], respectively).

Symptoms of smallpox[1)] manifest after a 7 to 16 day-incubation period as acute fever at around 39°C, headache, pain in extremities, and lower back pain, etc., followed by systemic rash prominently on the face and scalp. Smallpox is clinically classified into variola minor and variola major, with a mortality rate of ≤1% and 20% to 50%, respectively. The World Health Organization (WHO) declared the eradication of smallpox in May 1980, and there have been no cases since then.

Mpox[2)] has been prevalent mainly in the central and west Africa since its first case of infection to humans in 1970. Starting from May 2022, mpox cases surged in Europe and the US in persons without a history of traveling to the prevalent countries or contact with infected person. From January 1, 2022 to August 31, 2024, 106,310 cases (including 234 deaths) were reported in 123 countries or regions. In Japan, after the first case reported in July 2022, 249 cases (including ≥1 death) were reported as of September 22, 2024. There are 2 types of MPXV, Clade I (Ia and Ib) and Clade II (IIa and IIb), with mortality rates of around 10% and 1%, respectively. While the global outbreak in May 2022 and thereafter was led primarily by Clade IIb (lineage B.1 and its sublineages), recent outbreaks revealed the prevalence of not only Clade Ia mpox, predominantly in Africa, but also Clade Ib. In response, WHO declared a public health emergency of international concern[3)] on August 14, 2024.

Classic cases of mpox are characterized by prodromal symptoms including fever, headache, swollen lymph nodes, which were followed by rash that develops on the same day or within 4 days of the onset of fever. Rash is predominant on the face, also often appearing on the trunk, upper limbs, palms, lower limbs, soles, and oral mucosa, and it scab over within 7 to 14 days. Since May 2022, typical mpox is characterized by its prevalence predominant in young men, absence of prodromal symptoms in approximately 10% of patients, and rash in varying stages observable concurrently.

Cowpox[4)] is contracted mainly through contact with infected rodents or cats. Patients present with reddish blisters on the fingers, hands, or face. While human infection cases have been reported sporadically in Europe, its prevalence is unknown in Japan.

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1) "What is smallpox?" [in Japanese] National Institute of Infectious Diseases, Japan (last accessed on October 4, 2024): https://www.niid.go.jp/niid/ja/kansennohanashi/445-smallpox-intro.html

2) "Guidance on clinical treatment of mpox, ver.2.0,"
"2022-23 Mpox (Monkeypox) Outbreak: Global Trends" WHO: https://worldhealthorg.shinyapps.io/mpx_global/,
"About Mpox," Ministry of Health, Labour and Welfare:
https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou/kekkaku-kansenshou19/monkeypox_00001.html (last accessed on October 4, 2024)

3) The second declaration since the first one on July 23, 2022

4) The US CDC "Smallpox and Other Orthopoxvirus-Associated Infections":
https://wwwnc.cdc.gov/travel/yellowbook/2024/infections-diseases/smallpox-other-orthopoxvirus-associated-infections (last accessed on October 4, 2024)

Smallpox vaccines containing live vaccinia virus may lead to a variety of complications[5)] triggered by replicated vaccinia virus. The freeze-dried smallpox vaccine prepared in cell culture LC16 "KMB," a vaccine approved in Japan, contains attenuated LC16m8 strain, and the risk of developing complications after vaccination is considered extremely low. Conversely, smallpox vaccines in the second generation or earlier approved in other countries have a potential problem of viral replication.

Tecovirimat Hydrate (hereinafter referred to as "tecovirimat") is expected to inhibit interaction between VP37, a highly conserved protein, as with other orthopoxviruses, involving in envelope formation and extracellular release, and host cell transporters (Rab9 GTPase and TIP47), and thereby inhibits the release of viruses from infected cells. Tecovirimat was approved in the US in July 2018 for smallpox under the Animal Rule,[6)] and in Europe in January 2022 for the treatment of smallpox, mpox, and cowpox, and complications due to replication of vaccinia virus following smallpox vaccination (exceptional circumstances authorization[7)]).

In Japan, no drugs have been approved for the treatment of smallpox, mpox, and cowpox, or complications due to replication of vaccinia virus following smallpox vaccination. Based on "The concept of priority infectious diseases in terms of securing pharmaceutical products as part of public health emergency management and the tentative list" (dated on March 31, 2022, Review meeting on the availability of Medical Countermeasures), tecovirimat is intended for the treatment of smallpox and other priority infectious diseases. Tecovirimat will serve as a highly important medical countermeasure in public health crisis management in terms of life-saving, epidemic control, maintaining social activities, etc., thus the product should be introduced to Japan as soon as practicable and a framework should be set for its use. For this reason, the Ministry of Health, Labour and Welfare requested[8)] an expedited review and investigation based on the data submitted for marketing approval in Europe, taking into account the explanation about the data. Tepoxx was developed with the support of "Research Program on Emerging and Re-emerging Infectious Diseases" by the Japan Agency for Medical Research and Development (AMED).

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5) The US CDC "Smallpox, Vaccine Adverse Events": https://www.cdc.gov/smallpox/clinicians/vaccine-adverse-events5.html (last accessed on October 4, 2024)

6) The regulations that allow for the approval of drugs based on the efficacy investigation results in animals when human efficacy studies are practically or ethically infeasible. However, human safety data are required.

7) A type of marketing authorization for products with inadequate data because of extremely limited number of patients, etc. Approved products are subject to annual reviews of benefit-risk balance.

8) "Handling of application for marketing approval of Tepoxx Capsules 200 mg" (Joint PHB/ IDPCD/ IDPCD Notification No. 0416-3 and PSB/PED Notification No.0416-5, by the Director of Infectious Disease Prevention and Control Division, Infectious Disease Prevention and Control Department, Public Health Bureau, and by the Director of Pharmaceutical Evaluation Division, Pharmaceutical Safey Bureau, Ministry of Health, Labour and Welfare, dated April 16, 2024)

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Characterization

The drug substance is a white to grayish white solid. Its description, solubility, acid dissociation constant, melting point, distribution coefficient, isomers, crystal polymorphism, hygroscopicity, and particle size were determined. The drug substance has 3 types of crystal forms (hydrate I, hydrate III, and hemihydrate V). Its proposed specification is powder X-ray diffraction. Only hydrate I is used for the manufacture of the drug product.

The chemical structure of the drug substance has been elucidated by powder X-ray diffraction, elemental analysis, infrared absorption spectroscopy (IR), nuclear magnetic resonance spectroscopy (NMR) (^{1}H-NMR), and liquid chromatography/mass spectrometry (LC/MS).

2.1.2 Manufacturing process

The drug substance is synthesized using [redacted], [redacted], and [redacted] as starting materials.

The quality control strategy (Table 1) has been formulated based on the following:

- Identification of critical quality attributes (CQAs)
- Identification of critical process parameters (CPPs) through quality risk assessment and design of experiments
- Development of design space (DS)

Table 1. Outline of control strategies for the drug substance

CQA	Control method
Related substance	Manufacturing process and specifications
Water content	Manufacturing process and specifications
[redacted]	Manufacturing process and specifications
Particle size	Manufacturing process and specifications

Critical steps include the manufacturing of [redacted],[9] the manufacturing of [redacted], and [redacted] of [redacted]. The [redacted], [redacted],[10] and [redacted][11] are controlled as critical intermediates.

2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (IR, high performance liquid chromatography [HPLC]), water content, residue on ignition, [redacted], [redacted], residual solvent (gas chromatography [GC]), assays (HPLC), purity (related substances [HPLC]), and microbial limits.

The microbial limit specifications were established during the review process.

9) [redacted]
10) [redacted]
11) [redacted]

2.1.4 Stability of drug substance

Table 2 summarizes the main stability studies for the drug substance and the results showed that the drug substance is stable. The photostability study showed that the drug substance is photostable.

Table 2. Stability studies for the drug substance

Study	Primary batch	Temperature	Humidity	Storage package	Storage period
Long-term	3 commercial-scale batches	25°C	60% RH	Polyethylene bags (double layer) + aluminum foil-lined fiber drum	[redacted] months
Accelerated	3 commercial-scale batches	40°C	75% RH		6 months

Based on the above results, a shelf life of [redacted] months was proposed for the drug substance when placed in double-layer polyethylene bags and stored in a fiber drum lined with aluminum foil at ≤25°C.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is formulated as immediate release capsules, each containing 208.99 mg of the drug substance (equivalent to 200 mg of tecovirimat). It contains crystalline cellulose, lactose hydrate, croscarmellose sodium, light anhydrous silicic acid, hypromellose, sodium lauryl sulfate, and magnesium stearate as excipients.

2.2.2 Manufacturing process

The drug product is manufactured through a process comprising [redacted], granulation liquid preparation, dry mixing, addition of granulation liquid, mixing, [redacted], drying and particle size regulation of granulated product, mixing of the granulated product and excipients, capsule filling, bulk capsule packaging/storage, bottling and bottle packaging/labeling, testing, and storage. [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted] steps are critical steps. Process control items and values have been specified in the critical steps [redacted] and [redacted].

The quality control strategy (Table 3) has been formulated based on the following:

- Identification of CQAs
- Identification of CPPs through quality risk assessment and design of experiments
- Development of DS

Table 3. Outline of the control strategy for the drug product

CQA	Control method
Strength	Specifications
Identity	Specifications
Dissolution	Manufacturing process and specifications
Uniformity of dosage units	Manufacturing process and specifications
Degradation product	Specifications
[redacted]	Specifications

2.2.3 Control of drug product

The proposed specifications for the drug product consist of strength, description (appearance), identification (HPLC, ultraviolet-visible spectroscopy [UV/VIS]), dissolution, uniformity of dosage units, water content, assay (HPLC), purity (related substances [HPLC]), and microbial limit testing.

2.2.4 Stability of drug product

Table 4 shows the main stability studies for the drug product, and the results showed that the drug product is stable. The results of the photostability study showed that the drug product is photolabile.

Table 4. Stability studies for the drug product

Study	Primary batch	Temperature	Humidity	Storage package	Storage period
Long-term	3 commercial-scale batches	25°C	60% RH	HDPE bottle	60 months
Accelerated	3 commercial-scale batches	40°C	75% RH		6 months

Based on the above results, a shelf life of 60 months was proposed for the drug product when loaded into HDPE bottles and stored at ≤25°C protected from light.

2.R Outline of the review conducted by PMDA

Based on the data submitted, PMDA concluded that the quality of the drug substances and the drug product is adequately controlled except for the following issue.

2.R.1 Control of mutagenic impurities

The applicant's explanation about the potential presence of mutagenic impurities in tecovirimat:

Among the impurities potentially contained in the drug product, SG2 is an intermediate of the drug substance and a degradation product of the drug product. SG2 is mutagenic [see Section 5.6.3], and the maximum SG2 intake will exceed the acceptable limit (120 μg/day) according to the ICH M7 (R2) guidelines when tecovirimat with the currently proposed SG2 level (upper limit, 0.05%) is administered at the proposed dosage. However, the proposed SG2 level is justifiable based on the following factors:

- The proposed SG2 level was accepted in the authorization review in Europe and the US.
- Because SG2's limit of quantitation exceeds 0.0066%[12)] at present, ≤0.0066% is not possible.

PMDA's view:

In Japan, currently, there are no therapeutic drugs effective for the proposed indication. Tecovirimat is expected to be administered to patients in serious condition, and in this view, the use of tecovirimat is acceptable only when its benefits will outweigh the risks, after warning through the package insert that the drug product may contain mutagenic impurity at a level greater than the acceptable intake limit specified in the ICH M7 (R2) guidelines. Nevertheless, measures to control the impurity level at or below the acceptable limit are subject to further discussion, including the development of a highly sensitive detection method for SG2. Impurities

[12)] The content of SG2 in the drug product that allows the maximum daily intake of SG2 at or below the acceptable intake limit specified in the ICH M7 (R2) guidelines when tecovirimat 1,800 mg per day is administered.

other than SG2 that have not been assessed for mutagenic hazard in accordance with the ICH M7 (R2) guidelines are also subject to safety evaluation to establish necessary control strategy.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

The data submitted included the results from primary pharmacodynamic studies, secondary pharmacodynamic studies, safety pharmacology studies, and pharmacodynamic drug interaction studies. In this section, unless otherwise stated, values are expressed as mean values.

3.1 Primary pharmacodynamics

3.1.1 Mechanism of action (CTD 4.2.1.1.10, Study 246-PC-011, Reference CTD 4.3: *Virol. J* 2009;6:44)

After host cells are infected with orthopoxviruses such as MPXV, the replication and transcription of the virus genome occur in the cytoplasm, not in the cell nucleus. The virus is present in different forms within the cell, including intracellular mature virus (IMV) that refers to an intracellular mature virion with no envelope; intracellular enveloped virus (IEV) that has acquired an envelope from a lipid bilayer of the Golgi apparatus; and cell-associated enveloped virus (CEV) that is attached to the plasma membrane. The virus is then released from the cell as extracellular enveloped virus (EEV). The following study outcomes suggest that tecovirimat inhibits the interaction between VP37, a protein highly conserved across orthopoxviruses, which is involved in envelope formation and release from the cell, and host cell transport proteins (Rab9 GTPase and TIP47), thereby suppressing IEV production and inhibiting the release of viruses from infected cells.

- To RK-13 cells infected with VACV (IHD-J strain), ^{3}H-thymidine was added, and the cells were incubated in the presence (10 µmol/L) or absence of tecovirimat. Radioisotope-labeled virions in the culture supernatant and the cells were separated by equilibrium density-gradient centrifugation. In the absence of tecovirimat, peaks of IMV, IEV, CEV, and EEV were observed, while only IMV peaks were observed in the presence of tecovirimat. The results demonstrated that tecovirimat inhibits envelope formation in the virus replication process.
- After incubating BSC-40 cells infected with VACV (IHD-J strain) in the presence (5 µmol/L) or absence of tecovirimat, virus titers in the culture supernatant and the cell were determined by plaque assay. While intracellular virus titers did not differ significantly between the presence and absence of tecovirimat, the virus titer in the culture supernatant decreased in the presence of tecovirimat to approximately one tenth compared to that in the absence of tecovirimat, demonstrating tecovirimat's suppressive effect on the release of virions from the cells.
- After incubating BSC-40 cells infected with VACV (IHD-J strain) expressing VP37-green fluorescent protein (GFP)[13)] in the presence (10 µmol/L) or absence of tecovirimat, the interaction between the VP37 protein consisting of IEV and host cell transport proteins (Rab9 GTPase and TIP47)[14)] was investigated by immunoprecipitation. In the presence of tecovirimat, co-precipitation with host cell transport proteins (Rab9 GTPase and TIP47) decreased compared to that in the absence of tecovirimat. When tecovirimat-

[13)] Prepared by inserting a GFP reporter gene at the C-terminal of *F13L* gene encoding the VP37 protein.
[14)] Rab9 GTPase is primarily located in late endosome compartments, interacting with TIP47, a Rab9 GTPase-specific protein, thereby being involved in intracellular transport such as transport vesicle formation (*Science.* 2001;292:1373-76).

resistant variant VACV[15)] was used under the same conditions, the presence or absence of tecovirimat did not make difference in the amount of co-precipitated VP37 protein or Rab9 GTPase. The results demonstrated that tecovirimat inhibits the interaction between the VP37 protein of the virus and host cell transport proteins.

3.1.2 *In vitro* antiviral activity

3.1.2.1 Antiviral activity against Orthopoxviruses (CTD 4.2.1.1.7, Study 246-PC-007; CTD 4.2.1.1.35, Study 246-PC-035; CTD 4.2.1.1.45, Study SIGA-246-MET-001; CTD 4.2.1.1.70, Study PRB-0027; Reference: CTD 4.3, *J Virol.* 2005;79:13139-49; *Antimicrob Agents Chemother.* 2009;53:1007-12; *Antivir Ther.* 2007;12:1205-16; *PLoS One.* 2013;8:e55808)

The antiviral activity of tecovirimat was assessed in terms of cytopathic effects using Vero cells, BSC-40 cells, or HEL299 cells that were infected with clinical isolates of the members of the *Orthopoxvirus* genus, namely, VARV, MPXV, VACV, CPXV, or RPXV. The results (Table 5) demonstrated that tecovirimat has antiviral activity against all of the virus strains studied.

The cytotoxic activity of tecovirimat against Vero cells was assessed based on the mitochondrial dehydrogenase activity. The 50% cytotoxicity concentration (CC_{50}) was >40 μmol/L.

[15)] A virus with a tyrosine to aspartic acid conversion in the VP37 protein. Compared with wild-type VACV, the antiviral activity of tecovirimat (EC_{50}) decreased >1,000-fold.

Table 5. *In vitro* antiviral activity against Orthopoxviruses

Virus (Clade)	Virus strain	VP37 sequence conservation (%)[a)]	EC_{50} (nmol/L)
VARV (major)	Bangladesh74-sol	100	28
			50
	Brazil66-39	100	67
	Sierra Leone68-258	100	37
	Sudan47-juba	99	19
	Nepal73-175	100	21
	Japan1951 (Harper)	100	26
	UnitedKingdom1946	99	34
			16
	BeninDahomey1968	99	15
	Sumatra1970 - 228	99	19
	Sumatra1970 - 222	99	20
VARV (minor)	Somalia77 - ali	99	28
	Botswana1973 - 225	99	14
	Botswana1972 - 143	99	11
MPXV (Ia)	Zaire (V79-I-005)	98	39
	Zaire '79 (V79-I-079)	98	14
	Zaire (V77-I-823)	—	30
MPXV (II)	Benin (V78-I-3945)	—	23
	Ivory Coast (V81-I-179)	—	32
	2003-USA-039	98	36
VACV	Copenhagen	99	7
	New York City Board of Health (Wyeth)	—	10
	Western Reserve	98	10
	Cantagalo CM01	98	8.6
CPXV	Germany1980_EP4	99	30
	Germany1991_3	97	30
	Austria1999_867	98	20
	Finland2000_MAN	98	20
	Brighton Red	97	50
			210
			160
RPXV	Utrecht	—	14

"—," Not evaluated

a) The percent sequence conservation compared with the amino acid sequence of the VP37 protein of VARV (major clade, Bangladesh 74-sol strain)

3.1.2.2 Antiviral activity in the presence of serum (CTD 4.2.1.1.5, Study 246-PC-005)

The antiviral activity of tecovirimat was evaluated in terms of cytopathic effects using BSC-40 cells infected with VACV (Western Reserve strain) in the presence of human serum (0%-10%). The EC_{50} of tecovirimat was 3 to 12 nmol/L. Based on these values, the EC_{50} of 28 nmol/L in the presence of 100% human serum was estimated by linear regression. There was no significant correlation between human serum concentration and EC_{50}.

3.1.2.3 Antiviral activity of metabolites against rabbitpox virus (CTD 4.2.1.1.45, Study SIGA-246-MET-001)

The antiviral activity of the main tecovirimat metabolites (M4, M5, and trifluoromethyl benzoic acid [TFMBA]) was investigated in terms of cytopathic effects using Vero E6 cells infected with rabbitpox virus (RPXV, Utrecht strain). None of the metabolites showed antiviral activity up to the maximum concentration (5 µmol/L) studied. The cytotoxic activity of these metabolites in Vero E6 cells was investigated in terms of their cytopathic effects. The CC_{50} was >5 µmol/L.

3.1.2.4 Antiviral activity against non-orthopoxviruses (*Poxviridae*) (CTD 4.2.1.1.7, Study 246-PC-007)

The antiviral activity of tecovirimat against the following viruses was investigated: herpes simplex virus type 1 (*Herpesviridae*), cytomegalovirus (*Herpesviridae*), respiratory syncytial (RS) virus subtype A (*Paramyxoviridae*), rotavirus (*Reoviridae*), Rift Valley fever virus (*Bunyaviridae* [16)]), Tacaribe virus (*Arenaviridae*), and lymphocytic choriomeningitis virus (*Arenaviridae*). Tecovirimat did not show antiviral activity up to 40 μmol/L against any of these viruses.

3.1.3 *In vivo* studies

3.1.3.1 Antiviral activity in monkeys infected with MPXV

3.1.3.1.1 Dose-response evaluation in MPXV-infected monkeys (CTD 4.2.1.1.39, Study AP-09-026G)

Cynomolgus monkeys (27 male monkeys, N = 5 to 7/group[17)]) were intravenously inoculated with MPXV (Zaire strain [V79-I-005], 5.0×10^7 PFU). Starting on Day 4 post-MPXV challenge (when rash was observed in all animals), tecovirimat 0.3, 1, 3, 10 mg/kg, or placebo was orally administered QD for 14 days to assess the minimum effective dose of tecovirimat. The proportion of monkeys that survived up to 28 days post-MPXV challenge in the intention-to-treat (ITT) population,[18)] the primary endpoint, was 0% (0 of 7 animals) in the placebo group, 20% (1 of 5 animals) in the 0.3 mg/kg group, 0% (0 of 5 animals) in the 1 mg/kg group, 80% (4 of 5 animals) in the 3 mg/kg group, and 80% (4 of 5 animals) in the 10 mg/kg group, respectively. The results showed statistically significant differences at tecovirimat doses of ≥3 mg/kg compared to placebo.[19)] The viral DNA level in blood and pox lesion counts, the secondary endpoints, tended to decrease at tecovirimat doses of ≥3 mg/kg compared to placebo. Accordingly, the minimum effective dose was determined to be 3 mg/kg for the 14-day QD oral tecovirimat regimen.

3.1.3.1.2 Evaluation of the effect of the timing to start tecovirimat treatment on its therapeutic effect in MPXV-infected monkeys (CTD 4.2.1.1.48 through 4.2.1.1.55, Study SR10-037F)

Cynomolgus monkeys (21 male and female monkeys, N = 3 to 6/group[17)]) were intravenously inoculated with MPXV (Zaire strain [V79-I-005], 5.0×10^7 PFU). The monkeys received either tecovirimat 10 mg/kg orally QD for 14 days starting on Day 4, Day 5, or Day 6 post-MPXV challenge or placebo orally QD for 14 days starting on Day 4 post-MPXV challenge to evaluate the effect of timing to start treatment on its therapeutic effect. The proportion of monkeys that survived for up to 56 days post-MPXV challenge in the ITT population,[18)] the primary endpoint, was 0% (0 of 3 animals) in the placebo group, 83% (5 of 6 animals) in the tecovirimat Day 4 group, 83% (5 of 6 animals) in the tecovirimat Day 5 group, and 50% (3 of 6 animals) in the tecovirimat Day 6 group. The results showed a statistically significant difference in the tecovirimat Day 4 and Day 5 groups compared to the placebo group.[20)] The blood viral DNA level and pox lesion count, the secondary endpoints, tended to decrease in the tecovirimat Day 4 and 5 groups compared to those in the placebo group.

[16)] The Rift Valley fever virus belongs to the *Phenuiviridae* family according to the classification by International Committee on Taxonomy of Viruses (International Committee on Taxonomy of Viruses 2023, ICTV: https://ictv.global/taxonomy/ [last accessed on October 4, 2024])

[17)] Because an alternative hypothesis for hypothesis testing has not been established, this is not a number calculated to provide a high statistical power.

[18)] Randomized monkeys that received the study drug at least once

[19)] A two-sided significance level of 5%, Fisher's exact test; for comparison between each treatment group with placebo, multiplicity of hypothesis testing was adjusted by the closed testing procedure from the highest dose group.

[20)] A two-sided significance level of 5%, Fisher's exact test; for comparison between each treatment group with placebo, multiplicity of hypothesis testing was adjusted by the closed testing procedure from the shorter duration group.

These results showed a trend of greater therapeutic effect of tecovirimat obtained by early start after MPXV infection.

3.1.3.1.3 Evaluation of the effect of treatment duration of tecovirimat on treatment effectiveness in MPXV-infected monkeys (CTD 4.2.1.1.58 through 4.2.1.1.61, Study SR10-038F)

Cynomolgus monkeys (25 male and female monkeys, N = 4 to 6/group[17)]) were intravenously inoculated with MPXV (Zaire strain [V79-I-005], 5.0×10^7 PFU). Starting on Day 4 post-MPXV challenge, tecovirimat 10 mg/kg was administered orally QD for 3, 5, 7, or 10 days, or placebo was administered orally QD for 10 days to assess the effect of treatment duration with tecovirimat on its therapeutic effect. The proportion of monkeys that survived up to 28 days post-MPXV challenge in the ITT population,[18)] the primary endpoint, was 25% (1 of 4 animals) in the placebo group, 50% (2 of 4 animals) in the tecovirimat 3-day group, 100% (6 of 6 animals) in the tecovirimat 5-day group, 100% (6 of 6 animals) in the tecovirimat 7-day group, and 80% (4 of 5 animals) in the tecovirimat 10-day group.[21)] The blood viral DNA level and pox lesion count, the secondary endpoints, tended to decrease in animals receiving tecovirimat for ≥5 days compared to placebo. These results suggest the possibility that longer treatment leads to greater effect.

3.1.3.1.4 Effects of MPXV infection on pharmacokinetics of tecovirimat (CTD 4.2.1.1.41, Study FY10-087)

Cynomolgus monkeys (24 male and female monkeys, N = 6/group) were intravenously inoculated with MPXV (Zaire strain [V79-I-005], 5.0×10^7 PFU). A single dose of tecovirimat 3, 10, 20 mg/kg, or vehicle[22)] was orally administered to cynomolgus monkeys 10 days before MPXV challenge. Starting on Day 4 post-MPXV challenge, tecovirimat 3, 10, 20 mg/kg, or vehicle was orally administered QD for 14 days to assess the effect of MPXV infection on the pharmacokinetics (PK) of tecovirimat and its therapeutic effect against MPXV infection. The results showed no clear differences in tecovirimat exposure between 10 days prior to MPXV challenge (uninfected) and Day 4 or Day 17 post-MPXV challenge (infected) [see Section 4.1.3]. In the vehicle control group, all animals died or were euthanized by Day 28 post-MPXV challenge while all tecovirimat-treated animals survived up until the Day 28 post-MPXV challenge.

3.1.3.2 Antiviral activity in RPXV-infected rabbits

3.1.3.2.1 Dose-response evaluation in RPXV-infected rabbits (CTD 4.2.1.1.64, Study SR14-008F)

New Zealand White (NZW) rabbits (50 male and female rabbits, N = 10/group[17)]) were intradermally inoculated with RPXV (Utrecht strain, 1,000 PFU). Starting on Day 4 post-RPXV challenge (when fever and viremia were observed in all animals), tecovirimat 20, 40, 80, 120 mg/kg, or placebo was administered orally QD for 14 days to assess the minimum effective dose of tecovirimat. The proportion of rabbits that survived up to 30 days post-RPXV challenge was 0% in the placebo group, 90% (9 of 10 animals) in the 20 mg/kg group, 90% (9 of 10 animals) in the 40 mg/kg group, 80% (8 of 10 animals) in the 80 mg/kg group, and 80% (8 of 10

[21)] A two-sided significance level of 5%, Fisher's exact test; for comparison between each treatment group with placebo, multiplicity of hypothesis testing was adjusted by the closed testing procedure from the longer treatment duration group. The results showed no statistically significant difference between the tecovirimat 10-day group and the placebo group, and thereafter, no hypothesis tests were performed.

[22)] 1% (w/v) hydroxypropyl methylcellulose aqueous solution with 0.5% (w/v) polysorbate 80

animals) in the 120 mg/kg group. The proportion of survived animals tended to be higher in all tecovirimat dosage groups compared to the placebo group. All animals in the placebo group died before disappearance of lesions. In tecovirimat-treated animals, lesions disappeared in all animals by Day 18 post-RPXV challenge except for 1 animal in the 120 mg/kg group. In all tecovirimat dosage groups, the viral DNA level in blood (maximum) and that in lung and spleen tissue (final measurement point[23)]) decreased compared to those in the placebo group. Thus, no dose-response relationship was observed in the 14-day QD oral tecovirimat regimen, and the minimum effective dose was determined to be ≤20 mg/kg.

3.1.3.2.2 Effects of RPXV infection on PK of tecovirimat (CTD 4.2.1.1.63, Study SR13-025F)

A single dose of tecovirimat 40, 80, or 120 mg/kg was orally administered to NZW rabbits (24 male and female rabbits, N = 8/group) 7 days prior to RPXV challenge. The rabbits were intradermally inoculated with RPXV (Utrecht strain, 1,000 PFU). Starting on Day 4 post-RPXV challenge, tecovirimat 40, 80, or 120 mg/kg was orally administered QD for 14 days to assess the effect of RPXV infection on the PK of tecovirimat and its therapeutic effect against RPXV infection. Tecovirimat exposure at 7 days prior to RPXV challenge (uninfected) was similar to that on Day 4 post-RPXV challenge (infected) [see Section 4.1.3]. The proportion of rabbits that survived up to Day 18 post-RPXV challenge was 87.5% (7 of 8 animals) in the 40 mg/kg group, 87.5% (7 of 8 animals) in the 80 mg/kg group, and 100% (8 of 8 animals) in the 120 mg/kg group.

3.1.4 Resistance profiles

3.1.4.1 Frequency of the emergence of tecovirimat-resistant VACV (CTD 4.2.1.1.67, Study 246-PC-034)

The frequency of emergence of resistant virus variants (resistant virus frequency = resistant plaques / overall plaques), which was calculated based on the number of plaques formed after infecting BSC-40 cells with VACV (Western Reserve strain) in the presence of tecovirimat (5 μmol/L), was 0.8×10^{-6}. The resistant virus frequency in the absence of tecovirimat was 1.2×10^{-6}. The results suggest that the resistant variant virus observed in the presence of tecovirimat was not associated with exposure to tecovirimat, but was likely to have been present in the wild.

3.1.4.2 Tecovirimat resistance selection of VACV (CTD 4.2.1.1.31, Study 246-PC-035)

Random mutations were introduced into the *F13L* gene encoding the VP37 protein of wild-type VACV (Western Reserve strain; EC_{50}, 0.01 μmol/L), and viruses with reduced tecovirimat susceptibility (EC_{50}, 1.5 to >50 μmol/L) were selected. The identified mutations included 27 point mutations that lead to amino acid residue changes at 238 to 302 positions of the VP37 protein.

3.1.4.3 Replication capacity of VACV-resistant variants (CTD 4.2.1.1.31, Study 246-PC-035)

The point mutations identified in the *in vitro* resistance selection study [see Section 3.1.4.2] were introduced in the wild-type VACV (Western Reserve strain) to prepare VACV vv911 (N267D mutation) and VACV

[23)] The timepoint at which animals died due to RPXV infection or were euthanized, or, for survived animals, the final evaluation timepoint (Day 30 post-RPXV challenge)

vv331 (L302P mutation). The viral titer was evaluated using the viral replication capacity obtained by infecting BSC-40 cells with these variants. The change in virus titer over time was similar to that of the wild type.

The prepared variants, VACV vv911 (N267D) and VACV vv331 (L302P), were respectively mixed with the wild-type VACV (Western Reserve strain), which was used to infect BSC-40 cells for successive culture to assess the percentage of each variant viral load to the total viral load. The percentage of VACV vv331 (L302P) was consistent across passages, while the percentage of VACV vv911 (N267D) tended to decrease with increasing passage number. The results suggest that the wild-type VACV coinfected with VACV vv911 (N267D) may gradually become dominant.

3.1.4.4 Pathogenicity in tecovirimat-resistant VACV variants and effectiveness of tecovirimat in the treatment of mice infected with tecovirimat-resistant VACV variants (CTD 4.2.1.1.32, Study 246-PC-036)

The wild-type VACV (Western Reserve strain), VACV vv911 (N267D), or VACV vv331 (L302P) was intranasally inoculated (1×10^3 to 3×10^6 PFU) into BALB/c mice (N = 5/group), and the pathogenicity of each virus was evaluated based on mortality (lethal dose [LD_{50}]). The mortality after virus challenge was similar across the groups, suggesting that tecovirimat-resistant amino acid mutations (N267D and L302P) do not affect the pathogenicity of VACV. In addition, virus titers in the liver and spleen were higher in mice infected with VACV vv911 or VACV vv331 compared to that in mice infected with the wild-type VACV (Western Reserve strain), suggesting that these variants may have a higher replication capability in hosts.

The wild-type VACV (Western Reserve strain), VACV vv911, or VACV vv331 was intranasally inoculated (2.5×10^5 PFU) into BALB/c mice (N = 5/group). Starting at 1 hour post-VACV challenge, vehicle[24)] or tecovirimat 100 mg/kg was orally administered QD for 14 days, and the proportion of survived animals was evaluated. All animals in the vehicle control group died. Among tecovirimat-treated animals, those in the wild-type VACV group survived; conversely, those in the tecovirimat-resistant VACV variant groups (vv911 and vv331) died or were euthanized due to severe clinical symptoms, and tecovirimat was not shown to be effective in the treatment of these animals.

3.1.4.5 Tecovirimat-resistant CPXV mapping (CTD 4.2.1.1.13, Study 246-PC-015)

Vero cells were infected with a wild-type CPXV (EC_{50}, 0.01 μmol/L). After incubation in the presence of tecovirimat (10 μmol/L), viruses with reduced tecovirimat susceptibility (EC_{50}, >40 μmol/L) were selected. The identification of tecovirimat-resistance-related genes by the marker rescue method[25)] revealed the mutation of amino acid position 277 of the V061 gene encoding the VP37 protein of CPXV.

[24)] 0.75% hydroxypropyl methylcellulose aqueous solution with 1% polysorbate 80

[25)] A method to confirm restoration of phenotypes by introducing genes with specific mutations into the wild-type virus to identify the position of genetic mutations

3.2 Secondary pharmacodynamics

3.2.1 The effects of tecovirimat on reactogenicity to smallpox vaccines and on immunogenicity in immunosuppressed or immunodeficient monkeys (CTD 4.2.1.2.3, Study 1218-100004544; CTD 4.2.1.2.5, Study SR11-011F)

The effect of tecovirimat was evaluated on the alleviation of reactogenicity (injection site skin lesions) and on the immunogenicity of the vaccine (proportion of animals that survived post-MPXV infection) after smallpox vaccination to immunosuppressed cynomolgus monkeys. Smallpox vaccine (ACAM2000, live vaccinia virus vaccine) or mock vaccine was injected into the skin of immunosuppressant (tacrolimus)[26)]-treated and untreated cynomolgus monkeys by the multiple puncture technique using a bifurcated needle. Starting on the same day, tecovirimat 10 mg/kg or vehicle[27)] was orally administered twice daily (BID) for 14 days. At Day 30 post-vaccination, the monkeys were intravenously inoculated with MPXV (Zaire strain [V79-I-005], 2.1×10^7 PFU/animal).

The skin lesion at the vaccination site were within a small area and the lesion resolved in shorter time in the tecovirimat group compared to the vehicle control group, regardless of the use of immunosuppressant. The proportion of survived animals on Day 32 post-MPXV challenge (Table 6) tended to be lower in the tecovirimat group than in the vehicle control group, regardless of the use of immunosuppressant. The results suggest that tecovirimat alleviates reactogenicity of smallpox vaccine regardless of immunosuppression status but may attenuate the vaccine's immunogenicity.

Table 6. The survival rate after MPXV infection of immunosuppressed (tacrolimus-treated) monkeys vaccinated with smallpox vaccine and treated with tecovirimat

Group	N	Tacrolimus treatment	Smallpox vaccination	Tecovirimat dose (mg/kg)	Survival rate[a)] % (n/N)
1	4	Treated	Not vaccinated	0 (vehicle)	0 (0/4)
2	6		Vaccinated	0 (vehicle)	67 (4/6)
3	6			10	50 (3/6)
4	3	Not treated		0 (vehicle)	100 (3/3)
5	3			10	67 (2/3)

a) Animals that were euthanized by Day 32 post-MPXV challenge due to severe clinical symptoms caused by the challenge were handled as not survived.

The effect of ameliorating reactogenicity (injection site skin lesions) by tecovirimat and the effect of tecovirimat on the immunogenicity of the vaccine (proportion of animals that survived post-MPXV infection) was evaluated after smallpox vaccination to immunosuppressed rhesus monkeys. Smallpox vaccine (ACAM2000, live vaccinia virus vaccine) or mock vaccine was injected into the skin of rhesus monkeys inoculated[28)] with simian-human immunodeficiency virus (SHIV-89.6P) to induce immunodeficiency, and non-inoculated, immunocompetent rhesus monkeys by the multiple puncture technique using a bifurcated needle. Starting on the same day, tecovirimat 10 mg/kg or vehicle[29)] was orally administered QD for 14 days. At Day 32 post-vaccination, the monkeys were intravenously inoculated with MPXV (Zaire strain [V79-I-005], 5×10^7 PFU/animal).

[26)] Tacrolimus 0.05 mg/kg was administered BID orally for 10 days prior to and for 60 days post-smallpox vaccination.
[27)] 1% (w/v) hydroxypropyl methylcellulose aqueous solution with 0.5% (w/v) polysorbate 80
[28)] Inoculated at 28 days prior to smallpox vaccination
[29)] 1% (w/v) hydroxypropyl methylcellulose aqueous solution with 0.5% (w/v) polysorbate 80

The skin lesion at the vaccination site were within a smaller area and the lesion resolved in a shorter time in the tecovirimat group compared to the vehicle control group regardless of the use of immunosuppressant. The proportion of survived animals on Day 30 post-MPXV challenge (Table 7) was 100% (3 of 3 animals) in immunocompetent animals regardless of tecovirimat treatment, while that in immunodeficient animals was <100% regardless of tecovirimat treatment, with a trend toward a lower rate in the tecovirimat group than in the vehicle control group. The results suggest that tecovirimat alleviates reactogenicity of smallpox vaccine regardless of immunodeficiency status but may attenuate the vaccine's immunogenicity in immunodeficient animals.

Table 7. The survival rate after MPXV infection of immunodeficient (SHIV-infected) monkeys vaccinated with smallpox vaccine and treated with tecovirimat

Group	N	SHIV virus challenge	Smallpox vaccination	Tecovirimat dose (mg/kg)	Survival rate[a)] % (n/N)
1	4	Challenged	Not vaccinated	0 (vehicle)	0 (0/4)
2	5		Vaccinated	0 (vehicle)	40 (2/5)
3	5			10	20 (1/5)
4	3	Not challenged		0 (vehicle)	100 (3/3)
5	3			10	100 (3/3)

a) Animals that were euthanized by Day 30 post-MPXV challenge due to severe clinical symptoms caused by the challenge were handled as not survived.

3.2.2 Effects of tecovirimat on VACV infection in immunodeficient mice (CTD 4.2.1.2.1, Study 246-PC-009)

Immunodeficient nu/nu mice (N = 5 females/group) were challenged with VACV (Lister strain, 5×10^5 PFU/animal) inoculated by lumbosacral scarification. Starting from 2 hours post-challenge, tecovirimat 50 mg/kg was orally administered BID for 5, 10, or 15 days. Compared to the vehicle[30)] control group, lesion score[31)] decreased in all groups, and prolonged survival was also observed in the 15-day treatment group.

3.3 Safety pharmacology

3.3.1 Effects on the central nervous system (CTD 4.2.1.3.3, Study 246-PH-003)

A single dose of tecovirimat 500, 1,000, or 2,000 mg/kg was orally administered to BALB/c mice (male and female mice, N = 16/group), and the effects of tecovirimat on general symptoms and neurobehavioral function were evaluated by functional observational battery (FOB). The frequency of bowel movement and body temperature decreased in all tecovirimat groups. However, the frequency of bowel movement varied significantly among animals, and many animals in the control group had no bowel movements before and 24 hours after administration. The decrease in body temperature by approximately 2°C in the 1,000 mg group did not meet the endpoint for euthanasia of rodents, i.e., approximately 4°C to 6°C (10% of normal body temperature) (*LABIO21*. No.30 [in Japanese];2007:p27, Japan Society for Laboratory Animal Resources). Based on these outcomes, the applicant explained that the findings were not considered to be indicative of toxicity. Accordingly, a general decrease in arousal (decrease in exploration in the open field) and a decrease in body temperature (by approximately 4°C) in female animals in the 2,000 mg/kg group were determined to

[30)] 0.75% methylcellulose aqueous solution with 1% polysorbate 80 was administered BID for 15 days.
[31)] Grossly observed lesions were rated on a scale of 1 (no change) to 5 (severe).

be toxicities. The no observed adverse effect level (NOAEL) for the effect on the central nervous system was determined to be 1,000 mg/kg (exposure ratio to the clinical exposure,[32] 23-fold).

3.3.2 Effects on the cardiovascular system

3.3.2.1 *In vitro* studies

3.3.2.1.1 Effects on hERG potassium current (CTD 4.2.1.3.1, Study 246-PH-001)

The effects of tecovirimat at concentrations 0.03, 0.1, 1.0, 10, and 30 μmol/L on the human ether-a-go-go-related gene (hERG) potassium current were assessed using HEK-293 cells expressing hERG channel by a whole cell patch clamp technique. The percentage inhibition of hERG potassium channel was 1.30% (0.03 μmol/L), 1.19% (0.1 μmol/L), 0.02% (1.0 μmol/L), 2.01% (10 μmol/L), and 7.14% (30 μmol/L), with an IC_{50} of >30 μmol/L (exposure ratio to the clinical exposure, >5.4-fold).

3.3.2.2 *In vivo* study (CTD 4.2.3.2.5, Study 246-TX-007)

Oral repeated doses of tecovirimat 30, 100, or 300 mg/kg were administered to unanesthetized cynomolgus monkeys (male and female monkeys, N = 8/group), and the effects of tecovirimat on heart rate and electrocardiograms (ECGs; RR interval, PR interval, QRS duration, QT interval, and corrected QT interval) were assessed on Day 1 and Day 28, before and 8 hours after the administration of tecovirimat, and at the end of recovery evaluation. No abnormalities were detected in heart rates or ECGs after the administration of tecovirimat, and the NOAEL was determined to be 300 mg/kg (exposure ratio to the clinical exposure, 1.4-fold). Although not evaluated in this study, the effects on blood pressure were evaluated in the repeated-dose toxicity study in dogs [see Section 5.2], in which no blood pressure-related abnormalities were found at tecovirimat doses up to 100 mg/kg.

3.3.3 Effects on the respiratory system (CTD 4.2.1.3.2, Study 246-PH-002)

A single oral dose of tecovirimat 500, 1,000, or 2,000 mg/kg was administered to BALB/c mice (male and female mice, N = 16/group), and the effects on respiratory rate, tidal volume, and minute volume were evaluated. There were no effects associated with tecovirimat, and the NOAEL was determined to be 2,000 mg/kg (exposure ratio to the clinical exposure, 29-fold).

3.4 Pharmacodynamic drug interactions

3.4.1 Effects on the survival rates and immune response in monkeys to which smallpox vaccine and tecovirimat were administered 3 days post MPXV-challenge (CTD 4.2.1.4.2, Study SR12-005F)

Cynomolgus monkeys (male and female monkeys, N = 7 to 8/group) were intravenously inoculated with MPXV (Zaire strain [V79-I-005], 5×10^7 PFU/animal). At 3 days post-MPXV challenge, smallpox vaccine (ACAM2000, live vaccinia virus vaccine) or mock vaccine was injected into the skin by the multiple puncture technique using a bifurcated needle. Starting on the same day, tecovirimat 10 mg/kg or vehicle[33] was orally

[32] The plasma concentration on Day 14 following administration of tecovirimat 600 mg orally BID to healthy adults in Study SIGA-246-008, a foreign phase III study (C_{max}, 2,209 ng/mL) [see Section 6.2.1.3].
[33] 1% (w/v) hydroxypropyl methylcellulose aqueous solution with 0.5% (w/v) polysorbate 80

administered QD for 14 days. Animals that survived after the first MPXV challenge were rechallenged with MPXV (the same virus at the same dose level) on Day 63 post-first challenge.

Regardless of vaccination status, all animals in the vehicle control group died or were euthanized due to severe clinical symptoms by Day 12 post-first MPXV challenge, while all animals in the tecovirimat group survived up until Day 91 post-first MPXV challenge (28 days post-rechallenge). In the tecovirimat group, regardless of the vaccination status, MPXV-specific neutral antibody titer and IFN-γ-producing T cells increased from the first MPXV challenge to 31 days post-first MPXV challenge, and from before the MPXV rechallenge to 28 days post-MPXV rechallenge. These results suggest that although smallpox vaccine after virus exposure is unlikely to have sufficient protective effect, tecovirimat is expected to exert it effect regardless of the use of concurrent smallpox vaccine. It is also suggested that the administration of tecovirimat after the first infection may lead to the acquisition of immunity, regardless of the use of concurrent smallpox vaccine, and to potential protection against reinfection.

3.4.2 Effects of tecovirimat on the immune response elicited by smallpox vaccine in monkeys (CTD 4.2.1.4.3, Study SR11051.12 Part 2; CTD 4.2.1.4.4, Study SR11051.12 Part 3)

Cynomolgus monkeys (male and female monkeys, N = 3 to 7/group) were injected with smallpox vaccine (ACAM2000) or mock vaccine using a bifurcated needle. Starting from the same day, tecovirimat 10 mg/kg or vehicle[33)] was orally administered QD for 14 days, and MPXV (Zaire strain [V79-I-005], 5×10^7 PFU/animal) was intravenously injected at 45 days after vaccination. Regardless of tecovirimat treatment, by Day 28 post-MPXV challenge, all unvaccinated animals died or were euthanized due to severe clinical symptoms, while all vaccinated animals survived. The median neutral antibody titer at 45 days after vaccination was 55 (range, <10-1,280) in the tecovirimat group and 208 (range, 21-571) in the vehicle control group, showing slightly lower neutral antibody titer in the tecovirimat group.

The effects of tecovirimat were evaluated in a similar manner using another smallpox vaccine (Imvamune, attenuated vaccinia virus). The survival rates following MPXV challenge were 71% (5 of 7 animals) in the vaccinated group regardless of tecovirimat treatment. In the vaccinated group, there were no differences in the increase in neutralizing antibody titers between tecovirimat-treated animals and tecovirimat-untreated animals except for 1 animal with an abnormal value.[34)]

In these 2 studies, the possibility could not be ruled out that tecovirimat affect the elevation of neutralizing antibody titers, one of the immune responses elicited by smallpox vaccine. However, the result suggested that tecovirimat does not affect the survival rate after MPXV challenge.

[34)] Because 1 animal (No. 4609) in the tecovirimat group had an elevated neutralizing antibody titer prior to vaccination with no known cause, the values were considered abnormal and excluded from the neutralizing antibody titer analysis (2 days before vaccination, 915; immediately before vaccination, 1,192). The animal (No. 4609) presented with the fewest clinical symptoms and skin lesions after MPXV challenge, with no viral load detected, and survived until the end of the study period.

3.R Outline of the review conducted by PMDA

3.R.1 Efficacy of tecovirimat in non-clinical pharmacology studies

PMDA's view on the efficacy of tecovirimat in the non-clinical pharmacology studies:

Experimental use of VARV is restricted, and there are no known animal models that can completely mimic the pathology of human smallpox (VARV infection) patients due to varying pathology of orthopoxvirus infection across animal species. For these reasons, for the marketing authorization of tecovirimat in Europe and the US, the therapeutic effect of tecovirimat in patients with human smallpox was evaluated based on the data from *in vivo* studies that used 2 types of surrogate animal models,[35] monkeys infected with MPXV and rabbits infected with RPXV. In both infected animal species models, tecovirimat increased the survival rate and decreased blood viral DNA and lesion counts [see Sections 3.1.3.1 and 3.1.3.2]. Tecovirimat is thus expected to have efficacy in patients with human smallpox.

Furthermore, comparable antiviral activity (EC_{50}) of tecovirimat was observed against orthopoxviruses, i.e., VARV, MPXV, CPXV, and VACV [see Section 3.1.2.1], indicating the possibility that tecovirimat has efficacy in the treatment of smallpox, mpox, cowpox, and complications due to replication of vaccinia virus following smallpox vaccination, the diseases in humans caused by infection or growth of the orthopoxviruses. In 2022 and thereafter, prevalent MPXV lineages are different from the conventional type (clade IIb, lineage B.1[36]). Table 8 shows the antiviral activity (EC_{50}) of the viruses. The viral activity is similar to that for conventional MPXV [see Section 3.1.2.1]. Although the antiviral activity of tecovirimat against the clade Ib strain, which is prevalent since 2023, has not been evaluated, the amino acid sequence of the VP37 protein for clade Ib (Kamituga strain) is identical to that for clade Ia (Zaire 79-005 strain),[37] suggesting that the protein is highly conserved between both clades. Therefore, tecovirimat may possibly have efficacy against clade IIb (lineage B.1) and clade Ib as well, as seen against the conventional strains.

Table 8. *In vitro* antiviral activity against clinical isolates of MPXV (Clade IIb, lineage B.1)

Isolated area (isolated time)	Number of strains	Cells used and assessment measure	EC_{50} (nmol/L)	Source
Brazil (June to August 2022)	18	Cytopathic effect in BSC40 cells	5.6-7.2	*Mem Inst Oswaldo Cruz.* 2023;118:e230056
France (May 2022)	1	Cytopathic effect in Vero cells	12.7	*Nat Microbiol.* 2022;7:1951-55
Canada (2022)	1	Cytopathic effect in VeroE6 cells	6	*Sci Transl Med*. 2022;14 eade7646
China (September 2022)	1	Cytopathic effect in VeroE6 cells	0.01137	*Emerg Microbes Infect.* 2023;12:2208682

3.R.2 Resistance of orthopoxviruses against tecovirimat

PMDA's view on the resistance of orthopoxviruses against tecovirimat:

The US FDA's "Review Report"[38] provides the analysis results from *in vitro* resistance selection studies including literature on orthopoxviruses (VACV, CPXV, or CMLV). Among the observed single or multiple

[35] MPXV-infected monkeys and RPXV-infected rabbits developed skin lesions and fever, respectively, at Day 4 post-challenge. It was expected that the efficacy evaluation would be possible for the drug treatment which is started at the onset of these symptoms.
[36] It carries the E353K mutation in the VP37 protein (*Nat Microbiol*. 2022;7:1951-5).
[37] Reference sequence, GenBank Accession number AAY97243.1 (Zaire 79-005 strain, clade Ia) and GenBank Accession number WZB49151.1 (Kamituga strain, clade Ib)
[38] TPOXX (tecovirimat) Drug Approval Package, CLINICAL MICROBIOLOGY/VIROLOGY REVIEW(S): https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/208627Orig1s000MicroR.pdf (last accessed on October 4, 2024)

amino acid mutations in the VP37 protein, those that led to a decrease in tecovirimat's antiviral activity to ≤1/10 relative to that of the wild-type viruses are shown in Table 9.

Table 9. Changes in antiviral activity against viruses with amino acid mutations reported in *in vitro* resistance induction studies[a)]

Type	Amino acid mutation (change in susceptibility[b)])
Single amino acid substitutions	H238Q (600, >5,000), N267D (>5,000), N267S (500), G277C (97, 459, >800), D283G (>5,000), D283Y (44), A290V (31, 220), D294V (>5,000), A295E (1,600), L302P (>5,000), L302Q (>5,000)
Combinations of amino acid substitutions	F25V + I372N (>5,714), L178S + Y258C (>5,000), N179H + D283G (>5,000), H194N + 303insSVK (>333), N267D + I309T (>5,000), N267S + I317V (3,200), G277C + I372N (>10,600), D280G + D294G (2,200), A290V + L315M (>625), K68N + Y258C + T308S (>5,000), W2C + D225A + Y258C + D280G (500)

a) *In vitro* resistance mutation selection studies using VACV [see Section 3.1.4.2] and *in vitro* resistance mutation induction studies using VACV, CPXV, or CMLV in published literature (*J Antimicrob Chemother*. 2015;70:1367-80, *International Poxvirus, Asfarvirus and Iridovirus Conference*. 2012)

b) Fold change for the EC_{50} of the variants relative to the EC_{50} of the following wild-type strains, calculated based on EC_{50} = 1: wild-type VACV (Western Reserve strain, Copenhagen strain, or ACM2000 vaccine strain), CPXV (Brighton Red strain), or CMLV (Iran strain or Dubai strain)

The above-mentioned Review Report also shows that, in the tecovirimat groups of the studies in MPXV-infected monkeys (Studies SR10-037F and SR10-038F) and the studies in RPXV-infected rabbits (Studies SR13-025F, SR13-008F, and SR13-007F[39)]), the treatment resulted in failure or the virus was not eliminated in some animals. Table 10 shows amino acid mutations in the VP37 protein in found in the samples[40)] from these animals for which virus nucleotide sequencing was possible. Among these, H238Q, N267D, N267S, A290V, A295E, and I372N have been identified as amino acid mutations associated with resistance to tecovirimat [see Table 9].

Table 10. Amino acid mutations[a)] in the VP37 protein newly found after initiation of tecovirimat in MPXV or RPXV infection studies

Virus	Amino acid mutation (number of animals)
MPXV (Zaire strain [V79-I-005])	H238Q (1), N267del/K/S/I (2), N267D (1), R268G (1), D280Y (1), A290V (1), A295E (2), L297ins (1), I372N (2), I372 ILKIKNRK[b)] (1)
RPXV (Utrecht strain)	N179T (1)

a) Reference sequence, GenBank Accession number DQ011155 (MPXV) and AY484669 (RPXV)

b) Extension of the open reading frame due to mutation of the stop codon

Furthermore, MPXV isolates from tecovirimat-treated patients who were likely to have or suspected of having tecovirimat-resistance based on clinical data (124 specimens from 68 patients) were subjected to sequencing and phenotype testing. Amino acid mutations were found in the VP37 protein of variants belonging to clade IIb, with susceptibility change[41)] being −2.9 to >29,000, based on a report issued by the U.S. Centers for Disease Control and Prevention (*Emerg Infect Dis.* 2023;29:2426-32).

Based on the above, viruses with mutations that had reduced susceptibility to tecovirimat were detected in the tecovirimat groups *in vitro* resistance selection studies and *in vivo* animal infection models. In addition, although from limited information about resistant mutations to tecovirimat in clinical use, viruses with reduced susceptibility have also been found from tecovirimat-treated patients. Given these findings, the possibility cannot be ruled out that, in clinical settings, tecovirimat-resistant variants can emerge and affect the efficacy

[39)] In this study, NZW rabbits (N = 6 to 12/group) were intradermally inoculated with RPXV (Utrecht strain, 300 PFU), and starting 2 to 6 days post-RPXV challenge, tecovirimat 80 mg/kg was administered orally QD for 14 days, or starting 2 days post-RPXV challenge, placebo was administered orally QD for 14 days.

[40)] A total of the 129 blood and tissue samples were collected from animals that died of virus infection or were euthanized due to severe clinical symptoms. Of these,7 samples from 6 animals in the studies in MPXV-infected monkeys (Studies SR10-037F and SR10-038F) and 4 samples from 4 animals in the study in RPXV-infected rabbits (Study SR13-007F) were analyzable by next generation nucleotide sequencing.

[41)] Fold change for the variant relative to the EC_{50} of MPXV clade IIa strain (U.S., 2003) (0.0175 μmol/L), calculated based on EC_{50} = 1

of tecovirimat. Therefore, reports on the emergence of tecovirimat-resistant viruses, including published literature, warrants continuous attention. New findings should be promptly provided to healthcare professionals.

3.R.3 Effects of tecovirimat on the immunogenicity of smallpox vaccines

PMDA's view:

Based on the study results on the effects of tecovirimat on the immunogenicity of smallpox vaccines [see Section 3.2.1], tecovirimat may attenuate the immunogenicity through its antiviral effect against vaccinia virus in smallpox vaccines. The package insert should offer cautionary advice on the concomitant use of tecovirimat with smallpox vaccine.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

The submitted data included results from oral dose studies in mice, rabbits, dogs and monkeys and intravenous dose studies in mice, etc. Also included were data from studies using biological samples derived from humans or animals, such as the studies of plasma protein binding, drug metabolizing enzymes, and transporters.

The plasma concentrations of tecovirimat (unchanged) and main metabolites (M4, M5, and TFMBA) were measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS).[42)] Radioactivity levels in samples were measured by liquid scintillation counter. In this section, unless otherwise specified, PK parameters are expressed as mean or mean ± standard deviation.

4.1 Absorption

4.1.1 Single-dose studies (Reference, CTD 4.2.2.2.2, 4.2.3.1.2)

Table 11 shows the PK parameters of unchanged tecovirimat in plasma following the administration of a single oral dose of tecovirimat to mice and monkeys. The increase in plasma exposure ratio (C_{max} and AUC_{inf}) was lower than the dose ratio.

[42)] The limit of quantitation:
Mice; 2.0 or 5.0 ng/mL (tecovirimat); 5.0 ng/mL (M4), 10.0 ng/mL (M5), 5.0 ng/mL (TFMBA)
Rabbits; 2.0 or 5.0 ng/mL (tecovirimat)
Dogs, not evaluated
Monkeys; 5.0 ng/mL (tecovirimat), 5.0 ng/mL (M4), 10.0 ng/mL (M5), 5.0 ng/mL (TFMBA)

Table 11. PK parameters of unchanged tecovirimat in plasma following single-dose administration of tecovirimat

Species	Route of administration	Dose (mg/kg)	N	C_{max} (µg/mL)	t_{max} (h)	AUC_{inf} (µg·h/mL)	$t_{1/2}$ (h)	F (%)
Mouse	IV (non-fasting)	1	3 males/ 1 timepoint	4.01	0.50	18.2	2.96	—
			3 females/ 1 timepoint	4.90	0.25	24.6	2.87	—
	Oral gavage (non-fasting)	30	3 males/ 1 to 2 timepoints	30.4	2.00	243	2.83	44.5
			3 females/ 1 to 2 timepoints	37.5	2.00	293	2.36	39.7
		100	3 males/ 1 to 2 timepoints	38.4	2.00	343	2.02	18.9
			3 females/ 1 to 2 timepoints	43.8	2.00	457	2.24	18.6
		300	3 males/ 1 to 2 timepoints	48.5	2.00	497	2.91	9.1
			3 females/ 1 to 2 timepoints	64.0	2.00	685	4.08	9.1
		1,000	3 males/ 1 to 2 timepoints	61.1	3.00	974	11.89	4.0
			3 females/ 1 to 2 timepoints	66.3	2.00	882	4.49	3.5
Monkey	Oral gavage (non-fasting)	100	2 males	4.88, 5.32	1, 2	117, 185	28.0, 45.3	—
			2 females	7.57, 9.50	1, 4	136, 178	8.29, 36.5	—
		300	2 males	7.47, 7.48	3, 4	121, 281	9.26, 25.4	—
			2 females	9.82, 14.6	2, 3	172, 222	7.99, 11.0	—
		600	2 males	8.05, 8.78	2, 4	306, 330	26.75, 47.6	—
			2 females	13.9, 14.6	2, 4	225, 420	12.7, 26.9	—

Individual values (when N = 2) or mean; "—," Not calculated

4.1.2 Repeated-dose studies (CTD 4.2.2.2.1, 4.2.2.4.2, 4.2.2.4.3; reference, CTD 4.2.3.2.4)

Table 12 shows the PK parameters of unchanged tecovirimat and main metabolites (M4, M5, and TFMBA) following repeated oral administration of tecovirimat to mice, rabbits, dogs, and monkeys. With the exception of M5 in male mice and male and female monkeys, no clear increases in plasma exposure (C_{max} and AUC) were noted after repeated-dose administration.

Table 12. PK parameters of unchanged tecovirimat, M4, M5, and TFMBA following repeated oral administration of tecovirimat

Species	Route of administration	Dose (mg/kg/day)	Analyte	N	Timepoint	C_{max} (µg/mL)		t_{max} (h)		AUC[a)] (µg·h/mL)	
						Male	Female	Male	Female	Male	Female
Mouse	Oral gavage (non-fasting)	1,000	Tecovirimat	3/sex/ timepoint	Day 1	52.2	69.2	12.0	12.0	983	1200
					Day 14	48.7	45.5	12.0	8.00	845	809
			M4	3/sex/ timepoint	Day 1	2.24	4.19	12.0	4.00	40.8	67.5
					Day 14	2.74	2.58	2.00	4.00	44.5	37.3
			M5	3/sex/ timepoint	Day 1	0.927	1.93	12.0	12.0	17.9	35.7
					Day 14	1.85	2.50	12.0	8.00	30.9	32.0
			TFMBA	3/sex/ timepoint	Day 1	0.424	1.43	2.00	1.00	6.64	23.4
					Day 14	0.466	2.09	4.00	1.00	7.40	22.0
Rabbit	Oral gavage (after meal)	10	Tecovirimat	3/sex	Day 1	0.740	0.265	3.33	2	3.15 ± 0.745	1.69 ± 1.41
					Day 14	0.462	0.289	3.7	1.3	3.51 ± 0.658	1.67 ± 1.07
		40		3/sex	Day 1	0.524	0.601	3.67	3	4.76 ± 3.23	4.87 ± 1.88
					Day 14	0.492	0.741	4.7	2.3	3.91 ± 2.81	4.04 ± 1.17
		100		3/sex	Day 1	1.17	1.39	4.67	4	13.8 ± 8.26	18.0 ± 10.6
					Day 14	0.792	0.868	5	1.3	8.62 ± 6.44	10.9 ± 6.41
Dog	Oral gavage (non-fasting	30	Tecovirimat	3/sex	Day 7	2.05	2.24	0.83	0.83	10.7	8.13
		100		1/sex	Day 1	5.58	3.83	0.50	0.50	25.2	14.1
					Day 5	1.88	2.14	0.50	2.00	8.54	13.1
		300		1/sex	Day 1	16.5	4.88	0.50	1.00	67.5	25.8
Monkey	Oral gavage (after meal)	300	Tecovirimat	3/sex	Day 1	1.83 ± 0.645	1.90 ± 0.255	2.67 ± 1.15	2.00 ± 0.00	20.0 ± 2.46	21.9 ± 4.26
					Day 14	2.21 ± 0.570	2.48 ± 0.480	1.67 ± 0.577	2.00 ± 0.00	23.1 ± 4.36	27.6 ± 4.79
			M4	3/sex	Day 1	0.310 ± 0.039	0.343 ± 0.118	3.33 ± 1.15	8.00 ± 0.00	4.81 ± 0.617	4.68 ± 0.752
					Day 14	0.483 ± 0.119	0.345 ± 0.057	2.67 ± 1.15	3.33 ± 1.15	5.59 ± 1.30	5.05 ± 0.196
			M5	3/sex	Day 1	0.439 ± 0.041	0.302 ± 0.014	24.0 ± 0.00	24.0 ± 0.00	6.48 ± 0.307	4.67 ± 0.560
					Day 14	1.30 ± 0.287	1.00 ± 0.274	5.67 ± 5.69	13.3 ± 9.24	28.4 ± 5.46	22.1 ± 5.40
			TFMBA	3/sex	Day 1	1.78 ± 0.629	1.50 ± 0.382	6.00 ± 3.46	5.00 ± 6.08	27.4 ± 7.35	21.4 ± 2.47
					Day 14	2.36 ± 0.756	1.85 ± 0.193	2.00 ± 0.00	1.67 ± 0.577	31.6 ± 7.98	27.0 ± 6.13

Individual values (when N = 1); mean or mean ± standard deviation
a) $AUC_{0\text{-}24h}$ ($AUC_{0\text{-}48h}$ for rabbits on Day 14)

4.1.3 Effects of RPXV or MPXV infection on the PK of tecovirimat (CTD 4.2.1.1.41, 4.2.1.1.63)

Rabbits received a single oral dose of tecovirimat 40, 80, or 120 mg/kg 7 days prior to RPXV challenge (uninfected), or oral tecovirimat 40, 80, or 120 mg/kg QD from Day 4 post-RPXV challenge (infected) for 14 days. Table 13 shows the PK parameters of tecovirimat.

Monkeys received a single oral dose of tecovirimat 3, 10, or 20 mg/kg 10 days prior to MPXV challenge (uninfected), or oral tecovirimat 3, 10, or 20 mg/kg QD from Day 4 post-MPXV challenge (infected) for 14 days. Table 13 shows the PK parameters of tecovirimat.

In both rabbits and monkeys, no clear differences were observed in tecovirimat exposure (AUC and C_{max}) between the infected and uninfected state after the administration of tecovirimat (single-dose data for uninfected state; Day 1 of repeated-dose data for the infected state). RPXV-infected rabbits tended to show decreased tecovirimat exposure (AUC and C_{max}) after repeated oral administration of tecovirimat.

Following the 14-day repeated oral administration of tecovirimat 40 mg/kg/day to RPXV-infected rabbits and tecovirimat 10 mg/kg/day to MPXV-infected monkeys, the C_{min} on Day 14 was 0.031 µg/mL (rabbits) and 0.169 µg/mL (monkeys).[43)]

[43)] The dose levels (40 mg/kg/day and 10 mg/kg/day) are 1-level higher than the minimum dose levels at which tecovirimat efficacy was demonstrated (20 mg/kg/day and 3 mg/kg/day, respectively) in the *in vivo* studies in RPXV-infected rabbits and MPXV-infected monkeys [see Sections 3.1.3.1.1 and 3.1.3.2.1].

Table 13. PK parameters of unchanged tecovirimat in plasma in rabbits and monkeys by infection status with either RPXV or MPXV

Species	Dose (mg/kg/day)	N	Infection status	Dosing (timepoint)	C_{max} (µg/mL)		t_{max} (h)		AUC[a)] (µg·h/mL)	
					Male	Female	Male	Female	Male	Female
Rabbit	40	4/sex	Uninfected	Single dose (Day 1)	0.734 ± 0.372	0.663 ± 0.390	8.86 ± 2.03	6.95 ± 2.05	9.54 ± 4.58	7.56 ± 4.92
			Infected	Repeated dose (Day 1)	0.640 ± 0.369	0.566 ± 0.367	8.90 ± 2.11	6.89 ± 1.99	8.98 ± 4.09	6.83 ± 4.60
				Repeated dose (Day 14)	0.378 ± 0.192	0.496 ± 0.280[b)]	4.79 ± 2.13	4.17 ± 0.092[b)]	3.27 ± 2.41	4.95 ± 2.85[b)]
	80	4/sex	Uninfected	Single dose (Day 1)	1.25 ± 0.256	0.867 ± 0.570	7.85 ± 0.021	5.91 ± 2.32	15.0 ± 3.37	10.5 ± 7.61
			Infected	Repeated dose (Day 1)	1.20 ± 0.302	0.595 ± 0.273	8.85 ± 2.02	6.85 ± 3.86	17.8 ± 3.16	9.03 ± 5.63
				Repeated dose (Day 14)	0.762 ± 0.178[b)]	0.423 ± 0.291	4.11 ± 0.142[b)]	4.14 ± 0.092	7.78 ± 1.74[b)]	3.82 ± 2.43
	120	4/sex	Uninfected	Single dose (Day 1)	1.24 ± 0.234	1.19 ± 0.508	7.83 ± 0.017	7.94 ± 0.029	17.4 ± 5.16	16.5 ± 8.06
			Infected	Repeated dose (Day 1)	1.43 ± 0.312	0.966 ± 0.487	9.85 ± 2.41	4.89 ± 2.01	22.7 ± 4.06	13.8 ± 7.54
				Repeated dose (Day 14)	0.873 ± 0.201	0.743 ± 0.369	5.74 ± 4.06	3.93 ± 0.545	12.6 ± 6.39	7.83 ± 3.71
Monkey	3	3/sex	Uninfected	Single dose (Day 1)	0.406 ± 0.248	0.332 ± 0.034	1.67 ± 1.15	5.33 ± 5.86	3.05 ± 1.31	3.09 ± 1.10
			Infected	Repeated dose (Day 1)	0.365 ± 0.113	0.562 ± 0.349	2.33 ± 1.15	1.67 ± 1.15	3.56 ± 0.804	3.42 ± 1.57
				Repeated dose (Day 14)	0.335 ± 0.099	0.563 ± 0.193	1.67 ± 1.15	2.33 ± 1.15	2.32 ± 0.641	4.12 ± 1.98
	10	3/sex	Uninfected	Single dose (Day 1)	1.25 ± 0.352	0.924 ± 0.526	2.33 ± 2.08	4.67 ± 2.89	13.7 ± 2.38	9.02 ± 7.53
			Infected	Repeated dose (Day 1)	1.05 ± 0.284	0.570 ± 0.179	3.00 ± 0.00	3.00 ± 0.00	10.3 ± 3.15	6.21 ± 1.75
				Repeated dose (Day 14)	1.44 ± 0.242	1.45 ± 0.539	3.00 ± 0.00	2.33 ± 1.15	16.1 ± 2.88	12.6 ± 5.64
	20	3/sex	Uninfected	Single dose (Day 1)	2.42 ± 1.50	1.63 ± 0.684	3.67 ± 0.58	3.00 ± 0.00	33.5 ± 17.7	18.4 ± 7.18
			Infected	Repeated dose (Day 1)	1.41 ± 0.707	1.10 ± 0.397	3.33 ± 0.58	4.00 ± 0.00	19.6 ± 11.1	14.9 ± 5.81
				Repeated dose (Day 14)	2.74 ± 1.10	2.16 ± 1.03	3.00 ± 0.00	3.00 ± 0.00	33.0 ± 14.0	20.4 ± 8.98

a) AUC_{last} for rabbits, $AUC_{0\text{-}24h}$ for monkeys; b) N = 3

4.2 Distribution

4.2.1 Tissue distribution (CTD 4.2.2.3.4, 4.2.2.3.5, 4.2.3.2.6; reference, CTD 4.2.3.2.4)

A single oral dose of ^{14}C-tecovirimat 100 mg/kg was administered to white mice (N = 2/sex/timepoint) to investigate tissue distribution[44)] of radioactivity up to 96 hours post-dose. High radioactivity concentrations (≥1.0 µg eq/g) were detected in the gallbladder, liver, turbinate bone, gastrointestinal content, and urine. While radioactivity was detected in all tissues studied, the concentration in each tissue decreased with time, and were below the limit of quantitation in approximately half of the tissues at 96 hours post-dose.

A single oral dose of ^{14}C-tecovirimat 100 mg/kg was administered to pigmented mice (male mice, N = 3/timepoint) to investigate tissue distribution[45)] of radioactivity up to 168 hours post-dose. Radioactivity levels peaked at 1 hour post-dose in bone marrow, and at 4 hours post-dose in all the remaining tissues. Radioactivity

[44)] The tissues studied:
Blood, bone marrow, lymph node, spleen, thymus, gallbladder, renal cortex, renal medulla, liver, urinary bladder, urine, cerebellum, cerebrum, brain medulla, spinal cord, adrenal gland, pituitary gland, thyroid, Harderian gland, pancreas, salivary gland, brown adipose tissue, white adipose tissue, non-pigmented skin, epididymis, prostate, seminal vesicle, testis, ovary, uterus, vagina, bone, heart, skeletal muscle, lung, turbinate bone, cecum, cecal content, large intestine, large intestinal content, stomach, gastric content, small intestine, small intestinal content, uveal tract, lens

[45)] The tissues studied:
Bone, bone marrow, brain, eye, kidney, liver, lung, pigmented skin, testis, thyroid

concentration in each tissue decreased with time, and was below the lower limit of quantitation at 168 hours post-dose in all tissues except for bone marrow and the liver. The time-course of radioactivity concentration in the eye and pigmented-skin, melanin-containing tissues, did not differ markedly from that of other tissues, and the radioactivity concentrations decreased to below the lower limit of quantitation by 24 hours and 72 hours post-dose, respectively.

Dogs (N = 3/sex) received oral tecovirimat 30 mg/kg/day for 8 days or 100 mg/kg/day (N = 1/sex) for 7 days. Tecovirimat concentrations in the brain and cerebrospinal fluid (CSF) approximately 2 hours following the last dose were, respectively, 0.350 to 0.532 μg/g and 0.053 to 0.064 μg/g in males, and 0.371 to 0.600 μg/g and 0.023 to 0.076 μg/g in females in the 30 mg/kg/day group; 0.663 μg/g and 0.168 μg/g in males, and 0.616 μg/g and 0.145 μg/g in females in the 100 mg/kg/day group. The results show that tecovirimat can cross the brain-blood barrier.

Monkeys (N = 6/sex) received oral tecovirimat 300 mg/kg/day for 12 days. At 8 hours following the last dose, the ratio of tecovirimat concentration to plasma was 0.59 in the brain and 0.10 in CSF in males, and 0.60 in the brain and 0.09 in CSF in females. The results show that tecovirimat can cross the brain-blood barrier.

4.2.2 Plasma protein binding (CTD 4.2.2.3.1 through 4.2.2.3.3)

To mouse, rat, dog, monkey, and human plasma, ^{14}C-tecovirimat (0.03-50 μmol/L) was added. The plasma protein binding of tecovirimat evaluated by equilibrium dialysis was 87.1% to 88.3% (mouse), 95.1% to 96.3% (rat), 88.9% to 92.2% (dog), 87.1% to 87.9% (monkey), and 77.3% to 82.2% (human).

Plasma protein binding of tecovirimat at 5 μmol/L in rabbit plasma measured by equilibrium dialysis was 88.7%.

To mouse, monkey, and human plasma, 5 μmol/L of M4, M5, or TFMBA was added. The plasma protein binding of tecovirimat evaluated by equilibrium dialysis was 4.6% (mouse), 15.8% (monkey), and 20.7% (human) for M4; 16.6% (mouse), 17.6% (monkey), and 33.0% (human) for M5; and 50.0% (mouse), 97.1% (monkey), and 98.6% (human) for TFMBA.

4.2.3 Placental transfer (CTD 4.2.2.3.6)

A single oral dose of ^{14}C-tecovirimat 100, 300, or 1,000 mg/kg was administered to female mice on gestation day 15 (N = 12/group, N = 3/timepoint). The percentage of radioactivity detected in the fetus relative to the radioactivity administered to the dam at 1, 4, 8, and 24 hours post-dose was 0.07% to 0.90% in the 100 mg/kg group, 0.06% to 0.34% in the 300 mg/kg group, and 0.08% to 0.47% in the 1,000 mg/kg group, indicating that tecovirimat can cross the placenta to the fetus.

4.3 Metabolism

4.3.1 Estimated metabolic pathway

Based on the investigations in Section 4.3.2, Section 6.2.1.3, and other sections, the metabolic pathway of tecovirimat was estimated as shown in Figure 1.

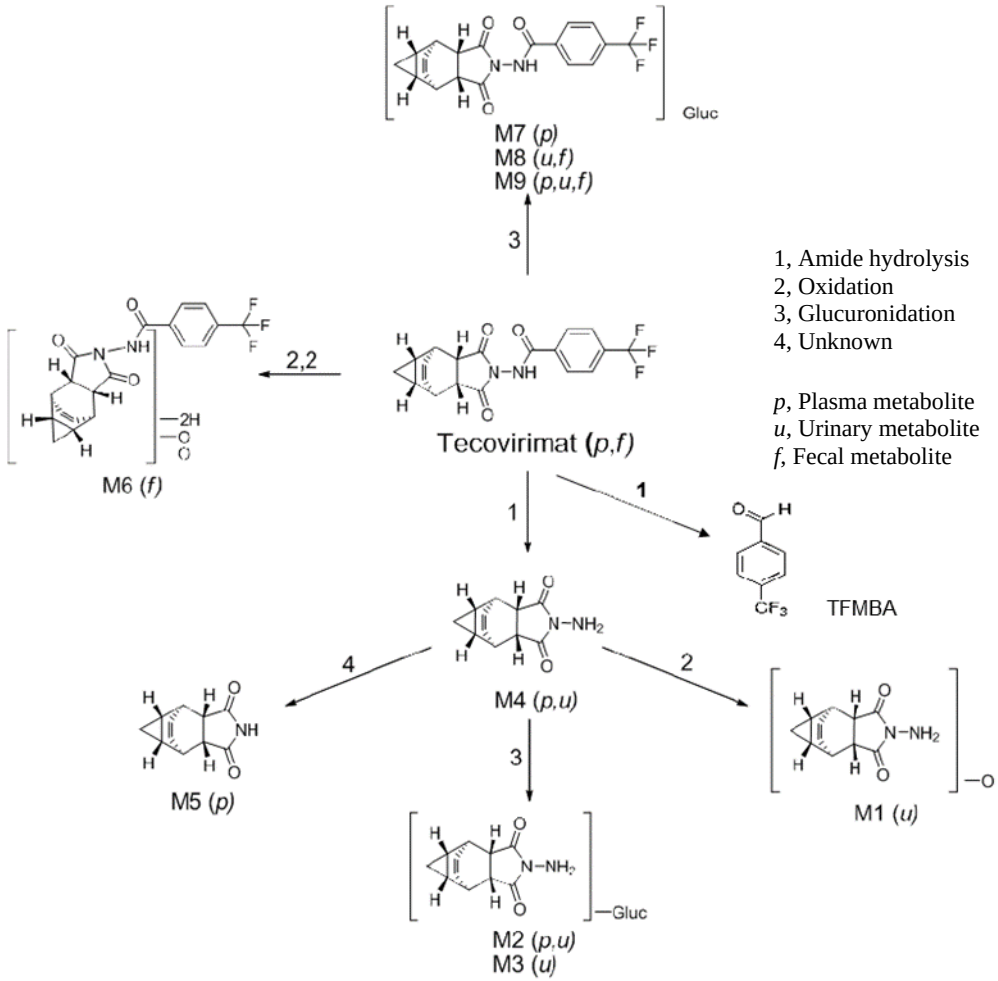

Figure 1. Estimated tecovirimat metabolic pathway in humans

4.3.2 *In vitro* metabolism (CTD 4.2.2.4.1, 4.2.2.4.4, 5.3.2.2.2, 5.3.2.2.11, 5.3.2.3.4)

The metabolic stability of ^{14}C-tecovirimat (1 and 10 μmol/L) was evaluated using mouse, rat, dog, monkey, or human liver microsomes. Tecovirimat was not metabolized by monkey and human liver microsomes but was metabolized by mouse, rat, and dog liver microsomes with maximum metabolites of 6%, 19%, and 4%, respectively.

The metabolism of tecovirimat was evaluated using human cytochrome P450 (CYP) isoform (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) expression systems. Tecovirimat was metabolized by none of these CYP isoforms.

The metabolism of tecovirimat was evaluated using human uridine glucuronosyl transferase (UGT) isoform

(UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, or UGT2B15) expression systems. Tecovirimat was metabolized by UGT1A1, UGT1A3, and UGT1A4, with a residual tecovirimat of 65%, 79%, and 59%, respectively, after 120 minutes of incubation.

The human mass balance study [see Section 6.2.1.4] and the foreign phase III study [see Section 6.2.1.3] identified hydrolyzed metabolites (M4, TFMBA) as main metabolites of tecovirimat in human plasma. To identify enzymes involved in tecovirimat hydrolysis, human plasma was analyzed in the presence and absence of calcium chloride. No amide hydrolysis of tecovirimat was induced by paraoxonase. In addition, in an analysis of human blood in the presence and absence of acetylcholine esterase inhibitor (BW284c51), hydrolysis of tecovirimat was not induced by acetylcholine esterase. Therefore, no specific enzymes involved in the hydrolysis of tecovirimat have been identified.

4.4 Excretion

4.4.1 Excretion in urine and feces (CTD 4.2.2.3.4)

A single oral dose of ^{14}C-tecovirimat 100 mg/kg was administered to mice (N = 4/sex). Up to 96 hours post-dose, 24.2% (male) and 18.2% (female) of the administered radioactivity was excreted in urine, and 71.6% (male) and 75.1% (female) of the administered radioactivity was excreted in feces. In both males and females, residual radioactivity in tissues was <0.2% at 96 hours post-dose.

4.4.2 Excretion in milk (CTD 4.2.2.3.6)

A single oral dose of ^{14}C-tecovirimat 100, 300, or 1,000 mg/kg was administered to mice on lactation day 10 or 11 (N = 5/group). The milk-to-plasma ratio of radiolabeled tecovirimat at 6 and 24 hours post-dose was 0.43 and 0.67 in the 100 mg/kg group, 0.40 and 0.83 in the 300 mg/kg group, and 0.83 and 0.72 in the 1,000 mg/kg group, respectively. The results suggest that tecovirimat can transfer to the fetus via breast milk.

4.5 Pharmacokinetic interactions

4.5.1 Enzyme inhibition (CTD 5.3.2.2.3 through 5.3.2.2.7)

Using human liver microsomes, the direct and time-dependent inhibition potential of tecovirimat[46)] on the metabolic activity of the substrates[47)] were evaluated for the CYP isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A). Tecovirimat showed no clear inhibition of the metabolism of substrates for any of the CYP isoforms.

[46)] The concentrations studied: 0 to 300 µmol/L for direct inhibition assay and 0 to 100 µmol/L for time-dependent inhibition assay.

[47)] The substrates (concentration) used (the direct inhibition potential on CYP2A6 was not evaluated):

- Direct inhibition assay:
  CYP1A2, phenacetin (50 µmol/L); CYP2B6, bupropion (80 µmol/L); CYP2C8, paclitaxel (10 µmol/L); CYP2C9, diclofenac (6 µmol/L); CYP2C19, S-mephenytoin (50 µmol/L); CYP2D6, bufuralol (10 µmol/L); CYP2E1, *p*-nitrophenol (100 µmol/L); CYP3A, midazolam (3 µmol/L); and testosterone (120 µmol/L)
- Time-dependent inhibition assay:
  CYP1A2, phenacetin (63 µmol/L); CYP2A6, coumarin (1 µmol/L); CYP2B6, bupropion (75 µmol/L); CYP2C8, amodiaquine (2 µmol/L); CYP2C9, diclofenac (10 µmol/L); CYP2C19, S-mephenytoin (40 µmol/L); CYP2D6, bufuralol (7 µmol/L); CYP2E1, chlorzoxazone (27 µmol/L); CYP3A, midazolam (2.5 µmol/L) and testosterone (55 µmol/L)

Using human liver microsomes, the direct and time-dependent inhibition potential of the main tecovirimat metabolites (M4, M5, and TFMBA)[48] on the metabolic activity of substrates[49] were evaluated for the CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A). None of the metabolites clearly showed direct inhibition of the substrates for the CYP isoforms. However, M4 inhibited CYP2C19 and CYP3A, and M5 and TFMBA inhibited CYP3A, both time-dependently. After a 30-minute incubation in the presence of nicotinamide adenine dinucleotide phosphate (NADPH), the IC_{50} for the metabolism of the substrates for CYP2C19 and CYP3A of M4 was 71.5 and 77 µmol/L, respectively, and M5 and TFMBA inhibited the metabolism of the CYP3A substrate by 33.3% and 31.7%, respectively, at the maximum concentration studied (100 µmol/L).

Using the human UGT (UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, and UGT2B15) expression systems, the inhibition potential of the main tecovirimat metabolites (M4, M5, and TFMBA: 50 µmol/L) on the metabolic activity of the substrates[50] for the UGT isoforms was evaluated. None of the metabolites showed clear inhibition potential on the metabolism of the UGT isoform substrates.

4.5.2 Enzyme induction (CTD 5.3.2.2.1, 5.3.2.2.8, 5.3.2.2.9)

Using human hepatocytes (3 strains[51]), the induction of CYP isoforms (CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A) by tecovirimat (0.1-100 µmol/L) was evaluated based on the enzymatic activity against the metabolism of the substrates[52] for each CYP isoform. Tecovirimat induced the enzymatic activity of CYP2B6, CYP2C9, CYP2C19, and CYP3A at the maximum concentration evaluated (100 µmol/L), corresponding to 1.8- to 5.1-fold, 3.9- to 9.5-fold, 2.7- to 4.9-fold,[53] and 2.6- to 12-fold, respectively, compared to vehicle control.

Using human hepatocytes (3 strains), the induction of CYP isoforms (CYP1A2, CYP2B6, and CYP3A4) by tecovirimat (0.4-100 µmol/L) was evaluated based on the mRNA expression level of each CYP isoform. Tecovirimat induced the mRNA of CYP3A4 at concentrations 4, 10, and 40 µmol/L.[54] The mRNA expression levels at tecovirimat 40 µmol/L was 1.50- to 9.89-fold compared to vehicle control.

Using human hepatocytes (3 strains), the induction of CYP isoforms (CYP1A2, CYP2B6, and CYP3A4) by M4 (10.4-412 µmol/L), M5 (7.93-266 µmol/L), and TFMBA (0.92-131.5 µmol/L) was evaluated based on the mRNA expression level of each CYP isoform. At all concentrations tested, M4 induced mRNA expression

[48] The concentrations used for all the main metabolites: 10 µmol/L for direct inhibition assay, 0 to 100 µmol/L for time-dependent inhibition assay.
[49] The substrates (concentration) used:
CYP1A2, phenacetin (63 µmol/L); CYP2B6, bupropion (75 µmol/L); CYP2C8, amodiaquine (2 µmol/L); CYP2C9, diclofenac (10 µmol/L); CYP2C19, S-mephenytoin (40 µmol/L); CYP2D6, bufuralol (7 µmol/L); CYP3A, midazolam (2.5 µmol/L) and testosterone (55 µmol/L)
[50] The substrates for UGT isoforms (concentration) used:
UGT1A1, UGT1A3, UGT1A6, UGT1A9, UGT2B7, and UGT2B15, 7-hydroxy-4-trifluoromethylcoumarin (50 µmol/L); UGT1A4, trifluoperazine (50 µmol/L)
[51] A total of 4 strains of human hepatocytes were used only for the evaluation of induction of CYP2C19.
[52] The substrates (concentration) used:
CYP1A2: phenacetin (100 µmol/L); CYP2B6, S-mephenytoin (100 µmol/L); CYP2C9, diclofenac (100 µmol/L); CYP2C19, S-mephenytoin (100 µmol/L); CYP3A, testosterone (200 µmol/L)
[53] Of the 4 strains of human hepatocytes used for the evaluation of induction of CYP2C19, 2 strains, which did not induce CYP2C19 after addition of the positive control, rifampicin 20 µmol/L, were excluded from the evaluation.
[54] Sedimentation of compound was observed at tecovirimat 100 µmol/L, and mRNA levels could not be determined.

of CYP2B6 and CYP3A4. The mRNA expression levels at the maximum tecovirimat concentration tested (412 µmol/L) were 46- to 128-fold (CYP2B6) and 4.8- to 15-fold (CYP3A4) compared to vehicle control. Conversely, M5 induced mRNA expression of CYP2B6 at all concentrations tested and CYP3A4 at concentrations ≥79.3 µmol/L. The mRNA expression levels at the maximum tecovirimat concentration tested (266 µmol/L) were 33- to 102-fold (CYP2B6) and 1.9- to 3.3-fold (CYP3A4) compared to vehicle control.

The results of the *in vitro* studies above demonstrated the induction of CYP2B6, CYP2C9, CYP2C19, and CYP3A4 by tecovirimat, and the induction of CYP2B6 and CYP3A4 by M4 and M5.

4.5.3 Transporters (CTD 5.3.2.3.1 through 5.3.2.3.3, 5.3.2.3.5, 5.3.2.3.7, 5.3.2.3.8)

Using Caco-2 cells, the ratio of the apparent permeability coefficient in the basal-to-apical direction to that in the apical-to-basal direction (efflux ratio) of tecovirimat (0.477-19.1 µmol/L) was evaluated. The obtained efflux ratios of 1.09 to 1.22, which are <2, indicate that tecovirimat is not a substrate of P-glycoprotein (P-gp).

Using Caco-2 cells and breast cancer resistance protein (BCRP) knockdown cells (CPT-B1 cells), the ratio of the efflux ratio with Caco-2 cells to the efflux ratio with CPT-B1 cells was evaluated in the presence of tecovirimat (0.5-19.1 µmol/L). The obtained ratios of 0.84 to 0.92, which are <2, indicate that tecovirimat is not a substrate of BCRP.

Transport of tecovirimat (0.5-19.1 µmol/L) was investigated using the expression systems for human organic anion transporting polypeptide (OATP) 1B1 or OATP1B3. No clear differences were found in the uptake rate of tecovirimat between the expression and non-expression systems for human OATP1B1 or OATP1B3, indicating that tecovirimat is not a substrate of OATP1B1 or OATP1B3.

The *in vitro* inhibition potential of tecovirimat[55)] and main metabolites (M4, M5, and TFMBA)[56)] on the transport of substrates[57)] for drug transporters (P-gp, BCRP, OATP1B1, OATP1B3, organic anion transporter [OAT]1, OAT3, or OCT2) were investigated. The results showed that within the concentrations studied, tecovirimat inhibited BCRP (IC_{50} = 6.03 µmol/L).

[55)] The inhibition potential of transporters was evaluated at the following tecovirimat concentrations, which were selected based on the maximum solubility in the test systems (19.1-20.0 µmol/L):
P-gp, OATP1B1, and OATP1B3, 19.0 µmol/L; BCRP, 0.0786 to 19.1 µmol/L; OAT1, OAT3, and OCT2, 20 µmol/L

[56)] The inhibition potential of transporters was evaluated at the following metabolite concentrations (M4, M5, and TFMBA):
- M4: P-gp, BCRP, OATP1B1, and OATP1B3, 104 µmol/L; OAT1, OAT3, and OCT2, 82.4 µmol/L
- M5: P-gp, BCRP, OATP1B1, and OATP1B3, 79.3 µmol/L; OAT1, OAT3, and OCT2, 53.1 µmol/L
- TFMBA: P-gp, BCRP, OATP1B1, and OATP1B3, 131 µmol/L; OAT1, OAT3, and OCT2, 1.84 to 11.5 µmol/L

[57)] The substrates for transporters (concentration) used:
P-gp, digoxin (10 µmol/L); BCRP, cladribine (10 µmol/L); OATP1B1 and OATP1B3, atorvastatin (0.15 µmol/L); OAT1, *p*-aminohippuric acid (10 µmol/L); OAT3, furosemide (5 µmol/L); OCT2, 1-methyl-4-phenylpyridinium iodide (5 µmol/L)

4.R Outline of the review conducted by PMDA

4.R.1 Drug interactions

The applicant's explanation about drug interactions:

The results of the *in vitro* metabolism studies and pharmacokinetic interaction studies [see Sections 4.3.2 and 4.5], as well as the clinical exposure[58)] of tecovirimat and its main metabolites suggest that in clinical use, tecovirimat may cause drug interactions through its effects, such as CYP2B6 and CYP3A4 induction and BCRP inhibition.

The necessity of cautionary advice concerning interactions through CYP2B6 and CYP3A4 induction is to be discussed [see Section 6.2.4.1] based on the results of the clinical drug interaction study with bupropion (CYP2B6 substrate) or midazolam (CYP3A substrate).

No clinical drug interaction studies were conducted to investigate drug interactions through the inhibition of BCRP by tecovirimat. However, foreign post-marketing safety data have revealed no drug interactions that could raise clinical concerns in the concomitant use of tecovirimat with BCRP substrates. Therefore, no cautionary advice will be offered pertaining to the concomitant use of tecovirimat with BCRP substrates. However, healthcare professionals will be informed of tecovirimat's inhibitory effect against BCRP via the package insert.

PMDA's view:

In principle, it was advisable to conduct a clinical drug interaction study to investigate drug interactions through BCRP inhibition by tecovirimat, and to discuss the necessity of the cautionary advice on the concomitant use of tecovirimat with BCRP substrates based on the study results. However, given the absence of data clearly indicating the necessity of such advice, it is reasonable to note in the package insert that tecovirimat is a BCRP inhibitor, without giving specific caution against the concomitant use with BCRP substrates, as in the US and Europe. The applicant, however, should continue to gather information about drug interactions of tecovirimat from post-marketing settings, and new findings should be promptly provided to healthcare professionals.

5. Toxicity and Outline of the Review Conducted by PMDA

The results of the toxicity studies submitted included single-dose toxicity, repeated-dose toxicity, genotoxicity, reproductive and developmental toxicity, and other studies (phototoxicity and impurity). Unless otherwise specified, a solution containing 1% hydroxypropyl methylcellulose and 0.5% Tween 80 was used as vehicle.

5.1 Single-dose toxicity

Single-dose toxicity studies were conducted in mice and cynomolgus monkeys. There were no deaths in either study. The approximate lethal dose was determined to be >2,000 mg/kg in mice and >2,000 mg/kg in cynomolgus monkeys (Table 14). Fatal/acute symptoms were evaluated in dogs in repeated-dose toxicity

[58)] In a foreign phase III study (Study SIGA-246-008), the total and unbound C_{max} (unbound C_{max} in parentheses) at steady state (Day 14) after oral administration of tecovirimat 600 mg BID under fed conditions for 14 days was 5.88 (1.33) μmol/L for tecovirimat, 6.32 (5.01) μmol/L for M4, 3.52 (2.36) μmol/L for M5, and 41.9 (0.587) μmol/L for TFMBA.

studies. In all studies, no deaths were reported after the first dose, and the approximate lethal dose was determined to be >100 mg/kg [see Section 5.2]. Observed common acute symptoms included ataxia, decreased activity, and vomiting in cynomolgus monkeys; convulsion, ataxia, vomiting, stereotypy, involuntary head movement, and gasping in dogs.

Table 14. Summary of the results of single-dose toxicity studies

Test system	Route of administration	Dose (mg/kg)	Key findings	Approximate lethal dose (mg/kg)	CTD (Study ID)
Male/female mice (BALB/c)	Oral gavage	0, 2,000	At 2,000: low body weight, low food intake (female)	>2,000	4.2.3.1.1 (264-TX-002)
Male/female cynomolgus monkeys	Oral gavage	0, 1,000, 2,000	At ≥1,000: ataxia (male/female); decreased activity (male) At 2,000: vomiting (female) At 1,000: vomiting, watery stool (male) At 1,000: listlessness, sparse hair (female)	>2,000	4.2.3.1.3 (246-TX-005)

5.2 Repeated-dose toxicity

Repeated-dose toxicity studies were conducted in mice and cynomolgus monkeys (28 days and 3 months) and in dogs (7 days) (Table 15). Major toxicity findings in dogs included vomiting, salivation, tremor, and convulsion, indicating effects on the central nervous system. In mice, tecovirimat-related laboratory abnormalities/findings included increased reticulocyte count, increased levels of mean corpuscular volume (MCV)/mean corpuscular hemoglobin (MCH)/blood cholesterol/creatinine, increased spleen and liver weights, and extramedullary hematopoiesis, which were, however, considered non-toxic due to the absence of associated changes and the degree of variation. Although lung adenoma and lymphosarcoma occurred in tecovirimat-treated animals, these changes were considered of spontaneous origin in the animal system based on its onset time, etc. and unlikely associated with tecovirimat. In the tecovirimat-treated cynomolgus monkeys, inflammatory changes in the tongue, esophagus, stomach, bladder, and trachea, and the presence of amebas in the lumen of the cecum and colon were noted. However, these findings were considered unlikely to be related to tecovirimat treatment based on their severity and possibility to be background lesions. Other laboratory abnormalities with significant fluctuation as compared to the vehicle group in the mice, dogs, and cynomolgus monkeys were not accompanied by related histopathological changes, and were thus considered of low toxicological significance. The NOAEL in the 3-month repeated-dose toxicity studies in mice and cynomolgus monkeys was determined to be 1,000 mg/kg/day and 300 mg/kg/day, respectively. The plasma tecovirimat exposure ($AUC_{0\text{-}24h}$, 700,618 ng·h/mL [mice] and 77,689 ng·h/mL [monkeys]) was approximately 22.9-fold in mice and approximately 2.5-fold in cynomolgus monkeys as compared to the clinical exposure.[59)]

Table 15. Summary of the results of repeated-dose toxicity studies

Test system	Route of administration	Dosing period	Dose (mg/kg/day)	Key findings	NOAEL (mg/kg/day)	CTD (Study ID)
Male/female mice (BALB/c)	Oral gavage	28 days (once daily) + 14-day recovery period	0, 500, 1,000, 2,000	At ≥500: high liver weight (female) At ≥1,000: low blood albumin, high liver weight (male) At 2,000: high spleen weight (male/female); high reticulocyte count/rate, chronic nephropathy (female) Recovery period None	2,000	4.2.3.2.2 (246-TX-006)

[59)] The plasma exposure on Day 14 following administration of tecovirimat 600 mg BID orally to healthy adults ($AUC_{0\text{-}24h}$, 30,632 ng·h/mL) in a foreign phase III study (Study SIGA-246-008) [see Section 6.2.1.3].

Male/female mice (BALB/c)	Oral gavage	3 months (once daily) + 28-day recovery period	0, 300, 600, 1,000	At ≥300: high MCH, low blood ALT, low BUN/creatinine ratio, high blood creatinine (male); high reticulocyte count, low blood A/G ratio (female) At ≥600: high blood cholesterol, low blood ALP, high MCV, high liver/spleen weights (female) At 1,000: lung adenoma (male/female) At 1,000: high liver to total body weight, chronic inflammation of the prostate (male); high percentage reticulocyte count, increased occurrence of extramedullary hematopoiesis in the spleen, chronic nephropathy (female) Recovery period At 1,000: lymphosarcoma (male)	1,000	4.2.3.2.8 (IITRI 2083-003-001 SN3)
Male/female cynomolgus monkeys	Oral gavage	28 days (once daily) + 14-day recovery period	0, 30, 100, 300	At 300: high blood chlorine, mineral deposits in the renal tubule (male); low eosinophil count, low peripheral blood monocyte count/macrophage count, low spleen to total body weight, lung pigmentation (female) Recovery period None	300	4.2.3.2.5 (246-TX-007)
Male/female cynomolgus monkeys	Oral gavage	3 months (once daily) + 28-day (female) or 29-day (male) recovery period	0, 30, 100, 300	At ≥30: low blood creatinine kinase (male/female); chronic inflammation in the stomach, ameba in the lumen of the cecum (male); chronic inflammation in the bladder, ameba in the lumen of the colon (female) At ≥100: esophageal inflammation (male) At 300: acute/chronic inflammation in the trachea (male); low peripheral blood monocyte count/macrophage count, chronic inflammation of the tongue (female) Recovery period None	300	4.2.3.2.9 (IITRI 2083-003-001 SN6)
Male dogs (Beagle)	Oral gavage	7 days (once daily)	30, 100	**Animals that died** At 100: 3 of 3 animals Vomiting, salivation, listlessness, lighter discoloration of the gums, rapid respiration/gasping, red nasal discharge, tremor, convulsion **Animals that survived** At 30: salivation, vomiting	—	4.2.3.2.3 (246-TX-014)
Male/female dogs (Beagle)	Oral gavage[a)]	Single-dose or repeated-dose for 7 or 8 days (once daily)	30 (for 8 days) 100 (for 7 days) 300 (single dose)	**Single-dose administration** <u>Animals that died</u> At 300, 1 of 1 animal (male) Involuntary head movement, vomiting, hyperactivity, ataxia, excessive blinking, excessive licking behavior, salivation, tremor, twitch, abnormal phonation, shallow and rapid respiration, stereotypy, skin discoloration, clonic-tonic convulsion, QTc prolongation <u>Animals that survived</u> At 300: involuntary head movement, vomiting, salivation, tremor, twitch (female) **Repeated-dose administration** At 100: salivation, excessive licking behavior (male/female); twitch (male); excessive licking behavior, hyperactivity, tremor, abnormal phonation (female)	—	4.2.3.2.4 (246-TX-015)

"—," NOAEL could not be determined

a) Vehicle, 1% hydroxypropyl methylcellulose solution

5.3 Genotoxicity

Genotoxicity studies consisted of an *in vitro* bacterial reverse mutation assay (Ames test), an *in vitro* gene mutation assay using mouse lymphoma L5178Y/*TK*$^{+/-}$ cells, and an *in vivo* micronucleus assay in mice (Table 16). The results of all assays were negative, and therefore, tecovirimat was determined to be non-genotoxic.

Table 16. Summary of genotoxicity study results

Study type		Test system	Metabolic activation (treatment)	Tecovirimat concentration or dose	Test result	CTD (Study ID)
In vitro	Ames test	*Salmonella* Typhimurium: TA98, TA100, TA1535, and TA1537 *E.coli*: WP2 *uvrA*	S9−/+	0,[a] 50, 150, 500, 1,500, 5,000 µg/plate	Negative	4.2.3.3.1.1 (246-TX-008)
	Gene mutation assay	Mouse lymphoma L5178Y/*TK*$^{+/-}$ cells	S9− (4 hours)	0[a] 10, 15, 25, 50, 75 µg/mL	Negative	4.2.3.3.1.2 (246-TX-009)
			S9+ (4 hours)	0,[a] 5, 15, 25, 50, 75 µg/mL		
			S9− (24 hours)	0,[a] 5, 10, 25, 50, 100 µg/mL		
In vivo	Mouse micronucleus assay	Male/female mice (ICR) Bone marrow		0, 500, 1,000, 2,000 mg/kg (oral gavage, single-dose)	Negative	4.2.3.3.2.1 (246-TX-010)

a) Vehicle, dimethyl sulfoxide

5.4 Carcinogenicity

No carcinogenicity studies were conducted because the usual treatment duration is 4 days and tecovirimat is non-genotoxic [see Section 5.3].

5.5 Reproductive and developmental toxicity

The studies conducted include a study on fertility and early embryonic development to implantation (FEED study) in mice, embryo-fetal development (EFD) studies in mice and rabbits, and a pre-and post-natal development study, including maternal function (PPND study) in mice (Table 17).

Major toxicity findings: In the EFD study in rabbits, maternal death associated with exacerbated clinical signs, premature birth, increased post-implantation embryonic losses, increased early embryo resorption, and decreased viable fetuses were noted in animals receiving tecovirimat at a less than clinical exposure level. In the FEED study in mice, decreased epididymal sperm motility and increased abnormal epididymal sperm morphology rate were noted in male mice. These changes, however, did not affect fertility or were not determined to be toxicities. In female mice, the number of dams with viable fetuses decreased; however, this was considered an incidental change due to the presence of infertile animals with low toxicological significance. In the EFD studies in mice and rabbits, skeletal/visceral malformation and skeletal malformation/change were noted. However, the frequency of these changes was not dose-associated and similar to that in the historical data. These findings were thus unlikely to be related to tecovirimat treatment. In F_1 live pups in the mouse PPND study, coarse fur, dehydration, and emaciation were noted. However, these findings were concluded to be unlikely related to tecovirimat treatment based on the relationship with the dose and the frequency.

The NOAEL for early embryo development in mice was determined to be 300 mg/kg/day, at which the estimated plasma tecovirimat exposure ($AUC_{0\text{-}24h}$, 526,551 ng·h/mL[60]) was approximately 17-fold the clinical exposure.[59] The embryo-fetal NOAEL was 1,000 mg/kg/day for mice and 30 mg/kg/day for rabbits, at which the estimated blood tecovirimat exposure in mice and rabbits ($AUC_{0\text{-}24h}$, 661,256 ng·h/mL for mice and 5,757 ng·h/mL for rabbits) was approximately 22-fold and 0.19-fold, respectively, the clinical exposure. The

[60] Estimated from the toxicokinetics data at Week 13 in female animals in the 3-month repeated oral dose toxicity study in mice (Study IITRI 2083-003-001 SN3)

NOAEL for the development of mouse F_1 live pups was determined to be 1,000 mg/kg/day, at which the estimated plasma tecovirimat exposure ($AUC_{0\text{-}24h}$, 661,256 ng·h/mL[61)]) was approximately 22-fold the clinical exposure.

Table 17. Summary of reproductive and developmental toxicity study results

Study type	Test system	Route of administration	Dosing period	Dose (mg/kg/day)	Key findings	NOAEL (mg/kg/day)	CTD (Study ID)
Fertility and early embryonic development to implantation[a)]	Male/ female mice (CD-1)	Oral gavage	Male: 4 weeks before mating to 1 day before necropsy Female: 2 weeks before mating until gestation day 7 (once daily)	0, 100, 300, 1,000	Parent animals: At 1,000: decreased sperm motility, increased abnormal sperm morphology rate (male) Fertility: None Early embryonic development: At 1,000: low number of parent animals with viable fetuses	Parent animals (general toxicity and fertility): 1,000 Early embryonic development: 1,000	4.2.3.5.1.1 (IITRI 2083-003-001 SN7)
Embryo-fetal development	Female mice (CD-1)	Oral gavage	Gestation days 6 to 15 (once daily) Cesarean section: on gestation day 18	0, 100, 300, 1,000	Dams None Embryo-fetal development At ≥100: 25 pre-sacral vertebrae[c)] At ≥300: increased number of malformed fetuses, increased number of external/visceral malformations, open eyelids,[b)] exencephaly,[b)] cleft palate,[b)] kidney (morphology) variation,[c)] seventh sternebra,[c)] increased number of fetuses with visceral variations At 1,000: increased number of fetuses with skeletal malformations, bent tail,[b)] fused sternebrae,[b)] increased number of fetuses with skeletal variations, displaced ophthalmia,[c)] hyoid body/arch unossified, additional sternebra(e),[c)] 13th rib rudimentary,[c)] At 100 and 1,000: cervical ribs[c)]	Dams (general toxicity): 1,000 Dams (reproductivity) : 1,000 Embryo-fetal development: 1,000	4.2.3.5.2.3 (IITRI 2083-003-001 SN4)
	Female rabbits (NZW)	Oral gavage	Gestation days 6 to 19 (once daily) Cesarean section: on gestation day 29	0, 10, 30, 100	Dams At ≥30: red vaginal discoloration, emaciation, increased frequency of scant feces, no feces, premature delivery, abscess formation At 100: deaths, lacrimation, discoloration around mouth, red nasal discharge, red discoloration around nose fur, rapid respiration, decreased body weight/body weight gain, decreased food consumption, increased number of dams with embryonic losses, decreased number of dams with viable fetuses, high MCV, high white blood cell/ lymphocyte/monocyte/basophil counts, low uterus weight Embryo-fetal development At ≥10: bent clavicle,[c)] retrocaval ureter[c)] At 100: increased number and rate of post-implantation losses, high early resorption rate, increased number and rate of resorptions in total, decreased viable fetuses, kidney/ureter absent,[b)] malaligned vertebrae,[b)] forked ribs,[b)] pre-sacral vertebrae,[c)] decreased number of fetuses with 13th rib rudimentary,[c)] full 14th ribs[c)] At 10 and 100: umbilical hernia,[b)] additional sternebra[c)] At 30: hyoid body/arch unossified	Dams General toxicity: 10 Reproductivity: 10 Embryonic development: 30 Fetal development: 100	4.2.3.5.2.4 (IITRI 2083-003-001 SN5)
Effects on pre- and post-natal development,	Female mice (CD-1)	Oral gavage	Gestation days 6 to lactation day 20	0, 100, 300,	Dams None	Dams (general toxicity/	4.2.3.5.3.1

[61)] Estimated from the toxicokinetics data in the embryo-fetal development study (Study ITRI 2083-003-001 SN4) in mice by oral administration

including maternal function			(once daily)	1,000	Live F_1 offspring At ≥100: coarse fur (after weaning) At ≥300: emaciation, dehydration (before weaning)	reproductivity): 1,000 Live F_1 offspring development: 1,000	(IITRI 2083-003-001 SN8)

a) Because of decreased pregnancy rate unrelated to tecovirimat treatment observed, a re-test was conducted in the same study; b) malformation findings; c) variation findings

5.6 Other toxicity studies

5.6.1 Phototoxicity

Since tecovirimat absorbed light in the wavelength range of 290 nm to 700 nm, an *in vivo* phototoxicity study was conducted in hairless mice (Table 18). The results showed that tecovirimat is not phototoxic.

Table 18. Summary of phototoxicity study results

Test system	Test method	Key findings	CTD (Study ID)
Female hairless mice (SKH1-*hr*)	Single dose of tecovirimat 0, 500, 1,000, or 2,000 mg/kg was administered by oral gavage. One hour later, mice were irradiated with ultraviolet light for approximately 30 minutes.	None	4.2.3.6.1 (246-TX-017)

5.6.2 Toxicity evaluation of metabolites

Following multiple administration tecovirimat to humans, M4, M5, and TFMBA were identified as metabolites observed at exposure greater than 10% of that to all substances related to the drug administration [see Sections 6.2.1.3 and 6.2.1.4].

The plasma exposure (AUC, see Section 4.1.2) of M4 and M5 following the oral doses of tecovirimat 1,000 mg/kg to mice exceeded 50% of the clinical exposure.[62)] The toxicity of M4 and M5 was characterized in accordance with the ICH M3 (R2) guidelines, based on data from the repeated-dose toxicity study of tecovirimat 1,000 mg/kg in mice [see Section 5.2], *in vivo* micronucleus study [see Section 5.3], and the embryo-fetal development study [see Section 5.5]. The toxicity of TFMBA has not been characterized in accordance with the ICH M3 (R2) guidelines.

5.6.3 Safety evaluation of impurities (Reference, CTD 4.2.3.7.6.2 through 4.2.3.7.6.6)

An Ames test was conducted for impurities in the drug substance or drug product, or those that may be generated during their manufacture or storage, namely, Impurity 1 (Study 9603768), SG2 (Study 9603766), Impurity 2 (Study 9603769), Impurity 3 (Study 9603767), and Impurity 4 (Study 9603770). Based on the results, SG2 was determined to be mutagenic.

5.R Outline of the review conducted by PMDA

5.R.1 Effects on the central nervous system

PMDA's view:

[62)] In a foreign phase III study (Study SIGA-246-008), the plasma exposure ($AUC_{0\text{-}24h}$) to M4 and M5 on Day 14 following oral administration of tecovirimat 600 mg BID to healthy adults was 23.5 ± 7.61 μg·h/mL and 13.1 ± 4.20 μg·h/mL, respectively[see Section 6.2.1.3].

Findings suggestive of the effects on the central nervous system, such as convulsions, tremor, and vomiting, were noted in dogs at ≥0.36-fold the clinical exposure following single or repeated dose administration of tecovirimat [see Section 5.2, Studies 246-TX-014 and 246-TX-015]. While the results suggest tecovirimat's potential toxicity in the central nervous system, the proposed dosage of tecovirimat is unlikely to pose safety concerns in humans at for the following reasons:

- These events did not occur in the repeated-dose toxicity studies in mice and cynomolgus monkeys, in which tecovirimat exposure exceeded the clinical exposure [see Section 5.2]. Dogs are likely to be more prone to these events.
- Unlike the non-clinical studies, the clinical studies did not reveal severe convulsion, tremor, vomiting, or other adverse events suggestive of the effects on the central nervous system associated with tecovirimat treatment[see Section 7.R.2].

Currently, there is only limited information about the extrapolability of the central nervous system toxicity findings to humans. Therefore, these findings should be offered via the package insert.

5.R.2 Effects on embryo-fetal development

PMDA's view:

The embryo-fetal development study in rabbits revealed toxicity associated with decreased embryonic development/survival at exposure lower than clinical exposure. Given tecovirimat's toxicity to post-implantation embryonic development, its risk should be informed via the package insert. In the EFD study in rabbits, dams died at exposure that was lower than clinical exposure, while the repeated-dose studies in pregnant mice and cynomolgus monkeys reported no death or other serious systemic toxicities at exposures exceeding the blood exposure in rabbits at which systemic toxicities were observed. Therefore, pregnant rabbits may be more susceptible to systemic toxicities of tecovirimat. No serious toxicities to fetal development were observed in tecovirimat-treated mice and rabbits, indicating that tecovirimat is unlikely to have teratogenicity or other impacts on fetal development. Based on these observations, with the assumption that tecovirimat will be administered to patients in serious condition, the use of tecovirimat in pregnant women or those who may be pregnant should be restricted to the cases where the benefits of tecovirimat treatment outweigh the risks, although no clinical studies have been conducted in pregnant women.

5.R.3 Qualification of metabolites

The applicant's explanation about the toxicity of TFMBA, a metabolite of tecovirimat, which remains uncharacterized in accordance with the ICH M3 (R2) guidelines:

No systemic toxicities were noted in the 3-month repeated-dose toxicity study in cynomolgus monkeys, albeit at exposures inadequate for the characterization of the toxicity of TFMBA [see Section 5.2]. A genotoxicity assessment conducted by the US FDA using an *in silico* (Quantitative) Structure-Activity Relationship model [(Q)SAR model], which is used to predict the results for bacterial mutagenicity studies, showed that TFMBA was negative for genotoxicity. Furthermore, tecovirimat was well tolerated in the clinical studies. Based on these outcomes, it is unlikely that TFMBA will cause safety concerns in humans.

PMDA's view:

The available study data are insufficient for the characterization of the toxicity of TFMBA in accordance with the ICH M3 (R2) guidelines. Albeit unknown effects by potential toxicity of the metabolites, TFMBA is considered of low safety concern based on the clinical studies conducted so far reporting no intolerable adverse events. Yet, the characterization of the toxicity of TFMBA is subject to further discussion.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

In the clinical development of Tepoxx, the main oral formulations used were Formulations 1, 2, and 3,[63)] and Formulation 3 was the proposed marketing formulation.

- Formulation 1: Capsules each containing 25 mg of tecovirimat (drug substance, tecovirimat hemihydrate Form V)
- Formulation 2: Capsules each containing 200 mg of tecovirimat (drug substance, tecovirimat hemihydrate Form V)
- Formulation 3: Capsules each containing 200 mg of tecovirimat (drug substance, tecovirimat monohydrate Form I)

Human plasma concentrations of tecovirimat and its main metabolites (M4, M5, and TFMBA) were determined by LC-MS/MS.[64)] Unless otherwise specified, dose levels and concentrations of tecovirimat are expressed as free-tecovirimat conversion values.

6.1.1 Food effect study (CTD 5.3.5.1.1 through 5.3.5.1.33, Study SIGA-246-008 [June 2015 to August 2016] Lead-in cohorts)

Tecovirimat 600 mg (proposed marketing formulation) was administered to non-Japanese healthy adults (32 subjects for PK evaluation) under fasted conditions or after a moderate fat meal (approximately 600 kcal, 25 g fat) orally BID for 14 days. Table 19 shows tecovirimat plasma PK parameters. Plasma tecovirimat exposure increased in the fed state compared to the fasted state.

[63)] Main clinical studies in which each of Formulations 1, 2, and 3 were used:
Formulation 1: foreign phase I studies (Studies SIGA-246-001 and SIGA-246-002); Formulation 2: foreign phase I studies (Studies SIGA-246-001, SIGA-246-002, and SIGA-246-PO-005); Formulation 3: Japanese phase I study (Study JBP-TPOXX-001), foreign phase I studies (Studies SIGA-246-004, SIGA-246-006, SIGA-246-009, SIGA-246-010, SIGA-246-012, SIGA-246-013, SIGA-246-015, and SIGA-246-018), and foreign phase III study (Study SIGA-246-008).

[64)] The lower limit of quantitation:
Tecovirimat, 0.50, 5.00, or 50.0 ng/mL; M4, 5.0 ng/mL; M5, 10.0 ng/mL; TFMBA, 5.00 ng/mL

Table 19. Plasma tecovirimat PK parameters following administration of oral tecovirimat 600 mg BID for 14 days to non-Japanese healthy adults under fasted conditions or after moderate fat meal

Timepoint	Meal condition	N	C_{max} (μg/mL)	t_{max} (h)[a)]	$AUC_{0\text{-}24h}$ (μg·h/mL)	C_{min} (μg/mL)
Day 1	Fasted conditions	15	1.26 ± 0.475	20.0 [14.0, 23.9]	17.2 ± 6.75	0.205 ± 0.147
	After a moderate fat meal	16	1.56 ± 0.624	6.04 [4.00, 20.0]	23.6 ± 9.14	0.393 ± 0.195
Day 14	Fasted conditions	15	1.71 ± 0.768	14.0 [1.00, 18.0]	23.5 ± 11.3	0.414 ± 0.267
	After a moderate fat meal	16	2.47 ± 0.958	3.92 [0.00, 18.0]	32.5 ± 14.2	0.678 ± 0.305

Mean ± standard deviation
a) Median [range]

6.1.2 Effects of capsule content of tecovirimat administered as a mixture with food or liquid (CTD 5.3.3.1.42, Study SIGA-246-018 [September 2016 to November 2016] Cohorts 3 and 4)

A study was conducted in non-Japanese healthy adults in the following cohorts (N = 12/cohort for PK evaluation).

- A single oral dose of tecovirimat 600 mg in intact capsules or tecovirimat 600-mg capsule content mixed in 2% milk after a moderate fat meal (approximately 600 kcal, 25 g fat)
- A single oral dose of tecovirimat 600 mg in intact capsules or tecovirimat 600 mg capsule content mixed in applesauce after a moderate fat meal (approximately 600 kcal, 25 g fat)

The geometric mean ratios of the mixed capsule content to the intact capsule [90% confidence interval (CI)] were 1.16 [1.06, 1.27] (milk) and 1.02 [0.93, 1.12] (applesauce) for plasma C_{max}, and 1.14 [0.99, 1.31] (milk) and 1.13 [1.02, 1.24] (applesauce) for plasma AUC_{last}. The results showed no clear differences.

6.2 Clinical pharmacology

The main study data submitted for the present application included the results from studies in healthy subjects (PK, pharmacokinetic interaction, QT/QTc, and mass balance studies), PK studies in subjects with renal or hepatic impairment, and PPK analysis.

Unless otherwise specified, dose levels and concentrations of tecovirimat are expressed as free-tecovirimat conversion values, and PK parameters are expressed as mean ± standard deviation.

6.2.1 Investigation in healthy subjects

6.2.1.1 Japanese phase I study (CTD 5.3.3.1.1 through 5.3.3.1.10, Study JBP-TPOXX-001 [July 2023 to August 2023])

Tecovirimat 600 mg was administered orally BID for 14 days under fed conditions to Japanese healthy adults (20 subjects for PK evaluation) to investigate the PK parameters of plasma concentrations of tecovirimat and its main metabolites (M4, M5, and TFMBA). Table 20 shows the results.

Table 20. PK parameters following administration of oral tecovirimat 600 mg BID under fed conditions for 14 days to Japanese healthy adults

Analyte	Timepoint	N	C_{max} (μg/mL)	t_{max} (h)[a)]	$AUC_{0\text{-}12h}$ (μg·h/mL)	$AUC_{0\text{-}24h}$ (μg·h/mL)
Tecovirimat	Day 1	20	1.73 ± 0.330	4.00 [4.00, 16.0]	9.70 ± 1.92	—
	Day 14	20	1.94 ± 0.515	4.00 [0.00, 8.00]	12.6 ± 3.26	23.7 ± 6.07
M4	Day 1	20	0.929 ± 0.190	23.8 [23.8, 23.8]	4.04 ± 1.04	—
	Day 14	20	1.18 ± 0.294	4.00 [0.00, 24.0]	11.7 ± 3.67	21.8 ± 6.44
M5	Day 1	20	0.120 ± 0.043	23.8 [23.8, 23.8]	0.223 ± 0.110	—
	Day 14	20	0.735 ± 0.382	8.91 [0.00, 48.0]	7.70 ± 4.54	15.7 ± 8.84
TFMBA	Day 1	20	5.05 ± 1.18	23.8 [6.00, 23.8]	24.3 ± 5.38	—
	Day 14	20	6.50 ± 1.69	4.00 [0.00, 24.0]	63.9 ± 21.1	122 ± 41.1

Mean ± standard deviation; "—," Not evaluated
a) Median [range]

6.2.1.2 Foreign phase I study (CTD 5.3.3.1.11, Study SIGA-246-001 [April 2006 to July 2006], CTD 5.3.3.1.2, Study SIGA-246-002 [February 2007 to January 2008])

A single dose of tecovirimat 500, 1,000, or 2,000 mg (fasted conditions), or 1,000 mg (fed conditions) was administered orally to non-Japanese healthy adults (N = 8/group for PK evaluation). Table 21 shows the evaluation results of plasma tecovirimat PK parameters.

Table 21. Plasma tecovirimat PK parameters following administration of a single dose of oral tecovirimat to non-Japanese healthy adults

Dose (mg)	Meal condition	N	C_{max} (μg/mL)	t_{max} (h)[a)]	AUC_{last} (μg·h/mL)	$t_{1/2}$ (h)
500	Fasted	8	0.934 ± 0.361	2.0 [1.5, 3.5]	9.88 ± 2.10	25.9 ± 15.5
1,000	Fasted	8	1.81 ± 0.907	2.8 [1.0, 6.0]	21.1 ± 11.8	40.4 ± 45.4
2,000	Fasted	7	2.55 ± 0.589	2.5 [1.1, 4.0]	24.5 ± 5.72	21.6 ± 8.5
1,000	Fed	8	2.94 ± 0.876	5.0 [3.0, 8.0]	34.1 ± 11.0	17.2 ± 6.1

Mean ± standard deviation;
a) Median [range]

Tecovirimat 250, 400, or 800 mg was administered orally QD for 21 days to non-Japanese healthy adults (N = 8/group for PK evaluation) under fed conditions. Table 212 shows the results of plasma tecovirimat PK parameters.

Table 22. Plasma tecovirimat PK parameters following administration of oral tecovirimat QD to non-Japanese healthy adults under fed conditions

Dose (mg)	Timepoint	N	C_{max} (μg/mL)	t_{max} (h)[a)]	$AUC_{0\text{-}24h}$ (μg·h/mL)	C_{min} (μg/mL)
250	Day 1	8	0.985 ± 0.346	3.0 [2.0, 4.0]	9.10 ± 3.49	—
	Day 21	7	1.10 ± 0.378	2.0 [2.0, 4.0]	10.1 ± 2.84	0.102 ± 0.087
400	Day 1	8	1.39 ± 0.411	4.0 [2.0, 4.0]	13.1 ± 3.63	—
	Day 21	7	1.46 ± 0.451	2.0 [2.0, 4.0]	16.2 ± 5.53	0.238 ± 0.101
800	Day 1	8	2.28 ± 0.395	3.0 [1.0, 4.0]	21.0 ± 6.09	—
	Day 21	7	2.44 ± 0.496	4.0 [1.0, 4.0]	22.7 ± 4.58	0.240 ± 0.067

Mean ± standard deviation; "—," Not evaluated
a) Median [range]

6.2.1.3 Foreign phase III study (CTD 5.3.5.1.1 through 5.3.5.1.33, Study SIGA-246-008 [June 2015 to August 2016] Lead-in cohorts and expanded cohorts)

Tecovirimat 600 mg was administered orally BID for 14 days to non-Japanese healthy subjects (63 subjects for PK evaluation) under fed conditions. Table 23 shows the results of plasma PK parameters of tecovirimat and its main metabolites (M4, M5, and TFMBA).

Table 23. PK parameters following administration of tecovirimat 600 mg orally BID for 14 days to non-Japanese healthy adults under fed conditions

Analyte	Timepoint	N	C_{max} (μg/mL)	t_{max} (h)[a)]	$AUC_{0\text{-}24h}$ (μg·h/mL)	C_{min} (μg/mL)
Tecovirimat	Day 1	48	1.59 ± 0.516	6.06 [2.00, 23.8]	25.9 ± 7.48	0.560 ± 0.364
	Day 14	48	2.21 ± 0.726	3.92 [0, 18.0]	30.6 ± 10.7	0.690 ± 0.259
M4	Day 1	48	0.907 ± 0.316	23.8 [15.8, 24.1]	13.6 ± 2.31	—
	Day 14	48	1.29 ± 0.433	6.00 [0, 24.0]	23.5 ± 7.61	—
M5	Day 1	48	0.109 ± 0.046	23.8 [14.0, 24.1]	0.929 ± 0.351	—
	Day 14	48	0.665 ± 0.403	15.8 [0, 24.0]	13.1 ± 4.20	—
TFMBA	Day 1	48	5.14 ± 2.19	23.8 [15.8, 24.1]	67.6 ± 18.8	—
	Day 14	48	7.96 ± 3.12	6.00 [0, 24.0]	160 ± 68.1	—

Mean ± standard deviation; "—," Not evaluated
a) Median [range]

6.2.1.4 Mass balance study (CTD 5.3.3.1.40, Study SIGA-246-009 [June 2014 to July 2014])

A single dose of ^{14}C-tecovirimat 600 mg (100 μCi) was administered orally to non-Japanese healthy subjects (N = 6) under fed conditions to evaluate mass balance. Up to 192 hours post-dose, 72.5% and 22.7% of the administered radioactivity was excreted in urine and feces, respectively. At 72 hours post-dose, mainly unchanged tecovirimat, M4, and M5 were detected in plasma, which accounted for 20.5%, 43.8%, and 18.9% of the total radioactivity in plasma, respectively. By 120 hours post-dose,[65)] mainly M2, M9, and M8 were detected in urine, accounting for 30.3%, 24.4%, and 5.66% of the administered radioactivity, respectively. By 168 hours post-dose,[66)] primarily unchanged tecovirimat, accounting for 15.9% of the administered radioactivity was detected in feces. The AUC_{inf} ratio of blood-to-plasma radioactivity levels ranged from 0.435 to 0.814. The blood radioactivity levels were lower than the plasma radioactivity levels at all measurement timepoints that were quantifiable.

6.2.3 Investigation of intrinsic factors

6.2.3.1 Foreign phase I study in subjects with renal impairment (CTD 5.3.3.3.26 through 5.3.3.3.49, Study SIGA-246-012 [June 2016 to February 2017])

A single dose of tecovirimat 600 mg was orally administered under fed conditions to non-Japanese adult subjects with varying degrees of renal function: normal function, creatinine clearance (CL_{cr}) ≥90 mL/min; mild impairment, estimated glomerular filtration rate (eGFR) ≥60 to <90 mL/min/1.73 m^2; moderate impairment, eGFR ≥30 to <60 mL/min/1.73 m^2; severe impairment, eGFR <30 mL/min/1.73 m^2; and end-stage renal disease (ESRD) requiring hemodialysis. The PK parameters (Table 24) show reduction of tecovirimat exposure in subjects with renal impairment compared to subjects with normal renal function. The exposure of the main metabolites (M4, M5, and TFMBA) tended to increase. While tecovirimat, M5, and TFMBA were hardly removed by hemodialysis, approximately 30% of M4 was removed.

[65)] The urine samples were collected 0 to 72 hours post-dose (2 subjects), 0 to 96 hours post-dose (3 subjects), and 0 to 120 hours post-dose (1 subject).
[66)] The fecal samples were collected 0 to 24 hours post-dose (1 subject), 0 to 24 hours and 72 to 120 hours post-dose (1 subject), 24 to 72 hours post-dose (1 subject), from 48 to 96 hours post-dose (1 subject), 48 to 72 hours and 120 to 168 hours post-dose (1 subject), 72 to 96 hours and 120 to 144 hours post-dose (1 subject).

Table 24. PK parameters following administration of a single dose of oral tecovirimat to subjects with normal renal function and subjects with renal impairment

Analyte	Degree of renal impairment	N	C_{max} (µg /mL)	AUC_{last} (µg·h/mL)	Geometric mean ratio [90% CI] (renal impairment/normal renal function)	
					C_{max}	AUC_{last}
Tecovirimat	Normal	7	1.22 (41.4)	17.8 (40.2)	—	—
	Mild impairment	8	1.44 (45.6)	20.9 (30.0)	1.17 [0.87, 1.56][a)]	1.17 [0.85, 1.60][a)]
	Moderate impairment	8	1.44 (30.5)	25.3 (45.5)	1.16 [0.87, 1.55][a)]	1.41 [1.02, 1.93][a)]
	Severe impairment	7	0.76 (30.6)	18.4 (33.9)	0.66 [0.49, 0.89][a)]	1.07 [0.77, 1.48][a)]
	ESRD (administered post-hemodialysis)	8	0.66 (46.6)	8.59 (44.0)	0.66 [0.48, 0.89][a)]	0.55 [0.39, 0.77][a)]
	ESRD (administered pre-hemodialysis)	8	0.74 (77.2)	8.77 (55.8)	—	—
M4	Normal	7	0.421 (46.1)	12.2 (42.9)	—	—
	Mild impairment	8	0.471 (16.8)	15.4 (24.3)	1.11 [0.83, 1.49][a)]	1.26 [0.89, 1.77][b)]
	Moderate impairment	8	0.615 (32.9)	21.1 (44.5)	1.44 [1.08, 1.94][a)]	1.73 [1.23, 2.44][b)]
	Severe impairment	7	0.414 (57.4)	19.9 (48.6)	1.02 [0.75, 1.39][a)]	1.63 [1.14, 2.33][b)]
	ESRD (administered post-hemodialysis)	8	0.460 (28.2)	28.0 (41.8)	1.27 [0.93, 1.73][a)]	2.30 [1.63, 3.24][b)]
	ESRD (administered pre-hemodialysis)	8	0.347 (19.0)	23.1 (37.3)	—	—
M5	Normal	7	0.062 (72.9)	4.08 (71.7)	—	—
	Mild impairment	8	0.072 (40.6)	5.79 (35.1)	1.15 [0.85, 1.56][a)]	1.37 [0.97, 1.93][c)]
	Moderate impairment	8	0.107 (44.1)	8.52 (37.7)	1.67 [1.23, 2.27][a)]	1.79 [1.23, 2.62][c)]
	Severe impairment	7	0.056 (41.9)	5.20 (41.2)	0.98 [0.71, 1.34][a)]	1.35 [0.94, 1.92][c)]
	ESRD (administered post-hemodialysis)	8	0.054 (46.2)	4.60 (37.9)	1.21 [0.87, 1.67][a)]	1.45 [1.00, 2.10][c)]
	ESRD (administered pre-hemodialysis)	8	0.047 (50.8)	4.27 (40.9)	—	—
TFMBA	Normal	7	2.41 (58.1)	73.1 (64.1)	—	—
	Mild impairment	8	2.81 (14.4)	98.2 (29.3)	1.16 [0.87, 1.54][a)]	1.33 [0.92, 1.93][a)]
	Moderate impairment	8	3.17 (30.5)	110 (49.4)	1.30 [0.98, 1.72][a)]	1.49 [1.03, 2.15][a)]
	Severe impairment	7	2.09 (42.3)	109 (52.7)	0.90 [0.67, 1.21][a)]	1.56 [1.06, 2.28][a)]
	ESRD (administered post-hemodialysis)	8	2.34 (30.2)	161 (37.2)	1.13 [0.84, 1.53][a)]	2.60 [1.76, 3.85][a)]
	ESRD (administered pre-hemodialysis)	8	2.95 (22.5)	184 (36.6)	—	—

Geometric mean ratio (coefficient of variation [CV], %); "—," Not applicable

a) Estimated values based on an analysis of covariance (ANCOVA) model with renal impairment degree as a stratification factor and body mass index (BMI) as a covariate

b) Estimated values based on an ANCOVA model with renal impairment degree as a stratification factor

c) Estimated values based on an ANCOVA model with renal impairment degree as a stratification factor and BMI and age as covariates

6.2.3.2 Foreign phase I study in subjects with hepatic impairment (CTD 5.3.3.3.1 through 5.3.3.3.25, Study SIGA-246-013 [June 2016 to January 2017])

A single dose of tecovirimat 600 mg was orally administered under fed conditions to non-Japanese subjects with mild, moderate, or severe hepatic impairment (Child-Pugh class A, B, or C) or with normal hepatic function (N = 8/group for PK evaluation). The PK parameters (Table 25) show no consistent trends in tecovirimat exposure depending on the presence/absence or degrees of hepatic impairment. Conversely, the exposures to the main metabolites (M4, M5, and TFMBA) tended to increase in subjects with hepatic impairment compared to subjects with normal hepatic function.

Table 25. PK parameters following administration of a single dose of oral tecovirimat to subjects with normal hepatic function and subjects with hepatic impairment

Analyte	Degree of hepatic impairment	N	C_{max} (μg /mL)	AUC_{last} (μg·h/mL)	Geometric mean ratio [90% CI] (hepatic impairment/normal hepatic function)	
					C_{max}	AUC_{last}
Tecovirimat	Normal	8	1.07 (20.5)	16.2 (22.1)	—	—
	Mild impairment	8	0.86 (50.7)	10.9 (63.2)	0.81 [0.63, 1.04]	0.59 [0.42, 0.84][a)]
	Moderate impairment	8	1.22 (23.6)	17.7 (46.4)	1.14 [0.89, 1.47]	1.09 [0.78, 1.52][a)]
	Severe impairment	8	1.15 (17.7)	18.3 (39.9)	1.08 [0.84, 1.39]	0.93 [0.65, 1.34][a)]
M4	Normal	8	0.382 (19.6)	11.7 (17.4)	—	—
	Mild impairment	8	0.419 (47.1)	11.1 (66.4)	1.02 [0.78, 1.34]	0.80 [0.57, 1.13][a)]
	Moderate impairment	8	0.549 (31.9)	16.5 (43.0)	1.49 [1.14, 1.94]	1.41 [1.02, 1.96][a)]
	Severe impairment	8	0.662 (34.6)	29.7 (48.9)	1.94 [1.46, 2.56]	1.99 [1.39, 2.83][a)]
M5	Normal	8	0.051 (21.5)	4.58 (19.1)	—	—
	Mild impairment	8	0.055 (44.4)	4.49 (58.9)	1.02 [0.78, 1.34][b)]	0.98 [0.72, 1.33]
	Moderate impairment	8	0.068 (34.5)	5.90 (27.9)	1.38 [1.06, 1.81][b)]	1.29 [0.95, 1.75]
	Severe impairment	8	0.083 (33.9)	7.47 (33.2)	1.84 [1.39, 2.43][b)]	1.63 [1.20, 2.21]
TFMBA	Normal	8	2.23 (18.6)	64.6 (17.3)	—	—
	Mild impairment	8	2.59 (42.8)	71.0 (64.0)	1.16 [0.88, 1.52]	1.10 [0.77, 1.56]
	Moderate impairment	8	3.07 (31.6)	90.2 (35.3)	1.38 [1.05, 1.81]	1.40 [0.98, 1.99]
	Severe impairment	8	3.23 (34.4)	96.4 (47.3)	1.45 [1.10, 1.90]	1.49 [1.05, 2.12]

Geometric mean ratio (CV, %); "—," Not applicable
a) Estimated values based on an ANCOVA model with hepatic impairment degree as a stratification factor and sex as a covariate
b) Estimated values based on an ANCOVA model with hepatic impairment degree as a stratification factor and BMI as a covariate

6.2.3.3 Foreign phase IV study in subjects weighing >120 kg (CTD 5.3.3.3.50 through 5.3.3.3.75, Study SIGA-246-022 [July 2019 to December 2019])

Tecovirimat 600 mg was orally administered BID for 7 days under fed conditions to non-Japanese adults weighing >120 kg (N = 34 for PK evaluation; median body weight [range] was 131.2 kg [120.3, 220.4]), and the plasma tecovirimat PK parameters are presented in Table 26. The results show decreased plasma tecovirimat PK parameters in subjects weighing >120 kg compared to the plasma tecovirimat PK parameters (C_{max} and $AUC_{0\text{-}24h}$) [see Section 6.2.1.3] in non-Japanese healthy adults (median body weight [range], 85.3 kg [54.3, 145.4]).

Table 26. Plasma tecovirimat PK parameters following administration of tecovirimat 600 mg orally BID for 7 days under fed conditions to non-Japanese adult subjects weighing >120 kg

Timepoint	N	C_{max} (μg/mL)	t_{max} (h)[a)]	$AUC_{0\text{-}24h}$ (μg·h/mL)	C_{trough} (μg/mL)
Day 1	34	0.847 ± 0.211	4.0 [2.0, 8.0]	11.9 ± 2.82	0.517 ± 0.206[b)]
Day 7	34	1.35 ± 0.393	4.0 [2.0, 12.0]	20.0 ± 4.59	0.617 ± 0.219[c)]

Mean ± standard deviation
a) Median [range]; b) Measured before the first dose on Day 2; c) Measured before the second dose on Day 7

6.2.4 Investigation of extrinsic factors

6.2.4.1 Pharmacokinetic interactions with flurbiprofen, omeprazole, midazolam, repaglinide, and bupropion (CTD 5.3.3.4.1 through 5.3.3.4.25, Study SIGA-246-015 [October 2016 to December 2016])

An open-label study was conducted to investigate the effect of tecovirimat on the PK of substrates for CYP isoforms (CYP2B6 substrate, bupropion; CYP2C8 substrate, repaglinide; CYP2C9 substrate, flurbiprofen; CYP2C19 substrate, omeprazole; CYP3A substrate, midazolam) in non-Japanese healthy adults (78 subjects for PK evaluation). Table 27 shows the geometric mean ratio [90% CI] for the PK parameters of CYP isoform substrates (co-administered/not co-administered).

Based on the obtained results, the administration of oral tecovirimat at the recommended clinical dosage regimen (tecovirimat 600 mg BID under fed conditions) may lead to an increase in exposure to CYP2C8 or CYP2C19 substrate drugs and a decrease in exposure to CYP2B6 or CYP3A substrate drugs because of tecovirimat's potential to inhibit CYP2C8 and CYP2C19 and to induce CYP2B6 and CYP3A. The applicant thus intends to offer cautionary advice on coadministration with these substrate drugs via the package insert.

Table 27. Effects of tecovirimat on PK parameters of CYP isoform substrate drugs

Co-administered drug	Co-administered drug dosage regimen	Tecovirimat dosage regimen	N (with/without tecovirimat co-administration)	Analyte	Geometric mean ratio [90% CI] (with/without tecovirimat co-administration)	
					C_{max}	AUC_{last}
Cocktail substrate (flurbiprofen + omeprazole + midazolam)	50/20/2 mg, single dose (fed conditions)	600 mg BID	24/24	Flurbiprofen	1.07 [0.98, 1.17]	1.04 [1.00, 1.09]
			24/24	Omeprazole	1.87 [1.51, 2.31]	1.90 [1.59, 2.28]
			24/24	5-hydroxy omeprazole	1.34 [1.15, 1.56]	1.50 [1.36, 1.66]
			24/24	Midazolam	0.61 [0.54, 0.68]	0.68 [0.64, 0.73]
			24/24	1-hydroxy midazolam	2.28 [2.01, 2.58]	3.57 [3.29, 3.87]
Repaglinide	2 mg, single dose (fed conditions)	600 mg BID	30/30	Repaglinide	1.27 [1.12, 1.44]	1.23 [1.14, 1.32]
Bupropion	150 mg, single dose (fed conditions)	600 mg BID	24/24	Bupropion	0.86 [0.79, 0.93]	0.83 [0.78, 0.89]

6.2.4.2 Investigation of pharmacokinetic interactions with phosphate binders (CTD 5.3.3.3.76, Study SIGA-246-023 [June 2022 to November 2022])

An open-label study was conducted to evaluate the effects of phosphate binders (sevelamer carbonate, sucroferric oxyhydroxide, calcium acetate, or lanthanum carbonate) on tecovirimat PK in non-Japanese healthy adults (44 subjects for PK evaluation). Table 28 shows the geometric mean ratio of tecovirimat PK parameters [90% CI] (with/without co-administration of phosphate binder).

Table 28. Effects of phosphate binders on tecovirimat PK parameters

Co-administered drug	Dosage regimen of co-administered drug	Dosage regimen of Tecovirimat	N (With/without co-administered phosphate binder)	Analyte	Geometric mean ratio [90% CI] (with/without co-administered phosphate binder)	
					C_{max}	AUC_{last}
Sevelamer carbonate	1,600 mg, single dose	600 mg, single dose (fed conditions)	39/44	Tecovirimat	1.16 [1.08, 1.26]	1.26 [1.17, 1.36]
Sucroferric oxyhydroxide	500 mg, single dose	600 mg, single dose (fed conditions)	37/44	Tecovirimat	1.15 [1.06, 1.24]	1.21 [1.12, 1.31]
Calcium acetate	1,334 mg, single dose	600 mg, single dose (fed conditions)	37/44	Tecovirimat	1.09 [1.01, 1.18]	1.16 [1.07, 1.25]
Lanthanum carbonate	500 mg, single dose	600 mg, single dose (fed conditions)	38/44	Tecovirimat	1.21 [1.12, 1.30]	1.21 [1.12, 1.31]

6.2.5 QT/QTc study (CTD 5.3.3.1.41, Study SIGA-246-010 [June 2016 to September 2016])

A 6-treatment, 3-period crossover study[67)] was conducted in non-Japanese healthy adults (48 subjects) to evaluate the effects on QT/corrected QT (QTc) interval. Subjects received a single oral dose of placebo or tecovirimat 1,000 mg under fed conditions with moxifloxacin 400 mg single oral dose as a positive control. After the administration of moxifloxacin 400 mg, the positive control, the peak change from baseline in QT

[67)] A ≥7 day washout period was set between the periods.

interval corrected using Fridericia's correction formula (QTcF) adjusted by placebo (ΔΔQTcF) [90% CI] was 11.2 milliseconds [8.1, 14.3] at 4 hours post-dose.

After the administration of tecovirimat 1,000 mg, the peak ΔΔQTcF [90% CI] was 5.1 milliseconds [2.9, 7.3] at 4 hours post-dose. The upper limit of the two-sided 90% confidence interval for the ΔΔQTcF was <10 milliseconds, demonstrating that there was no effect of tecovirimat on QT/QTc prolongation within the range of exposure to tecovirimat and its main metabolites (M4, M5, and TFMBA) (C_{max}, 2.50 μg/mL [tecovirimat], 0.710 μg/mL [M4], 0.121 μg/mL [M5], and 4.25 μg/mL [TFMBA]) up to a single dose of tecovirimat 1,000 mg.

The C_{max} values of the main metabolites (M4, M5, and TFMBA) in this study were below the clinical exposure,[58)] restricting the evaluation of the effect of the main metabolites on QT/QTc prolongation. In the foreign phase I study (Study SIGA-246-015) and foreign phase III study (Study SIGA-246-008), tecovirimat was administered at the proposed dose levels. No subjects had an absolute QTcF value of >500 milliseconds or a change from baseline in QTcF of >60 milliseconds. No clinically important cardiovascular-related findings were noted in these studies.

6.2.6 Population pharmacokinetic analyses

6.2.6.1 Population pharmacokinetic analysis to justify the selection of dosage regimen for patients weighing <40 kg (Reference, CTD 5.3.5.4.9)

A population pharmacokinetic (PPK) analysis was conducted using PK data (3,403 timepoints from 202 subjects) of oral tecovirimat from non-Japanese healthy adults participated in 3 clinical studies[68)] (Phoenix NLME version 8.1). The final model was described by a 2-compartment model with first-order absorption by oral administration. The following covariates were selected: meal conditions (fasted or fed conditions) on first order absorption rate constant (Ka); body weight on apparent total clearance (CL/F), apparent volume of distribution in central compartment (Vc/F), apparent intercompartmental clearance (Q/F), and apparent volume of distribution in peripheral compartment (Vp/F); meal conditions (fasted or fed conditions) and clinical study on relative bioavailability (F).[69)]

6.2.6.2 Population pharmacokinetic analysis to justify the selection of dosage regimen for patients weighing ≥40 kg (CTD 5.3.5.3.13)

A PPK analysis was conducted using PK data (4,322 timepoints from 217 subjects) after oral administration of tecovirimat to non-Japanese healthy adults or subjects weighing >120 kg, obtained from 4 clinical studies[70)] (Phoenix NLME version 8.3). The final model was described by a 2-compartment model with first-order

[68)] Study SIGA-246-018 (phase I study), Study SIGA-246-004 (phase II study; tecovirimat 400 or 600 mg was administered orally QD for 14 days under fed conditions to non-Japanese healthy adults [N = 87/group for PK evaluation]), and Study SIGA-246-008 (phase III study)

[69)] Age, body weight, sex, meal conditions (fasted or fed conditions), and clinical study were evaluated as covariates. The median [range] for age and body weight evaluated was 36 years [18, 73] and 78.8 kg [42.3, 145.4].

[70)] Study SIGA-246-018 (phase I study), Study SIGA-246-004 (phase II study), Study SIGA-246-008 (phase III study), and Study SIGA-246-022 (phase IV study)

absorption by oral administration. The following covariates were selected: body weight on CL/F, Vc/F, Q/F, and Vp/F; clinical study on relative bioavailability (F).[71)]

6.R Outline of the review conducted by PMDA

6.R.1 Rationales for selection of dosage regimen

6.R.1.1 Rationale for selecting dosage regimen for patients weighing ≥40 kg

The applicant's explanation about the rationale for selecting dosage regimen for patients weighing ≥40 kg:

Based on the following observations, a target exposure to tecovirimat associated with efficacy in humans was determined to be 0.169 μg/mL, which was the C_{min} of the repeated doses of tecovirimat 10 mg/kg/day administered to MPXV-infected monkeys.

- The minimum dose levels which demonstrated the efficacy of tecovirimat were 3 mg/kg/day in MPXV-infected monkeys and 20 mg/kg/day in RPXV-infected rabbits. Higher doses (10 mg/kg/day and 40 mg/kg/day, respectively) provided greater efficacy [see Sections 3.1.3.1.1 and 3.1.3.2.1].
- The plasma tecovirimat exposures (C_{max}, AUC_{last}, and C_{min}) on Day 14 were higher in MPXV-infected monkeys receiving 10 mg/kg/day than in RPXV-infected rabbits receiving 40 mg/kg/day [see Section 4.1.3].
- It is important to keep the concentration level above the effective concentration in order to maintain the antiviral effect of tecovirimat. C_{min} is considered the PK parameter most correlated with the efficacy of tecovirimat.

Figure 2 (left) shows the PPK model-based predicted C_{min} at steady state after oral administration of tecovirimat 600 mg BID under fed conditions in patients weighing ≥40 kg[72)] [see Section 6.2.6.2]. Although the predicted C_{min} values were generally higher than the target exposure associated with efficacy (C_{min}, 0.169 μg/mL), the C_{min} decreased with increasing body weight, suggesting that the C_{min} was below the target exposure in a certain number of individuals, particularly in the ≥120 kg group. Accordingly, C_{min} at steady state following oral administration of tecovirimat 600 mg TID under fed conditions was simulated[72)] in individuals weighing ≥120 kg. As shown in Figure 2 (right), the results suggested that the C_{min} would far exceed the target exposure. It is recommended that tecovirimat be administered under fed conditions, because tecovirimat exposure (e.g., C_{min}) decreases under fasted conditions compared to fed conditions [see Section 6.1.1].

[71)] Age, body weight, sex, dose level, and clinical study were evaluated as covariates. The median [range] for age and body weight evaluated were 36 years [18, 73] and 82.1 kg [42.3, 220.4].

[72)] Using a PPK model developed with PK data in adult subjects weighing ≥40 kg [see Section 6.2.6.2], hypothetical populations (each consisting of 250 subjects) every 5 kg from ≥40 kg to ≤100 kg, and every 10 kg from ≥100 kg to ≤220 kg were generated to simulate the PK of tecovirimat in these populations.

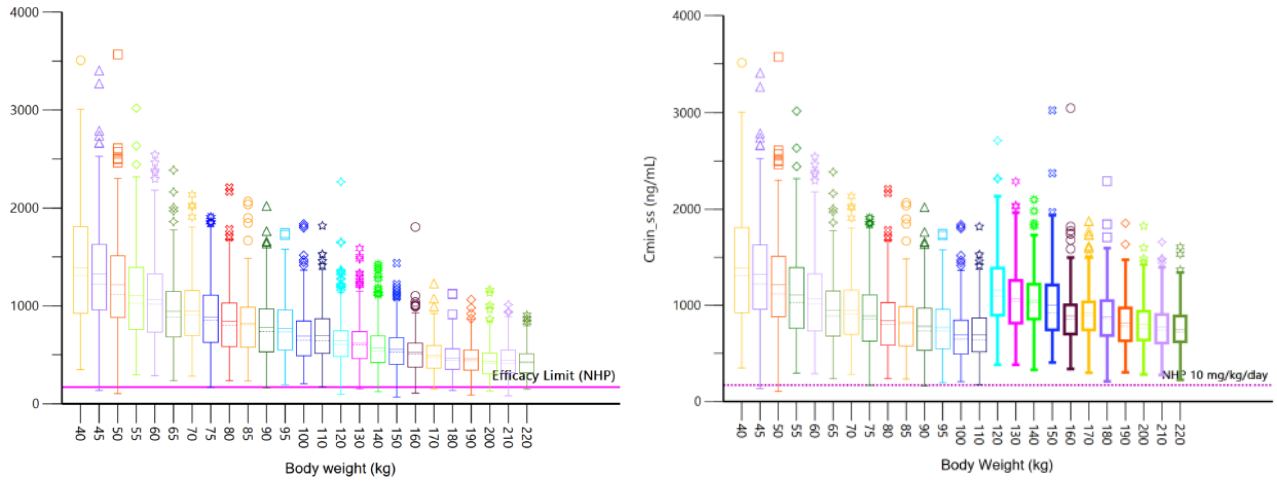

Figure 2. Predicted plasma tecovirimat C_{min} values at steady state when tecovirimat 600 mg was administered orally BID under fed conditions to the group of individuals weighing ≥40 kg (left); tecovirimat 600 mg was administered orally BID under fed conditions to the group of individuals weighing ≥40 kg to <120 kg and TID under fed conditions to the group of individuals weighing ≥120 kg (right)

Box, 25th to 75th percentile of values; solid line in the box, median; dotted line in the box, mean; whiskers, the minimum or maximum value within the range of y = ±2 in the plot of conditional weighted residuals on measured tecovirimat concentrations (the x-axis represents time or predicted tecovirimat concentration); solid and dotted lines in pink, target exposure associated with efficacy (169 ng/mL)

Figure 3 shows the simulated[72] C_{max} at steady state after tecovirimat 600 mg was administered orally under fed conditions BID to the body weight ≥40 kg to <120 kg group or TID to the ≥120 kg group using the PPK model [see Section 6.2.6.2]. The results show that the simulated C_{max} values were generally lower than 5.58 µg/mL, the C_{max} at the NOAEL for central nervous system events such as convulsions noted in dogs.

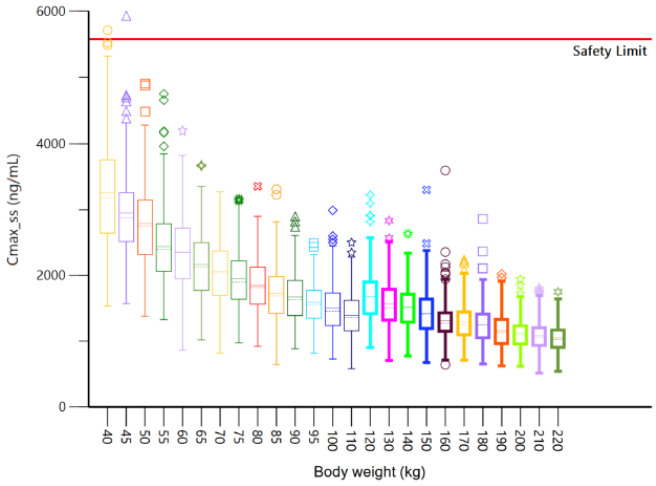

Figure 3. Predicted plasma tecovirimat C_{max} values at steady state when tecovirimat 600 mg was administered orally under fed conditions BID to the ≥40 kg to <120 kg group and TID to the ≥120 kg group

Box, 25th to 75th percentile of values; solid line in the box, median; dotted line in the box, mean; whiskers, the minimum or maximum value within the range of y = ± 2 in the plot of conditional weighted residuals on measured tecovirimat concentrations (the x-axis represents time or predicted tecovirimat concentration); solid line in red, target exposure associated with safety (5,580 ng/mL)

The above results are plasma tecovirimat exposures (C_{max} and C_{min}) estimated based on the PPK model developed using the plasma tecovirimat concentrations in healthy subjects (uninfected humans) [see Section 6.2.6.2]. Given that there were no clear differences in AUC or C_{max} of tecovirimat between uninfected and infected monkeys or rabbits in the non-clinical pharmacokinetic studies [see Section 4.1.3], there will be no clear differences in tecovirimat PK between uninfected and infected humans as well.

While tecovirimat 10 mg/kg/day was demonstrated to be effective in MPXV-infected monkeys when treatment was given for ≥5 days [see Section 3.1.3.1.2], the efficacy of a lower dose (tecovirimat 3 mg/kg/day) was assessed in the 14-day regimen [see Section 3.1.3.1.1]. The mechanism of action of tecovirimat is expected to suppress viral egress from cells before the acquisition of immunity against the virus. Given this, the duration of tecovirimat treatment was determined to be 14 days to be on the safe side.

Based on the above, the dosage regimen was proposed as tecovirimat 600 mg BID for patients weighing ≥40 kg to <120 kg and tecovirimat 600 mg TID for patients weighing ≥120 kg, administered orally under fed conditions for 14 days.

PMDA's view:
It is reasonable to define the dosage regimen, "tecovirimat 600 mg BID for patients weighing ≥40 kg to <120 kg and tecovirimat 600 mg TID for patients weighing ≥120 kg, administered orally under fed conditions for 14 days" aiming to achieve a C_{min} of >0.169 μg/mL and a C_{max} of <5.58 μg/mL based on the data from the non-clinical studies. Although no clinical studies were conducted to evaluate the efficacy of the dosage regimen for tecovirimat in patients with smallpox, etc., the proposed dosage regimen of tecovirimat will be discussed in Section 7.R.5 taking into account the safety data in healthy adults treated with tecovirimat.

6.R.1.2 Rationale for selecting dosage regimen for patients weighing ≥13 kg to <40 kg

The applicant's explanation about the rationale for selecting the dosage regimen for patients ≥13 kg to <40 kg:
The dosage regimen of tecovirimat was explored for patients weighing <40 kg aiming to achieve the target exposure based on non-clinical study data (C_{min} of >0.169 μg/mL and C_{max} of <5.58 μg/mL) [see Section 6.R.1.1], taking into account the range of PK parameters (C_{max}, $AUC_{0\text{-}24h}$, and C_{min}) in healthy adults who had treated with the proposed regimen of oral tecovirimat.

Using the PPK model developed based on the PK data in healthy adults weighing ≥40 kg [see Section 6.2.6.1], simulations[73)] were performed with oral tecovirimat 50, 100, 200, 400, and 600 mg administered BID under fed conditions for 14 days to patients weighing ≥3 kg to <6 kg, ≥6 kg to <13 kg, ≥13 kg to <25 kg, ≥25 kg to <40 kg, and ≥40 kg to <45 kg, respectively, to obtain plasma tecovirimat PK parameters (C_{max}, $AUC_{0\text{-}24h}$, and C_{min}) on Day 1 and at steady state. Figure 4 shows the simulation results, which suggest that C_{min} of >0.169 μg/mL and C_{max} of <5.58 μg/mL are generally achieved in each body weight group.

[73)] Using the PPK model developed based on PK data in adult subjects weighing ≥40 kg [see Section 6.2.6.1], hypothetical groups (N = 250/group) were established by body weight category in the range of ≥3 kg and ≤45 kg, and tecovirimat PK in the hypothetical groups were predicted according to respective dosage regimens for each body weight category.

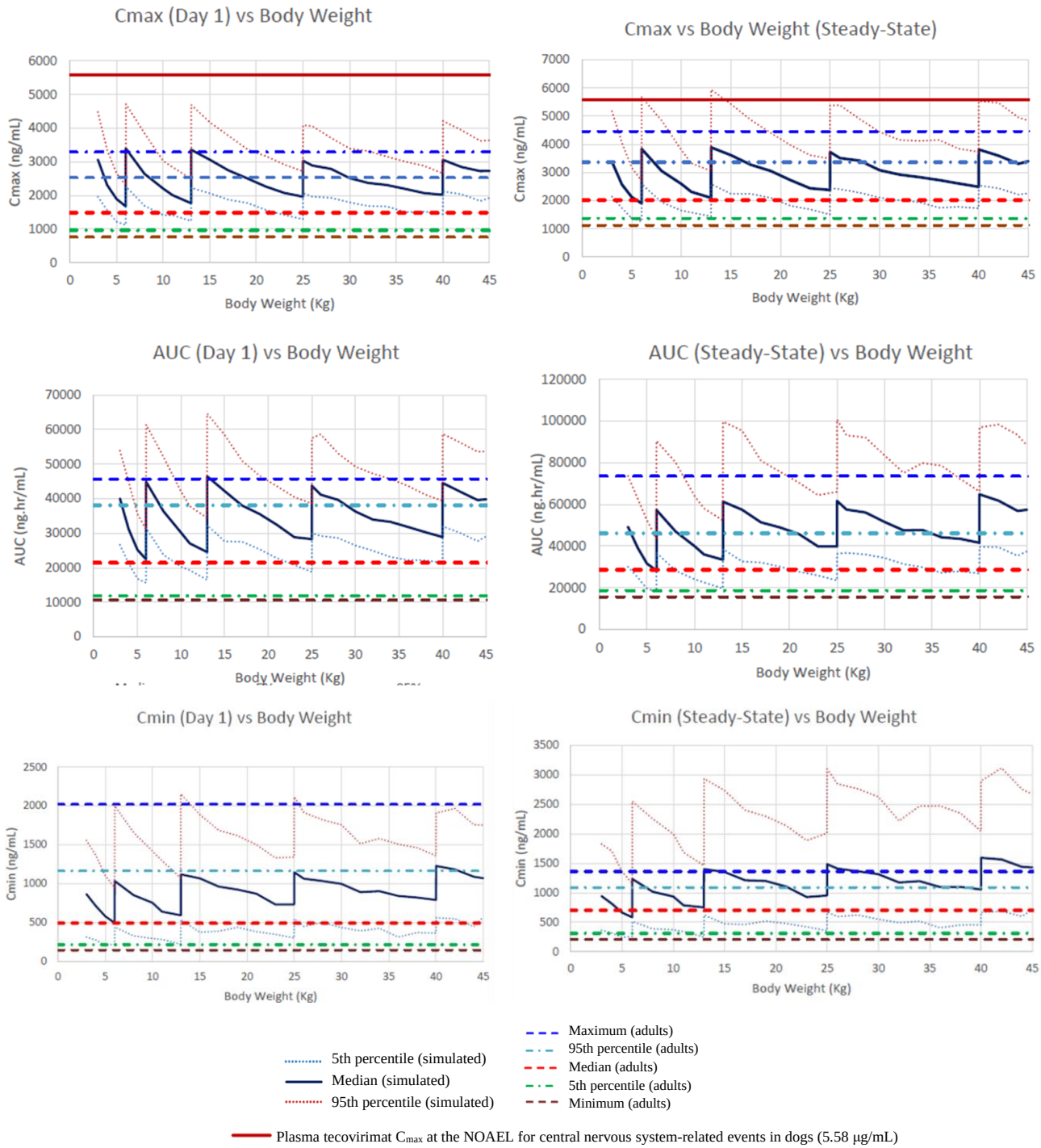

Figure 4. Simulated plasma tecovirimat PK parameters (C_{max}, top; AUC, middle; C_{min}, bottom) on Day 1 (left) and at steady state (right) in patients weighing <40 kg for oral tecovirimat 50, 100, 200, 400, and 600 mg BID by body weight category

According to the plasma tecovirimat PK parameters simulated above (C_{max}, $AUC_{0\text{-}24h}$, and C_{min}), the recommended dosage for patients weighing <13 kg was lower than that per capsule (200 mg), and the need for the development of a new formulation arose. For this reason, the dosage regimen for patients weighing <13 kg was not included in the proposed dosage regimen. The development of a formulation of oral tecovirimat <200 mg is currently underway.

Based on the above, dosage regimens of tecovirimat 200 mg BID for patients weighing ≥13 kg to <25 kg and 400 mg BID for patients weighing ≥25 kg to <40 kg, administered orally under fed conditions for 14 days, were selected.

PMDA's view:

There are no PK data from subjects weighing <40 kg, and the PPK model developed based on PK data from healthy adults weighing ≥40 kg [see Section 6.2.6.1] do not take into account the differences between adults and children in the expression level of drug metabolizing enzymes, organ system maturity, and digestive tract absorption, etc. Therefore, uncertainties remain in the dosage regimens for patients weighing <40 kg including children determined by the PPK model-based PK simulations.

PK data should have been obtained from children, the likely main patient population weighing <40 kg to be treated with tecovirimat. Yet, it is also understandable that difficulty remains in conducting a clinical study immediately to evaluate tecovirimat's PK in pediatric patients and healthy children, in terms of the number of patients and consent acquisition. In addition, the majority of children weighing ≥13 kg, the population covered in the proposed dosage regimen, are aged ≥2 years.[74)] Generally, in children in this age group, digestive tract absorption and most of drug clearance pathways (liver and kidneys) have matured.[75)] Taken together, there is an urgent need to introduce tecovirimat to Japan and have a framework for its use as a measure for public health crisis management, the dosage regimens of tecovirimat for patients weighing ≥13 kg to <40 kg, as in the US and Europe, are acceptable on the premise that post-marketing safety/efficacy data are collected from pediatric patients and the package insert cautions about no clinical studies conducted in children.

6.R.2 Differences in tecovirimat PK between Japanese and non-Japanese populations

The applicant's explanation about the PK in Japanese subjects following the administration of tecovirimat:

Plasma tecovirimat PK parameters (Table 29) following the administration of tecovirimat 600 mg BID orally under fed conditions for 14 days in the Japanese phase I study (Study JBP-TPOXX-001) and foreign phase III study (Study SIGA-246-008) show the parameters comparable between Japanese and non-Japanese subjects. The PK parameters of the main metabolites (M4, M5, and TFMBA) on Day 14 were also similar between these studies [see Sections 6.2.1.1 and 6.2.1.3].

Table 29. PK parameters following administration of tecovirimat 600 mg BID orally under fed conditions for 14 days to Japanese or non-Japanese healthy adults

	Timepoint	N	C_{max} (μg/mL)	t_{max} (h)[a)]	AUC[b)] (μg·h/mL)	$t_{1/2}$ (h)
Japanese JBP-TPOXX-001	Day 1	20	1.73 ± 0.330	4.00 [4.00, 16.0]	21.4 ± 4.63	—
	Day 14	20	1.94 ± 0.515	4.00 [0.00, 8.00]	23.7 ± 6.07	16.4 ± 5.98
Non-Japanese SIGA-246-008	Day 1	48	1.59 ± 0.516	6.06 [2.00, 23.8]	22.0 ± 7.62	—
	Day 14	48	2.21 ± 0.726	3.92 [0.00, 18.0]	30.6 ± 10.7	19.3 ± 5.60

Mean ± standard deviation; "—," Not calculable
a) Median [range]; b) AUC_{last} for Day 1 and $AUC_{0\text{-}24h}$ for Day 14

[74)] Minister of Health, Labour and Welfare, "National growth survey on preschool children FY2010": https://www.mhlw.go.jp/toukei/list/73-22.html (last accessed on October 4, 2024)
[75)] *J Clin Pharmacol*. 2018;58:s10-25

PMDA's view:

Because tecovirimat is metabolized primarily by hydrolysis [see Sections 4.3.1 and 6.2.1.4], it is unlikely that tecovirimat PK varies by ethnicity. However, the mean body weight in the Japanese phase I study (Study JBP-TPOXX-001, 61.9 ± 7.22 kg for Japanese) was lower than that in the foreign phase III study (Study SIGA-246-008, 88.2 ± 27.6 kg for non-Japanese subjects), and body weight was selected as the covariate for volume of distribution and clearance in the PPK model.[76)] Given these outcomes, tecovirimat exposure in Japanese patients may be lower than that in non-Japanese patients with the same weight. Conversely, the lower limit of the target exposure for efficacy (C_{min}, 0.169 μg/mL) is based on the exposure obtained at doses for MPXV-infected monkeys (10 mg/kg/day) and RPXV-infected rabbits (40 mg/kg/day) that are respectively one level higher than the minimum doses (3 mg/kg/day in monkeys, 20 mg/kg/day in rabbits) at which tecovirimat efficacy was demonstrated. Since decreased exposure is unlikely to affect efficacy in Japanese patients, a proposed dosage regimen that is the same as that of the US and Europe is acceptable.

6.R.3 PK of tecovirimat in patients with renal or hepatic impairment

The applicant's explanation about the PK of tecovirimat in patients with renal or hepatic impairment:

The exposure to main metabolites (M4, M5, and TFMBA) following a single oral dose of tecovirimat 600 mg tended to increase in patients with renal or hepatic impairment compared to that in patients with normal renal or hepatic function [see Sections 6.2.3.1 and 6.2.3.2]. However, it is considered possible to administer tecovirimat to patients with renal or hepatic impairment without dose adjustment based on the following:

- In the foreign phase I studies (Studies SIGA-246-012 and SIGA-246-013) in subjects with renal or hepatic impairment, there were no consistent trends in the degree of renal or hepatic impairment, or the type and incidence of adverse events.
- While adverse events resulted in death (cholecystitis, sepsis, acute myocardial infarction, and acute cardiac event) in 1 subject with moderate hepatic impairment in Study SIGA-246-013, a causal relationship to the study drug was ruled out for these events, which occurred 18 to 20 days after the administration of tecovirimat. Other than this case, no subjects with renal or hepatic impairment experienced serious adverse events in either Study SIGA-246-012 or SIGA-246-013.

PMDA's view:

The foreign phase I studies were conducted as single-dose studies in subjects with renal impairment (Study SIGA-246-012) and in subjects with hepatic impairment (Study SIGA-246-013). It is considered that the exposure to the main metabolites (M4, M5, and TFMBA) at steady state increases after multiple doses of tecovirimat administered to patients with renal or hepatic impairment as compared to that after single-dose administration. The safety of multiple oral doses of tecovirimat was demonstrated in subjects including those with mild and moderate renal impairment in the foreign phase III study (Study SIGA-246-008), for which subjects with CL_{cr} ≥30 mL/min/1.73 m^2 were eligible.[77)] However, the safety of multiple oral doses of tecovirimat has not been evaluated in subjects with other degrees of renal or hepatic impairment. The exposure

[76)] The volume of distribution and clearance tended to increase with increased body weight.
[77)] The minimum baseline CL_{cr} in subjects who actually received tecovirimat was 48 mL/min/1.73 m^2.

to the main metabolites (M4, M5, and TFMBA) may increase in patients with end-stage kidney disease or severe hepatic impairment compared to those with mild or moderate renal impairment, in whom the safety of multiple oral doses of tecovirimat was demonstrated in the foreign phase III study (Study SIGA-246-008) [see Sections 6.2.3.1 and 6.2.3.2].

Based on the above, the package insert should caution that the use of tecovirimat in patients with end-stage kidney disease or severe hepatic impairment may lead to increased plasma concentrations of metabolites, and that no clinical studies have been conducted to evaluate the safety of multiple oral doses of tecovirimat in these populations. In the post-marketing setting, safety data on multiple doses of tecovirimat should be gathered from these patients treated with the proposed dosage regimen, and healthcare professionals should be promptly provided with new findings.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

For the present application, the applicant submitted the main safety data at the proposed dosage regimen in the form of results data from the clinical studies shown in Table 30.

Table 30. Outline of main clinical studies

Data	Location	Study ID	Phase	Study population	Number of subjects enrolled	Summary of dosage regimen	Main endpoint
Evaluation	Japan	JBP-TPOXX-001	I	Healthy adults	20	Tecovirimat 600 mg BID orally for 14 days	Safety PK
	Foreign	SIGA-246-015	I	Healthy adults	78	Period 2: Tecovirimat 600 mg BID orally under fed conditions for 15 days [for the dosage regimens for Periods 1 and 3, see Section 7.2]	Safety PK
		SIGA-246-008	III	Healthy adults	(1) 338 (2) 84	(1) Tecovirimat 600 mg BID orally for 14 days (2) Placebo BID orally for 14 days	Safety PK

7.1 Japanese phase I study (CTD 5.3.3.1.1 through 5.3.3.1.10, Study JBP-TPOXX-001 [July 2023 to August 2023])

An open-label, uncontrolled study was conducted in Japan to assess the safety and PK of tecovirimat in healthy adults aged ≥18 years and ≤50 years (target sample size, 20 subjects).

Subjects received tecovirimat 600 mg BID orally for 14 days.
All 20 subjects enrolled in the study received the study drug, and were included in the safety analysis set.

Table 31 shows the adverse events and adverse reactions[78)] reported in the study. There were no serious adverse events nor any adverse events resulting in death or treatment discontinuation.

Table 31. Reported adverse events and adverse reactions (safety analysis set, N = 20)

Event	Adverse events	Adverse reactions
Overall	9 (45.0)	7 (35.0)
Headache	7 (35.0)	4 (20.0)
Diarrhoea	2 (10.0)	2 (10.0)
Malaise	1 (5.0)	1 (5.0)

n (%); MedDRA/J ver.26.0

78) Adverse events that were determined to be causally related to the study drug

7.2 Foreign phase I study (CTD 5.3.3.4.1 through 5.3.3.4.25, Study SIGA-246-015 [October 2016 to December 2016])

An open-label, randomized study was conducted in the US to evaluate the PK and safety of tecovirimat in combination with substrates for CYP isoforms in healthy adults aged ≥18 years and ≤50 years (target sample size, approximately 78 subjects).

This was a 3-arm study consisting of 3 periods. The dosage regimen for each arm and period is presented in Table 32.

Table 32. Dosage regimens of the foreign phase I study (Study SIGA-246-015)

Treatment period	Arm 1	Arm 2	Arm 3
Period 1 (Day 1)	A single oral dose of each of the CYP isoform substrates (flurbiprofen 50 mg, omeprazole 20 mg, and midazolam 2 mg in combination) under fed conditions	A single oral dose of the CYP isoform substrate (repaglinide 2 mg) under fed conditions	A single oral dose of the CYP isoform substrate (bupropion 150 mg) under fed conditions
Washout period[a)] (Days 2-7)	No treatment	No treatment	No treatment
Period 2 (Days 8-21)	Oral tecovirimat 600 mg BID under fed conditions for 14 days	Same as on the left	Same as on the left
Period 3 (Day 22)	A single oral dose of each of the CYP isoform substrates (flurbiprofen 50 mg, omeprazole 20 mg, and midazolam 2 mg) in combination with tecovirimat under fed conditions	A single oral dose of the CYP isoform substrate (repaglinide 2 mg) in combination with tecovirimat under fed conditions	A single oral dose of the CYP isoform substrate (bupropion 150 mg) in combination with tecovirimat under fed conditions

a) The washout period was approximately ≥5 half-lives for each CYP isoform substrate.

This section describes safety results from Period 2, in which tecovirimat alone was administered.

All 78 randomized subjects (24 subjects in Arm 1; 30 subjects in Arm 2; and 24 subjects in Arm 3) received the study drug and were included in the safety analysis set.

In Period 2 (Arms 1-3 combined), the incidence of adverse events was 28.2% (22 of 78 subjects) and the incidence of adverse reactions[79)] was 17.9% (14 of 78 subjects). Table 33 shows the adverse events and adverse reactions occurring in ≥2 subjects. There were no serious adverse events nor any adverse events leading to death or treatment discontinuation.

[79)] Adverse events that were determined to be causally related to the study drug. The causal relationship to the study drug was rated by the principal investigator, etc. into 5 levels (definitely related, probably related, possibly related, unlikely related, and not related). Adverse events rated as "definitely related," "probably related," or "possibly related" were determined to be causally related to the drug.

Table 33. Adverse events and adverse reactions occurring in ≥2 subjects in Period 2 (Arms 1-3 combined) (safety analysis set, N = 78)

Event	Adverse events	Adverse reactions
Overall	22 (28.2)	14 (17.9)
Nausea	5 (6.4)	3 (3.8)
Headache	5 (6.4)	5 (6.4)
Dizziness	5 (6.4)	1 (1.3)
Decreased appetite	4 (5.1)	4 (5.1)
Abdominal pain	4 (5.1)	4 (5.1)
Infrequent bowel movements	4 (5.1)	4 (5.1)
Insomnia	3 (3.8)	2 (2.6)
Vomiting	2 (2.6)	2 (2.6)
Acne	2 (2.6)	0
Diarrhoea	2 (2.6)	2 (2.6)
Nasopharyngitis	2 (2.6)	0

n (%); MedDRA ver.19.0

7.3 Foreign phase III study (CTD 5.3.5.1.1 through 5.3.5.1.33, Study SIGA-246-008 [June 2015 to August 2016])

A double-blind, randomized, placebo-controlled, parallel-group study was conducted in the US to evaluate the safety and PK of tecovirimat in healthy adults aged ≥18 years and ≤ 80 years (target sample size, 422 subjects [338 in the tecovirimat group and 84 in the placebo group]).

Subjects received tecovirimat 600 mg or placebo BID orally for 14 days. The study drug was administered under fed or fasted conditions in the lead-in cohorts (20 subjects each [16 in the tecovirimat group and 4 in the placebo group]), and under fed conditions in the expanded cohorts to all subjects (306 in the tecovirimat group and 76 in the placebo group).

Of the 452 randomized subjects (361 in the tecovirimat group and 91 in the placebo group), 449 subjects (359 in the tecovirimat group and 90 in the placebo group) received ≥1 dose of the study drug and were included in the safety analysis set.

In the tecovirimat group, the incidence of adverse events was 37.3% (134 of 359 subjects), and the incidence of adverse reactions[79)] was 19.8% (71 of 359 subjects). In the placebo group, the incidence of adverse events was 33.3% (30 of 90 subjects) and the incidence of adverse reactions was 16.7% (15 of 90 subjects). Table 34 shows adverse events and adverse reactions occurring in ≥2% in either group.

Table 34. Adverse events and adverse reactions occurring in ≥2% of subjects in either group (safety analysis set)

Event	Adverse events		Adverse reactions	
	Tecovirimat (N = 359)	Placebo (N = 90)	Tecovirimat (N = 359)	Placebo (N = 90)
Overall	134 (37.3)	30 (33.3)	71 (19.8)	15 (16.7)
Headache	61 (17.0)	13 (14.4)	44 (12.3)	7 (7.8)
Nausea	20 (5.6)	5 (5.6)	16 (4.5)	4 (4.4)
Diarrhoea	11 (3.1)	3 (3.3)	7 (1.9)	2 (2.2)
Dizziness	9 (2.5)	3 (3.3)	4 (1.1)	1 (1.1)
Vomiting	9 (2.5)	0	7 (1.9)	0
Fatigue	5 (1.4)	4 (4.4)	3 (0.8)	3 (3.3)
Constipation	5 (1.4)	2 (2.2)	2 (0.6)	2 (2.2)
Somnolence	2 (0.6)	2 (2.2)	2 (0.6)	1 (1.1)
Back pain	1 (0.3)	2 (2.2)	0	0
Oropharyngeal pain	1 (0.3)	2 (2.2)	1 (0.3)	0

n (%); MedDRA ver.18.0

In the tecovirimat group, 1 subject had an adverse event (pulmonary embolism) resulting in death, and its causal relationship to the study drug was ruled out. No serious adverse events occurred. Adverse events led to treatment discontinuation in 6 subjects in the tecovirimat group (nausea [3 subjects]; pyrexia [2 subjects]; electroencephalogram abnormal, fatigue, abdominal discomfort, dry mouth, dysphoria, disturbance in attention, diarrhoea, headache, palpable purpura, chills, erythema, pruritus, and swelling face [1 subject each]; some subjects experienced >1 event) and in 2 subjects in the placebo group (fatigue [2 subjects]; nausea, nightmare, and dizziness [1 subject each]; some subjects experienced >1 event). Among these events, a causal relationship to the study drug could not be ruled out for 5 subjects in the tecovirimat group (nausea [3 subjects]; pyrexia [1 subject]; electroencephalogram abnormal, fatigue, abdominal discomfort, dry mouth, dysphoria, disturbance in attention, diarrhoea, headache, and palpable purpura [1 subject each]; some subjects experienced >1 event) and 2 subjects in the placebo group (fatigue [2 subjects], nausea, nightmare [1 subject each]; some subjects experienced >1 event). All events resolved.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

PMDA's view:

The US approved tecovirimat for smallpox under the Animal Rule based on the non-clinical study results using 2 types of surrogate animal models, i.e., monkeys infected with MPXV and rabbits infected with RPXV. In Europe, tecovirimat was also approved for the treatment of not only smallpox but also mpox, cowpox, and complications due to replication of vaccinia virus following smallpox vaccination (exceptional circumstances authorization) caused by infection or replication of MPXV, CPXV, or VACV, for which antiviral activity of tecovirimat was demonstrated in the non-clinical studies. In Japan, the marketing application was submitted without data from clinical studies targeting patients with smallpox, mpox, cowpox, or complications due to replication of vaccinia virus following smallpox vaccination, as in the US and Europe. Nevertheless, the submitted non-clinical study data and PK data of healthy subjects [see Sections 3.R.1, 6.R.1, and 6.R.2] suggest potential efficacy of tecovirimat against these diseases and complications.

The applicant should, however, gather as much data on the efficacy of tecovirimat as possible from patients with these illnesses in the post-marketing setting, and healthcare professionals should be provided with new findings promptly.

The above conclusion by PMDA will be further discussed at the Expert Discussion.

7.R.2 Safety

The applicant's explanation about the safety profile of tecovirimat:

Table 35 summarizes the safety data from the foreign phase III study (Study SIGA-246-008). The incidences of adverse events and adverse reactions in the tecovirimat group were similar to those in the placebo group. Adverse events occurring more frequently in the tecovirimat group compared to the placebo group were headache (14.4% in the placebo group and 17.0% in the tecovirimat group) and vomiting (0% in the placebo group and 2.5% in the tecovirimat group) [see Table 34 and Section 7.3].

Table 35. Summary of safety data in the foreign phase III study (Study SIGA-246-008) (safety analysis set)

	Tecovirimat (N = 359)	Placebo (N = 90)
Adverse events	134 (37.3)	30 (33.3)
Adverse reactions	71 (19.8)	15 (16.7)
Serious adverse events	0	0
Adverse events resulting in death	1 (0.3)	0
Adverse events leading to treatment discontinuation	6 (1.7)	2 (2.2)

n (%)

Adverse events resulted to death in 1 subject (pulmonary embolism) in the tecovirimat group in the foreign phase III study (Study SIGA-246-008) and 1 subject (cholecystitis, sepsis, acute myocardial infarction, acute cardiac event) in the tecovirimat group in the foreign phase I study in patients with hepatic impairment (Study SIGA-246-013) [see Section 6.2.3.2]. A causal relationship to the study drug was ruled out for these events. The most of other reported adverse events were mild or moderate in severity, with no significant safety issues.

In the Japanese phase I study (Study JBP-TPOXX-001), the incidence of adverse events was 45.0% and the incidence of adverse reactions was 35.0%. There were no serious adverse events or adverse events leading to death or treatment discontinuation. There were no particular safety concerns in Japanese patients.

PMDA's view:
The present application was submitted without results from clinical studies targeting patients eligible for tecovirimat. However, given no safety concerns with tecovirimat in Japanese and foreign clinical studies targeting healthy adults, the safety risk of tecovirimat is considered manageable.

The above conclusion by PMDA will be further discussed at the Expert Discussion.

7.R.3 Clinical positioning

PMDA's view on clinical positioning of tecovirimat:
Currently, there are no therapeutic drugs for smallpox, mpox, and cowpox, and complications due to replication of vaccinia virus following smallpox vaccination in Japan. Tecovirimat will be a novel therapeutic drug for the treatment of these diseases.

The current lack of clinical study data from patients precludes data-based discussion on the clinical positioning of tecovirimat. According to mpox treatment guidelines (the Guidance on clinical treatment of mpox, ver.2.0 [in Japanese]), patients with severe mpox and those at a high risk of potentially severe mpox (e.g., children, pregnant women, and immunocompromised patients) may suffer serious deterioration in condition, and early start of tecovirimat treatment should be considered for these patients, taking into account the recommendation by the US CDC. Tecovirimat is intended for use primarily in a public health crisis or in preparation for a crisis anticipated. Thus, recommended target populations for tecovirimat treatment are assumed to be determined as the situation demands.

The above conclusion by PMDA will be further discussed at the Expert Discussion.

7.R.4 Indication

In view of the discussions on efficacy [see Section 7.R.1] and safety [see Section 7.R.2], PMDA concluded that the indication may be modified as follows, with reference to medical terminology-based disease names and indications used for other products.

Proposed indication

Treatment of the following viral infections in adult and pediatric patients weighing ≥13 kg:
Smallpox, mpox, and cowpox
Treatment of complications due to replication of vaccinia virus following smallpox vaccination

Modified indication

Treatment of smallpox, mpox, and cowpox, and complications due to replication of vaccinia virus following smallpox vaccination

The above conclusion by PMDA will be further discussed at the Expert Discussion.

7.R.5 Dosage and administration

In view of the discussions on the rationale for the dosage regimen [see Section 6.R.1], differences in PK between Japanese and non-Japanese populations [see Section 6.R.2], efficacy [see Section 7.R.1], and safety [see Section 7.R.2], PMDA concluded that the proposed dosage and administration may be modified as follows.

Proposed dosage and administration

Patients weighing 13 kg to <25 kg:
Tecovirimat 200 mg orally twice daily (every 12 hours) for 14 days, within 30 minutes after a meal
25 kg to <40 kg:
Tecovirimat 400 mg orally twice daily (every 12 hours) for 14 days, within 30 minutes after a meal
40 kg to <120 kg:
Tecovirimat 600 mg orally twice daily (every 12 hours) for 14 days, within 30 minutes after a meal
≥120 kg:
Tecovirimat 600 mg orally 3 times daily (every 8 hours) for 14 days, within 30 minutes after a meal

Modified dosage and administration

The usual dosages for adults and children are as follows, administered orally after a meal for 14 days:
Patients weighing 13 kg to <25 kg:
Tecovirimat 200 mg twice daily (every 12 hours)
25 kg to <40 kg:
Tecovirimat 400 mg twice daily (every 12 hours)

40 kg to <120 kg:
Tecovirimat 600 mg twice daily (every 12 hours)
≥120 kg:
Tecovirimat 600 mg 3 times daily (every 8 hours)

The above conclusion by PMDA will be further discussed at the Expert Discussion.

7.R.6 Post-marketing investigations

PMDA's view of post-marketing investigations:
The evaluation results based on non-clinical study data [see Section 3.R.1] submitted, as in Europe, etc., suggest that tecovirimat may have efficacy in the treatment of the indicated diseases. However, because of the lack of clinical study data from these patients, the applicant needs to collect as much efficacy data as possible through post-marketing surveillance, etc. Also, because of the lack of clinical study data from children, uncertainties remain on appropriate dosage regimens for pediatric patients [see Section 6.R.1.2]. The post-marketing surveillance, etc. should also serve to collect safety and efficacy data from pediatric patients.

In view of the extremely small number of patients with the indicated diseases, the surveillance needs to involve all patients on tecovirimat to collect efficacy data certainly and promptly from patients treated. However, because of anticipated difficulty in conducting all-case surveillance in an actual public health crisis, the surveillance should be planned and implemented flexibly as the situation demands.

The following issues also need to be addressed as soon as practicable after the market launch:

- Discuss measures to control the impurity SG2 within acceptable intake levels according to ICH M7 (R2) guidelines, and develop a highly sensitive SG2 detection method [see Section 2.R.1].
- Evaluate the safety of other impurities for which mutagenic hazard assessments have not been fully performed in accordance with the ICH M7 (R2) guidelines, and establish a necessary control strategy [see Section 2.R.1].
- Keep vigilance against potential tecovirimat-resistant viruses including those reported in published literature, and offer new findings to healthcare professionals promptly [see Section 3.R.2].
- Continue to collect information about drug interactions with tecovirimat, and offer new findings to healthcare professionals promptly[see Section 4.R.1].
- Plan and conduct necessary non-clinical toxicity studies on the metabolite TFMBA for the qualification of safety in accordance with the ICH M3 (R2) guidelines [see Section 5.R.3].
- Continue to collect information about the safety of multiple doses of tecovirimat administered as per the proposed regimen to patients with end-stage kidney disease or severe hepatic impairment. Offer new findings to healthcare professionals promptly [see Section 6.R.3].
- Confirm the results of ongoing or planned clinical studies to assess the efficacy and safety of tecovirimat in patients treated for the proposed indication as soon as the results and relevant published literature become accessible, and offer new findings to healthcare professionals promptly.

The above conclusion by PMDA will be further discussed at the Expert Discussion.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.3.1.1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation during Preparation of the Review Report (1)

The data submitted do not adequately demonstrate the efficacy of tecovirimat due to the lack of studies evaluating efficacy in humans against smallpox, mpox, and cowpox, and complications due to replication of vaccinia virus following smallpox vaccination. However, based on data including non-clinical study results that have demonstrated its antiviral effect, tecovirimat has promising efficacy with acceptable safety in view of benefits expected. Therefore, it is meaningful to approve the product for its potential use primarily in a public health crisis or in preparation for a crisis anticipated.

PMDA has concluded that tecovirimat may be approved if tecovirimat is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

November 26, 2024

Product Submitted for Approval

Brand Name	Tepoxx Capsules 200 mg
Non-proprietary Name	Tecovirimat Hydrate
Applicant	Japan Biotechno Pharma Co., Ltd.
Date of Application	April 10, 2024

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations, etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy

At the Expert Discussion, the expert advisors supported PMDA's conclusion presented in Section "7.R.1 Efficacy" in Review Report (1).

Separately from the present application, a preliminary report was released in August 2024 from ongoing randomized, placebo-controlled, double-blind, parallel-group study (Study PALM007, NCT05559099[80]) conducted in the Democratic Republic of the Congo, led by the US National Institute of Allergy and Infectious Diseases (NIAID), etc., to assess the safety and efficacy of tecovirimat in adult and pediatric patients with mpox. The report provided the following outcomes.[81]

- The results did not demonstrate the statistical superiority of tecovirimat over placebo in terms of time to lesion resolution, the primary endpoint.
- The results suggested clinical benefits of tecovirimat compared to placebo in patients who were treated early and those with serious diseases.

[80] CrinicalTrials.gov: https://clinicaltrials.gov/study/NCT05559099 (last accessed on November 26, 2024)

[81] SIGA Technologies Inc. Press release: https://investor.siga.com/investors/news/news-details/2024/Topline-Results-from-PALM-007-Study-of-SIGAs-Tecovirimat-in-Treatment-of-Mpox-Released/default.aspx (last accessed on November 26, 2024)
US NIH Press release: https://www.nih.gov/news-events/news-releases/antiviral-tecovirimat-safe-did-not-improve-clade-i-mpox-resolution-democratic-republic-congo (last accessed on November 26, 2024)

- The overall mortality in patients enrolled in the study was 1.7%, which is lower than the mpox mortality of ≥3.6% reported in the Democratic Republic of the Congo. This suggests that high quality supportive care under hospitalization contributes to the lower mortality of patients with mpox.
- The mortality of patients in the placebo group was lower than expected, which may have led to the reduction in benefits measured in the tecovirimat group.
- The results demonstrated tecovirimat's favorable safety profile.

At the Expert Discussion, PMDA expressed the following views on the influence of the preliminary results of Study PALM007 on this review. The expert advisors supported the PMDA's conclusions.

- Albeit unknown details of Study PALM007 in patients with mpox, the efficacy of tecovirimat was not demonstrated possibly because of the lower-than-estimated mortality in the placebo group, as mentioned in published literature. This might have prevented the demonstration of statistically significant efficacy of tecovirimat in the overall population.
- The efficacy of tecovirimat against mpox is subject to further evaluation based on more detailed results of Study PALM007 or data from ongoing or planned other clinical studies.
- Based on the currently available preliminary results of Study PALM007, the approval of tecovirimat remains meaningful in preparation for a potential public health crisis.
- The preliminary report of Study PALM007 suggested clinical benefits of tecovirimat in patients who had started treatment early and in those with serious diseases. On this point, the following actions have been taken appropriately in this approval:
  - In the non-clinical studies, tecovirimat treatment started soon after infection tended to produce to greater effect [see Section 3.1.3.1.2 in Review Report (1)]. The package insert will advise immediate start of tecovirimat treatment after the onset of symptoms.
  - The treatment guidance in Japan (the Guidance on clinical treatment of mpox, ver.2.0) states that early start of tecovirimat treatment should be considered for patients with severe mpox and those at an increased risk of potentially severe mpox such as children, pregnant women, and immunocompromised patients.

Based on the above, PMDA instructed the applicant to confirm more detailed results of Study PALM007 and other ongoing or planned clinical studies, including published literature, as soon as they become accessible, and offer new findings to healthcare professionals promptly. The applicant agreed.

1.2 Safety, clinical positioning, indication, and dosage and administration

At the Expert Discussion, the expert advisors supported PMDA's conclusion presented in Sections "7.R.2 Safety," "7.R.3 Clinical positioning," "7.R.4 Indication," and "7.R.5 Dosage and administration" in Review Report (1). The expert advisors also made the following comments.

- Highly fatal mpox clade I has begun to spread worldwide. It can further spread, affecting children, pregnant women, and immunocompromised patients, etc., who are at an increased risk of potentially

severe diseases. The use of therapeutic drugs needs to be actively promoted among the populations with increased risk of severe mpox, and such therapeutic drugs must be made ready for use urgently.

1.3 Risk management plan (draft)

At the Expert Discussion, the expert advisors supported PMDA's conclusion presented in Section "7.R.6 Post-marketing investigations" in Review Report (1).

In view of the discussions in Review Report (1) and at the Expert Discussion, PMDA has concluded that the risk management plan (draft) for tecovirimat should be modified and include the safety and efficacy specifications presented in Table 36, and that the applicant should conduct additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities presented in Table 37. PMDA instructed the applicant to implement post-marketing surveillance so that these issues are investigated. PMDA also instructed to address the issues mentioned in Section 7.R.6 in Review Report (1) in the post-marketing setting as soon as practicable.

Table 36. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
None	None	• Safety in pediatric patients
Efficacy specification		
• Collect efficacy information in practical use		

Table 37. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified use-results survey (all-case surveillance)	• Specified use-results survey (all-case surveillance) • Confirm the results of ongoing or planned clinical studies in patients eligible for tecovirimat treatment to assess its efficacy and safety, based on actual study results and relevant published literature accessible.	• Disseminate information from early post-marketing phase vigilance

The applicant plans to conduct a specified use-results survey (all-case surveillance) as shown in Table 38 to assess the safety and efficacy of tecovirimat in clinical use. The applicant stated that other issues mentioned in Section 7.R.6 in Review Report (1) will also be addressed in the post marketing setting as early as practicable.

Table 38. Outline of specified use-results survey (draft)

Objective	To assess the safety and efficacy of tecovirimat in clinical use
Survey method	All-case surveillance (however, in case of a public crisis or other situations where initiation of the survey or implementation of all-case surveillance is difficult, consult with PMDA)
Population	All patients receiving tecovirimat
Observation period	For 28 days after the start of tecovirimat
Planned sample size	All patients receiving tecovirimat
Main survey items	• Patient characteristics • Disease name, tecovirimat treatment status • Pretreatment drugs, concomitant drugs, concomitant therapy • Time to fever reduction, time to clinical symptom resolution, outcome (hospitalization/death) • Laboratory data • Adverse events

PMDA accepted the applicant's response. Obtained data should be provided to healthcare professionals in an appropriate manner.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the modified proposed indication and dosage and administration below, with the following approval conditions. Because the product is a drug with a new active ingredient, the re-examination period is 8 years. The product is not classified as a biological product or a specified biological product. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

Indication

Treatment of smallpox, mpox, and cowpox, and complications due to replication of vaccinia virus following smallpox vaccination

Dosage and Administration

The usual dosages for adults and children are as follows, administered orally after a meal for 14 days:
Patients weighing 13 kg to <25 kg:
Tecovirimat 200 mg twice daily (every 12 hours)
25 kg to <40 kg:
Tecovirimat 400 mg twice daily (every 12 hours)
40 kg to <120 kg:
Tecovirimat 600 mg twice daily (every 12 hours)
≥120 kg:
Tecovirimat 600 mg 3 times daily (every 8 hours)

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to conduct a post-marketing use-results survey involving all patients treated with the product wherever possible until data are obtained from a specified number of patients.

Appendix

List of Abbreviations

(Q)SAR	(Quantitative) Structure-Activity Relationship
A/G	Albumin/Globulin ratio
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AUC	Area under the concentration versus time curve
$AUC_{0\text{-}t\ h}$	Area under the concentration-time curve from time 0 to t hours post-dose
AUC_{inf}	Area under the concentration-time curve from time 0 to infinity
AUC_{last}	Area under the concentration-time curve from time 0 to the last observed concentration
BCRP	Breast cancer resistance protein
BID	bis in die
BMI	Body mass index
BUN	Blood urea nitrogen
CC_{50}	50% cytotoxicity concentration
CEV	Cell-associated enveloped virus
CL/F	Apparent total clearance
CL_{cr}	Creatinine clearance
C_{max}	Maximum concentration
C_{min}	Minimum concentration
CMLV	Camelpox virus
CPP	Critical process parameter
CPXV	Cowpox virus
CQA	Critical quality attribute
C_{trough}	Trough concentration
CV	Coefficient of variation
CYP	Cytochrome P450
DNA	Deoxyribonucleic acid
DS	Design space
EC_{50}	50% effective concentration
EEV	Extracellular enveloped virus
eGFR	Estimated glomerular filtration rate
F	Bioavailability
GC	Gas chromatography
GFP	Green Fluorescent protein
HDPE	High-density polyethylene
HPLC	High performance liquid chromatography
IC_{50}	50% inhibitory concentration
ICH	International Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human Use
ICH M3 (R2) guidelines	ICH M3 (R2) Guidelines: Regarding “the Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals” (PFSB/ELD Notification No. 0219-4 dated February 19, 2010)
ICH M7 (R2) guidelines	ICH M7 (R2) Guidelines: Partial Revision of “the Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk” (PSB/PED Notification No. 0214-1 dated February 14, 2024)
IEV	Intracellular enveloped virus
IFN-γ	Interferon-γ
IMV	Intracellular mature virus
IR	Infrared absorption spectroscopy

ITT	Intention-to-treat
Ka	First order absorption rate constant
LC/MS	Liquid chromatography/mass spectrometry
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LD_{50}	Lethal dose
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MPXV	Monkeypox virus
NADPH	Nicotinamide adenine dinucleotide phosphate
NMR	Nuclear magnetic resonance spectroscopy
NZW	New Zealand White
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
PFU	Plaque forming unit
P-gp	P-glycoprotein
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	Population pharmacokinetics
Q/F	Apparent intercompartmental clearance
QD	quaque die
QTc	Corrected QT
QTcF	QT interval corrected using Fridericia's correction formula
RH	Relative humidity
RPXV	Rabbitpox virus
$t_{1/2}$	Estimate of the terminal half-life
Tecovirimat	Tecovirimat or tecovirimat hydrate
Tepoxx	Tepoxx Capsules 200 mg
TFMBA	Trifluoromethyl benzoic acid
TID	ter in die
t_{max}	Time to maximum concentration
UGT	Uridine glucuronosyl transferase
US CDC	The U.S. Centers for Disease Control and Prevention
US FDA	The U.S. Food and Drug Administration
UV-VIS	Ultraviolet-visible spectroscopy
VACV	Vaccinia virus
VARV	Variola virus
Vc/F	Apparent volume of distribution in central compartment
Vp/F	Apparent volume of distribution in peripheral compartment
WHO	World Health Organization