11 November 2021
EMA/703119/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tecovirimat SIGA

International non-proprietary name: tecovirimat

Procedure No. EMEA/H/C/005248/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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List of abbreviations

AUC	Area under the plasma concentration-time curve
AUC_{0-24}	Area under the plasma concentration-time curve from time zero to 24 hours
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to time t
AUC_{last}	Area under the plasma concentration-time curve from time zero to last quantifiable concentration
AUC_r	Area under the plasma concentration-time curve for the dosing interval
BCS	Biopharmaceutics Classification System
CFU	Colony Forming Units
C_{avg}	Average plasma concentration at steady state
CL/F	Total body clearance normalised for fraction of dose absorbed
CLR	Renal clearance
C_{max}	Maximum plasma concentration
C_{min}	Minimim plasma concentration
CPP	Critical process parameter
CQA	Critical Quality Attribute
DoE	Design of experiments
EC_{50}	Concentration that causes 50% maximal effect
FT-IR	Fourier Transform Infrared Spectroscopy
GC	Gas Chromatography
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
IC_{50}	Concentration that causes 50% maximal inhibition
ICP-MS	Inductively coupled plasma mass spectrometry
IR	Infrared
K_2	Absorption rate constant
KF	Karl Fischer titration
NMR	Nuclear Magnetic Resonance
Ph. Eur.	European Pharmacopoeia
QbD	Quality by design
Q/F	Inter-compartmental clearance
QTPP	Quality target product profile
R_{AC}	Accumulation ratio
RH	Relative Humidity
$t_{1/2}$	Terminal elimination half-life (also defined as $t_{1/2\beta}$ for multi-compartmental models)
t_{lag}	Time from dose to the first measurable (non-zero) plasma concentration
t_{max}	Time to maximum plasma concentration
TSE	Transmissible Spongiform Encephalopathy
TTC	Threshold of toxicological concern
TYMC	Total Combined Yeasts/Moulds Count
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
V_c/F	Apparent central volume of distribution normalised for the fraction of dose absorbed
V_p/F	Apparent peripheral volume of distribution normalised for the fraction of dose absorbed
V_z/F	Apparent volume of distribution during the terminal phase normalised for the fraction of dose absorbed
XRPD	X-Ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant SIGA Technologies Netherlands B.V. submitted on 24 July 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Tecovirimat SIGA, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 15 November 2018.

The applicant applied for the following indication:

Tecovirimat SIGA is indicated for the treatment of orthopoxvirus disease (smallpox, monkeypox, cowpox, and vaccinia complications) in adults 18 years of age and older and paediatric and adolescent patients weighing at least 13 kg (see section 5.1).

1.2. Legal basis, dossier content

1.3. The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.4. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0274/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0274/2020 was not yet completed as some measures were deferred.

The PDCO issued an opinion on compliance for the PIP P/0274/2020.

1.5. Information relating to orphan market exclusivity

1.5.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.6. Applicant's request(s) for consideration

1.6.1. Marketing authorisation under exceptional circumstances

The applicant requested consideration of its application for a marketing authorisation under exceptional circumstances in accordance with Article 14(8) of the above-mentioned Regulation.

1.6.2. New active Substance status

The applicant requested the active substance tecovirimat contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.7. Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
20 November 2008	EMEA/H/SA/1104/1/2008/SME/III	*Dr Hans Ovelgönne and Dr Elmer Schabel*
21 October 2010	EMEA/H/SA/1104/1/FU/1/2010/SME/III	*Dr Bertil Jonsson and Dr Elmer Schabel*

The Scientific advice pertained to the following *non-clinical, and clinical* aspects:

- Nonclinical package to support approval
- Agreement that demonstration of efficacy in various animal models, together with PK and safety data in healthy volunteers can support approval
- Dose regimen selection for human
- Design of the healthy volunteer study and expanded safety study in human
- Plan to not include children in clinical studies
- Safety database to support approval
- Study special populations post approval
- Data requirements for treatment and post exposure prophylaxis
- Agreement with Marketing authorisation under exceptional circumstances

1.8. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jayne Crowe Co-Rapporteur: Romaldas Mačiulaitis

The application was received by the EMA on	24 July 2020
The procedure started on	29 October 2020
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	18 January 2021
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	19 January 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	1 February 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 February 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	21 May 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	28 June 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	08 July 2021
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	22 July 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	12 October 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	27 October 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Tecovirimat SIGA on	16 September 2021
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	11 November 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Orthopoxviruses are large linear double-stranded deoxyribonucleic acid (DNA) viruses that replicate in the cytoplasm of cells and have a high degree of antigenic similarity. The orthopoxviruses that can cause disease in humans are:

- Variola virus (VARV), which causes smallpox and has been eliminated from global circulation;
- Monkeypox virus (MPXV);
- Cowpox virus (CPXV); and
- Vaccinia virus (VACV).

Other orthopoxviruses that have been used in nonclinical studies with tecovirimat include rabbitpox virus (RPXV) and ectromelia virus (ECTV), the causative agents of rabbitpox and mousepox, respectively. These viruses do not cause human disease.

2.1.2. Epidemiology

Cowpox

Cowpox is endemic in many regions of the world and is maintained in the environment through infection of mammals, birds, domestic animals, cattle, and rodent hosts. Contact with these reservoirs by susceptible animals or people can lead to the onset of disease characterised by lesions mainly on fingers, hands or face. Cowpox is typically limited to the UK, Europe and some Eastern adjacent countries. Sequence analysis of virus isolates from human cases revealed a close association with VACV strains used during the smallpox eradication vaccination campaign. While CPXV is not normally associated with lethal infection in primates, an outbreak of a cowpox-like virus in a monkey colony in Germany resulted in 80 animal deaths. Thus, circulating orthopoxvirus strains continue to evolve, causing periodic zoonotic infections, and they represent an emerging threat to humans.

Monkeypox

Monkeypox is endemic in central Africa and causes epizootic disease in humans. This virus is easily transmitted. In 2003 a monkeypox outbreak occurred in the US caused by pet dealers, pet owners and veterinary care workers handling infected rodents imported from Africa, resulting in 37 human infections. Europe has also faced problems of monkeypox outbreaks in primate-holding facilities as well as transmission to the UK from people traveling from Nigeria. Worldwide, the incidence of MPXV infection has increased due to increased exposure to virus-infected animals through ecosystem degradation, changing population densities and fewer people having received smallpox vaccination.

In regions where monkeypox is endemic, poor nutrition, co-infections with other pathogens, and waning immunity to smallpox have made humans more susceptible to severe MPXV infections.

Smallpox

Smallpox is a serious, contagious, and often fatal infectious disease with an incubation period of 7-17 days. Prior to the worldwide eradication campaign, there were two clinical forms of smallpox, variola major and variola minor.

- Variola major represented the more severe and more common form of smallpox, with an extensive rash and high fever. There were four observed clinical variants of variola major smallpox: 1) ordinary (the most frequent type accounting for 90% or more of cases); 2) modified (mild and occurring in previously vaccinated persons); 3) flat; and 4) haemorrhagic (both rare and very severe). Historically, variola major had an overall fatality rate of about 30%; however, flat and haemorrhagic smallpox is usually fatal.
- Variola minor was a less common presentation of smallpox, causing a much less severe disease, with death rates historically of 1% or less.

The WHO's current worldwide emergency response plan to a smallpox outbreak is mass vaccination. Some countries have stockpiled smallpox vaccine and have deployment plans in place in the event of a smallpox outbreak due to an accidental or deliberate release of virus, with or without genetic manipulation. It is also possible that variola virus could be produced through *de novo* synthesis based on the published sequence or by modifying a related agent such as monkeypox. In case of such an event, drug treatment would be especially important for individuals who are too late in the incubation period to benefit from vaccination or in case of vaccine shortages. A self-administered antiviral drug would supplement, rather than replace, vaccination. As with other types of antimicrobial therapy, drug treatment would be most effective if began before the development of full-blown disease, when the clinical picture is dominated by host inflammatory responses. However, even the treatment of individuals with full rash could reduce the morbidity and mortality of smallpox.

Vaccinia complications

If in response to a smallpox outbreak the existing live VACV vaccines (such as ACAM2000) with replication capacity were to be used, the availability of an antiviral drug for the treatment of vaccinia complications would be of potential importance.

2.1.3. Aetiology and pathogenesis

The VARV that causes smallpox is highly infectious by aerosol or microdroplet transmission in a susceptible population and is capable of rapidly causing massive epidemics that originate from a single index case. The clinical course of human smallpox infection resembles that of ECTV infection of mice or RPXV infection of rabbits, where acute systemic infection results from inoculation with a small amount of virus at the periphery.

In addition, intravenous MPXV infection of non-human primates closely mimics human smallpox from the point of the eruptive phase of disease, including fever and viraemia and the development of dermal lesions that progress in a manner identical to human smallpox. While no single animal model is likely to be fully predictive of human disease outcome, either the use of multiple animal models using host adapted viruses or viruses that cause smallpox-like disease in a surrogate host are informative in assessing antiviral activity and predicting efficacy in humans.

2.1.4. Clinical presentation, diagnosis

The orthopoxviruses usually present with fever followed by rash and systemic upset (see above). Diagnosis may be by visualisation of virus in samples obtained from lesions and PCR and/or culture of virus identity.

2.1.5. Management

There is no antiviral agent approved in the EU for the prevention or treatment of orthopoxvirus diseases. Cidofovir has been recognised to have activity against orthopoxviruses but it is not licensed for this use and it has recognised safety issues. Nevertheless, it is mentioned as an option in some guidelines for management in case of a deliberate release of smallpox virus. Some EU countries have their own replication-competent VACV-based vaccines in storage. The only smallpox vaccine licensed via the centralised procedure in the EU is the MVA-based product Imvanex, which was approved under exceptional circumstances by the CHMP.

While human zoonotic orthopoxvirus infections are rare, they are increasingly being encountered outside their usual geographic range. This said, cases are still too sporadic, and in many instances, occur in regions that are either too difficult or too dangerous to conduct controlled clinical trials. The ability to treat one orthopoxvirus disease is highly indicative of efficacy against other poxviruses.

2.2. About the product

Tecovirimat is a synthetic small molecule provided for clinical use as the monohydrate in 200 mg capsules for oral administration. Tecovirimat targets the F13L gene product of VACV, which encodes a highly conserved (among orthopoxviruses) 37 KDa peripheral membrane protein (VP37) required for the production of extracellular forms of virus. VACV VP37 (and homologues in other orthopoxviruses) likely nucleates formation of a wrapping complex derived from endosomal and/or trans-Golgi network membranes that catalyse the envelopment of intracellular mature virus particles to produce egress competent forms of virus. The wrapping complex is formed through interactions of VP37 with some components of endosome derived transport vesicles, which shuttle cellular "cargo" between endosomal and Golgi compartments. Endosomal vesicles assemble around cargo proteins through specific interactions with the Rab9 guanosine triphosphatase (GTPase) and TIP47, which is a Rab9-specific effector protein. VACV VP37 acts like cellular cargo and interacts with Rab9 and TIP47 to nucleate a virus specific wrapping complex required for assembly of extracellular forms of virus. Tecovirimat blocks interaction of VP37 with Rab9 and TIP47, but not VP230, a Golgi specific marker protein. Thus, tecovirimat prevents wrapping complex formation by inhibiting interaction of VP37 with components of endosomal transport vesicle biogenesis.

In cell culture, the mean effective concentration (EC_{50}) that inhibits virus-induced cytopathic effect (CPE) is similar for all orthopoxviruses tested (VARV, MPXV, VACV, CPXV, ECTV and RPXV), including multiple strains within species, and ranges from 10-70 nM. In animals, tecovirimat has been used to successfully treat VARV in NHPs and RPXV in rabbits in the pivotal nonclinical efficacy studies. It was also sued to treat VACV, CPXV and ECTV infections in mice. On this basis, the applicant proposes that tecovirimat would be an effective treatment for orthopoxvirus infections in humans in addition to VARV (smallpox) using the same dose regimen.

2.3. Type of application and aspects on development

The applicant requested consideration of its application for a Marketing Authorisation under exceptional

circumstances in accordance with Article 14(8) of the above-mentioned Regulation based on:

- Orthopoxvirus diseases are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence of clinical safety and efficacy data in patients and,
- It would be contrary to generally accepted principles of medical ethics to collect such information.
    - Smallpox has been eradicated in humans, and as such, the disease can no longer be studied or treated in humans.
    - The occurrence of cowpox is a rare event worldwide, with fewer than 200 human cases reported since 1969.
    - Vaccinia complications of smallpox infection are very rare. Routine vaccination of the public against smallpox with vaccinia virus-based vaccines was discontinued after the disease was eradicated. Vaccinia virus vaccines are now used very rarely to vaccinate "vanguard cohorts" in case of a deliberate release.
    - Monkeypox is a rare disease that occurs mostly in central and western Africa. The cases of monkeypox that are reported in African countries typically happen in the bush where people have a higher level of contact with animal host reservoirs. These cases are typically reported after the fact and occur in areas in which conducting controlled clinical studies are both technically challenging (no clinics, little electricity, poor transportation conditions) and/or dangerous for the staff due to armed conflicts amidst political strife. There has only been one outbreak ever reported elsewhere in the world, and this occurred in the United States in early June 2003, when several persons became ill after contact with pet prairie dogs with suspected monkeypox. However, the recent outbreak in Nigeria led to two UK citizens acquiring monkeypox in the country and one healthcare worker contracted monkeypox from one of the travellers.

Thus, the applicant is unable to provide comprehensive clinical efficacy and safety data of tecovirimat in humans with orthopoxvirus diseases. The applicant proposes the following post-authorisation measures to maximize data collection and safety reporting of orthopoxvirus events whenever possible:

- SIGA will provide data from the United States Field Study to evaluate the clinical response, drug concentrations, and safety profile of tecovirimat when used in the treatment of subjects with variola virus infection. This protocol is currently in place and will be activated in the event that any cases of variola virus are reported to the CDC.
- SIGA will provide summary case report information for all treated in the indications (monkeypox, cowpox or the treatment due to replication of vaccinia virus following vaccination against smallpox), and in particular pregnant / lactating women and immunosuppressed patients will be provided and discussed in context of healthy individuals whom have taken Tecovirimat SIGA and other patients who were either pregnant and lactating or immunosuppressed. As it is uncertain how often these types of infections will occur, it is not expected that enough cases will occur over any five-year period to be able to provide useful integrated data.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as hard capsule containing 200 mg of tecovirimat as active substance. The product contains the tecovirimat monohydrate.

Other ingredients are:

Capsule content: silica, hydrophobic colloidal; croscarmellose sodium (E468), hypromellose (E464), lactose monohydrate, magnesium stearate; cellulose, microcrystalline (E460); sodium laurilsulfate (E487).

Printing ink: shellac (E904); titanium dioxide (E171); isopropyl alcohol; ammonium hydroxide (E527); butyl alcohol; propylene glycol; simethicone.

The product is available in high-density polyethylene (HDPE) bottles with a polypropylene child-resistant cap as described in section 6.5 of the SmPC.

2.4.2. Active Substance

2.4.2.1. General information

The chemical name of tecovirimat monohydrate is benzamide, *N*-[(3a*R*,4*R*,4a*R*,5a*S*,6*S*,6a*S*)-3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1*H*)-yl]-4-(trifluoromethyl), rel-(monohydrate) corresponding to the molecular formula $C_{19}H_{15}F_3N_2O_3 \bullet H_2O$. It has a relative molecular mass of 394.35 g/mol and the following structure:

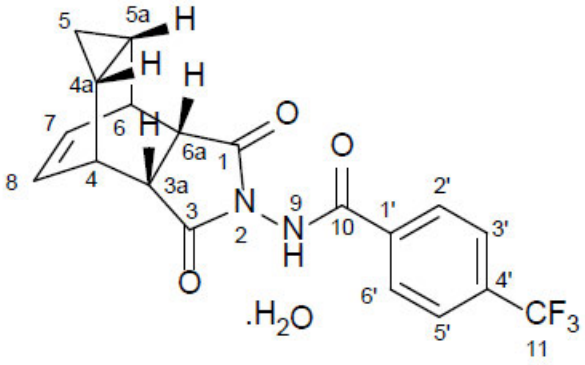


Figure 1: active substance structure

The chemical structure of tecovirimat was elucidated by a combination of elemental analysis, FT-IR spectroscopy, ^{1}H NMR, and liquid chromatography-mass spectrometry. The correct isomeric form has been confirmed by ^{1}H NMR. The solid-state properties of the active substance were measured by X-ray powder diffraction (XRPD) and infrared spectroscopy.

The active substance is a white to off-white solid and is manufactured in crystalline form (Form I). Tecovirimat monohydrate exhibits low solubility in water and buffers of the gastrointestinal pH range (solubility in water and aqueous buffers in pH range 1.2-6.8 is approximately 2 µg/mL at 37°C). Tecovirimat monohydrate exhibits high CaCo-2 permeability and is therefore classified as a BCS-II active substance according to the Biopharmaceutics Classification System.

Tecovirimat exhibits stereoisomerism due to the presence of several chiral centres. The active substance is produced in the *endo* formation. The *exo*-isomer is the only stereoisomer identified in the active substance. It is a synthesis by-product originating from the *exo*-isomer impurity formed during synthesis of the corresponding intermediate (SG1, see below for details). The isomer containing the *anti*-orientation of cyclopropane ring relative to alkene is highly unlikely to form in the Diels-Alder reaction used to manufacture the corresponding intermediate (SG1) based on the literature information and knowledge of the chemistry involved.

Polymorph screening demonstrated that tecovirimat can exist in three predominant physical forms: monohydrate Form I and Form III, and hemihydrate Form V. The different polymorphs can be differentiated by X-ray powder diffraction patterns and their characteristic IR spectra. Form I was found to be the most thermodynamically stable form of tecovirimat under common storage and handling conditions, and hence was chosen for commercial development. Form I is consistently produced from recrystallisation in an ethyl acetate/water mixture which is the final step in the synthesis of the active substance. Form III was observed as a result of conversion from Form V during storage but was not observed in active substance manufactured by the current process (which produces Form I), or during stability studies (of Form-I).

Since the commercial-scale active substance manufacturing process involves micronisation followed by rehydration, studies were performed to determine the effect of these processing steps on the active substance polymorph. It was observed that trace amounts of Form V can form during micronisation as a result of dehydration of the active substance. Consequently, a rehydration step following micronisation is implemented as final part of the active substance manufacturing process. The polymorphic form of the active substance is routinely controlled in the active substance specification.

Both unmicronised and micronised tecovirimat monohydrate are not hygroscopic.

2.4.2.2. Manufacture, characterisation and process controls

Tecovirimat is synthesised in four main steps using three well defined starting materials with acceptable specifications.

Initially, the intermediates SG1 and SG2 were proposed as active substance starting materials. A major objection (MO) was raised on the proposed starting materials. In response to the MO, the starting materials were re-defined. The re-defined starting materials were considered acceptable and this resolved the Major Objection.

Following manufacture of the active substance as outlined in the scheme above, the active substance is micronised and rehydrated. The particle size of the active substance is routinely controlled as part of the active substance specification. Rehydration ensures any trace amounts of the undesired polymorph Form V (hemihydrate) are converted to Form I (thermodynamically stable polymorph, monohydrate).

One manufacturing site is used to manufacture the active substance and one other manufacturing site is used to micronise the active substance.

Adequate in-process controls are applied during the synthesis. In-process controls are used to ensure reaction completion. The specifications and control methods for intermediate products, starting materials and reagents have been presented and are acceptable.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on Chemistry of Active Substances. Potential and actual impurities and their carry-over has been discussed with regards to their origin, and an acceptable control strategy has been provided.

An acceptable discussion is provided on the fate and control of hydrazine, which is used in the manufacture of SG2. During the procedure, a Major Objection (MO) was raised in relation to the information provided on genotoxic impurities, as only hydrazine had initially been discussed. Several points were raised. The applicant was requested to provide an assessment in line with ICH M7 covering actual or potential impurities, solvents, reagents, and intermediates with appropriate controls put in place as a result of the assessment. This request is linked to the MO raised on the designation of the active substance starting materials (see above) and the applicant was requested to consider risks from the manufacture of SG1 and SG2. The applicant was further requested to control SG2 (which was also observed in forced degradation studies) in line with ICH M7 due to the alerting structures present in SG2 and as a consequence to tighten the proposed specification limits. In addition, the initially proposed control strategy for SG2 was not considered acceptable. In response to the MO, a more comprehensive discussion has been provided and the applicant has sufficiently explained how impurities are classified as non-mutagenic. While the discussion was considered limited, it was accepted considering the indication of the product, the duration of use, the low impurity profile of the active substance and finished product, and the overall risk. SG2 is not controlled in line with the Threshold of Toxicological Concern (TTC) of 120 µg/day. Instead, the justification for its control at a higher level in the active substance and finished product refers to the ICH M7 cumulative lifetime dose of 38.3 mg (Less-than-Lifetime approach) i.e. when factoring in up to 14 days of potential dosing at 1200 mg of tecovirimat per day, the maximum exposure is calculated to be 8.4 mg. The severity of smallpox and monkey pox infection, specifically the potential 10-30% mortality rate for those with the disease, is used to justify levels higher than 120 µg/day of SG2. The CHMP concluded that levels above 120 µg/day can be accepted considering the indication of the product and the fact that the specification limit of SG2 has been reduced in the active substance and finished product, as requested by the CHMP. The CHMP recommends that an Ames test be conducted on the impurity SG2 and its control strategy potentially amended based on the results (see chapter below on recommendations).

The commercial manufacturing process for the active substance was developed in parallel with the clinical development programme. A systematic approach using QbD principles was used to guide process development. Changes introduced have been presented in sufficient detail and have been justified. Only minor changes to the manufacturing process have been made in comparison to the process used to manufacture active substance for Phase I clinical studies. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process. A detailed discussion is provided which outlines how it is assured that the desired polymorphic from (Form I) is consistently produced.

The active substance is packaged in zip-tied double virgin polyethylene liners, which are inserted into aluminium foil-lined fibreboard drums. The primary packaging material complies with EC 10/2011 as amended.

2.4.2.3. Specification

The active substance specification includes tests for appearance (visual), identity (IR, HPLC), water content (KF), residue on ignition (Ph. Eur.), polymorphic form (XRPD), particle size distribution (laser diffraction), residual solvents (GC), assay (HPLC), related substances (HPLC), total impurities (HPLC) and microbial purity (Ph. Eur.).

The specifications for unmicronised and micronised active substance are the same with the exemption of the particle size limit, which is not specified for unmicronised active substance.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

An acceptable justification for the specification has been provided. The active substance specifications are based on the active substance critical quality attributes (CQAs). The CQAs identified are assay and impurities, water content, particle size, and polymorphic form.

Batch analysis data for 22 batches of the active substance (micronised and unmicronised) are provided. All batches were manufactured at the two sites proposed for commercial manufacturing and micronisation. Batches used in in Phase 1 and Phase 3 clinical studies and in animal efficacy studies are included. The data also include validation batches and representative commercial batches. The results are within the specifications and consistent from batch to batch. All batches conform to polymorph Form I.

2.4.2.4. Stability

Stability data has been provided for both micronised and unmicronised active substance.

Stability data from 8 commercial-scale batches of *micronised* active substance from the proposed manufacturers stored in a container closure system representative of that intended for the market for up to 84 months under long term conditions (25ºC / 60% RH) according to the ICH guidelines were provided. Stability data covering 84 months is available for 3 of the batches. Stability data from those 3 batches for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The other 5 batches are part of the annual stability programme and data is available for 72 months, 60 months, 48 months, 36 months and 3 months, respectively under long term conditions (25ºC / 60% RH).

Stability data from 8 commercial-scale batches of *unmicronised* active substance from the proposed manufacturers stored in a container closure system representative of that intended for the market for up to 84 months under long term conditions (25ºC / 60% RH) according to the ICH guidelines were provided. Stability data covering 84 months is available for 3 of the batches. Stability data from those 3 batches for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The other 5 batches are part of the annual stability programme and data is available for 72 months, 60 months, 48 months, 12 months, and 9 months, respectively under long term conditions (25ºC / 60% RH).

While the stability testing programme was ongoing, some changes were made to the specifications: the HPLC method for impurity testing was changed and impurity limits were tightened, and the XRPD and particle-size distributions methods were changed. Detailed information on the changes has been provided. Samples were tested for appearance, water content, polymorphic form, assay and impurities.

All tested parameters were within the specifications and no significant trends were observed. Impurity levels remain very low. No changes in polymorphic form were seen in any stability sample. A variable trend for increase in the particle-size distribution was noted, but results remain within specification.

Photostability testing following the ICH guideline Q1B, option 2 was performed on one batch. No degradation was observed, and the results demonstrate that the active substance can withstand short-term exposure to light.

Results of forced degradations studies were provided. Tecovirimat monohydrate was exposed to heat, oxidation, strong acid and strong base. Tecovirimat monohydrate was stable under heat, oxidation and

strong acid stress conditions. Under strong basic stress conditions, degradation was observed (SG2 and two unknown peaks were the main degradation product observed).

The stability results indicate that the active substance manufactured by the proposed suppliers is very stable. The stability results justify the proposed retest period of 84 months when stored at 25°C in the proposed container.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The finished product is an immediate release orange/black opaque hard gelatin capsule, containing 200 mg of tecovirimat (as monohydrate). The capsules are imprinted using white ink with "SIGA" text, the SIGA symbol, followed by "®" on an orange body and "ST-246®" on the black cap.

Size "0" capsules are used, which have the following dimensions: 21.7 mm ±0.3 (overall closed length), 7.34 mm ±0.06 (body diameter), 7.64 mm ±0.06 (cap diameter). The proposed daily dose is 600 mg, twice daily.

The active substance tecovirimat monohydrate has a melting point of approximately 196˚C. Tecovirimat exhibits low solubility in water and buffers of the gastrointestinal pH range but good permeability (LogP of 2.94) and is therefore classified as a BCS II substance according to the Biopharmaceutics Classification System. Particle size is considered critical and is controlled through in-process control testing and as part of the active substance specification (see active substance specification above). Micronised tecovirimat monohydrate is not hygroscopic. The active substance exhibits polymorphism but it has been demonstrated that Form I is stable throughout the proposed shelf life.

All excipients of the non-encapsulated bulk product are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. The components of the hard gelatin capsules are well known pharmaceutical ingredients and comply with Ph. Eur. Standards, except for the colourants used which comply with Regulation EU 231/2012. The components of the Opacode White printing ink comply with Ph. Eur. Standards, except for N-butyl alcohol.

Two excipients of known effect (as per EMA/CHMP/302620/2017 Rev. 1*) are used, namely lactose monohydrate and Sunset Yellow (E110). The required warnings are present in the product information. The inclusion of Sunset Yellow in the capsule shell is considered a poor formulation choice. However, it is present at a level below the EFSA recommended acceptable daily intake and therefore acceptable. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The compatibility of tecovirimat monohydrate with excipients was assessed in studies conducted at accelerated storage conditions (three weeks at 50°C) using binary mixtures of tecovirimat monohydrate Form I and excipients both in the presence and absence of water. Excipients assessed as part of this study included microcrystalline cellulose, lactose monohydrate, colloidal silicon dioxide, croscarmellose sodium, hypromellose (5 centipoise and 15 centipoise), sodium laurilsulfate and magnesium stearate. No degradation or incompatibilities of tecovirimat monohydrate with these excipients were detected in the samples stored with or without water.

A systematic approach to pharmaceutical development of the product using Quality by Design (QbD) along with the knowledge gained from laboratory batches was taken whereby the applicant initially defined a Quality Target Product Profile (QTTP) and subsequently identified CQAs.

Capsule dissolution was identified as the CQA with the highest potential to be impacted by formulation and process parameters and was therefore used as the primary indicator in all development studies. To improve the dissolution rate, tecovirimat monohydrate is micronised. Micronised tecovirimat monohydrate was used for all preclinical and Phase I clinical studies. For Phase 2 and 3 clinical studies micronised active substance with a slightly reduced particle size was used.

The composition of the capsules used during clinical studies is the same as the proposed commercial composition, with the exceptions that active substance in polymorphic Form V was used in phase I clinical studies and Form I was used thereafter and in the commercial formulation. In addition, minor adjustments were made in the quantities of microcrystalline cellulose and lactose monohydrate used.

The development of the manufacturing process has been described. A wet granulation process is used. This process was selected to densify the active substance with excipients and improve the flow properties of the final blend during encapsulation. At the start of Design of Experiments (DoE), a risk analysis in accordance with ICH Q9 was conducted and an Ishikawa diagram is provided. Critical Process Parameters (CPPs) which could impact the CQAs of the product (assay, dissolution, content uniformity and degradation) were identified. There is a clear progression from lab scale (4-7 kg) parameters to 1/10th scale (62 kg granulation, 139 kg blend) to final commercial scale DoE (355 – 370 kg granulation). A design space was investigated but manufacture will be conducted in line with the manufacturing parameter ranges validated.

The dissolution method has been investigated and has been justified. During the procedure, two Major Objections (MOs) were raised in relation to the dissolution method(s).

The first MO concerned the information provided in relation to the Tier I dissolution method, which was considered not sufficient and several points were raised. The applicant was asked to provide data to justify the use of a surfactant. The applicant was also asked to justify the choice of surfactant and the amount used and was requested to provide data on other surfactants tested as well as on test results with lower levels of the chosen surfactant. The applicant was further asked to provide data to support the paddle stirring speed. In addition, the applicant was asked to provide further evidence to demonstrate the dissolution method is discriminatory, including against manufacturing process deviations. Finally, the applicant was asked to provide dissolution data of batches used in Phase 3 clinical studies to support the proposed specification limit in line with the Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic acid (EMA/CHMP/CVMP/QWP/336031/2017). The questions raised were addressed in a satisfactory way. It was accepted that a surfactant is used. The justifications for the selected surfactant and the concentration used are acceptable. It was demonstrated that the paddle speed has been investigated and the justification for the chosen speed is acceptable. The discriminatory power of the dissolution method is accepted as sufficient as part of the overall control measures to ensure the quality of the finished product (control of other ingredients, manufacturing and in-process controls) and the proposed specification limit was also accepted.

The second MO concerned the initially proposed Tier II dissolution method and the applicant was asked to justify the inclusion of this method in the release specification of the finished product. In response to the MO, Tier II dissolution method was removed from the dossier. This resolved the Major objection.

The primary packaging is high-density polyethylene (HDPE) bottles with a polypropylene child-resistant cap. The material complies with Ph. Eur. requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.4.3.2. Manufacture of the product and process controls

The manufacturing process consists of five main steps: raw material preparation, wet granulation, blending, encapsulation and packaging. The quantity of active substance in the blend is >50%, The process is considered to be a standard manufacturing process. Three granulation/drying batches are combined into one final batch for blending and subsequent encapsulation as outlined in the scheme below.

The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

The manufacturing process has been validated (traditional process validation). For the process validation, 9 batches of tecovirimat granulation were manufactured at commercial scale. Three batches of tecovirimat blend were manufactured, using three granulation batches per blend batch. The blend batches were encapsulated at 200 mg strength (three finished drug product batches). It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

2.4.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual), identification (HPLC, UV), dissolution (in-house), content uniformity (Ph. Eur.), moisture content (KF), assay (HPLC), related substances (HPLC), impurities (HPLC) and microbiological purity (Ph. Eur.).

The proposed specifications are acceptable.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on 7 batches using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification.

During the procedure, a Major Objection was raised in relation to the required nitrosamine risk assessment for the finished product as this was absent in the initial application. In response, a risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed (as requested) in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. With regard to the HPLC method for assay, identification and related substances, full method validation is provided and results from forced degradation studies indicate that the method is stability indicating.

Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for seven commercial-scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.4.3.4. Stability of the product

Stability data from nine batches representative of those for marketing and packed in the primary container proposed for marketing according to the ICH guidelines were provided. Stability data is presented from three commercial-scale batches (validation batches) stored under long term conditions (25ºC / 60% RH) and intermediate conditions (30°C / 65% RH) for 60 months and under accelerated conditions (40ºC / 75% RH) for 6 months. Further supportive stability data from five annual stability batches (2013 (60 months), 2014 (60 months), 2016 (36 months), 2017 (24 months) & 2019 (6 months)) stored under long term conditions (25°C / 60% RH) is presented (no batches were manufactured in 2015 and 2018). Finally, stability data from one batch which was used to qualify the capsule filler is also presented, with data available for up to 60 months under long term conditions (25°C / 60% RH) and 6 months under accelerated conditions (40°C / 75% RH).

Samples were tested for appearance, assay, related substances, moisture content, dissolution and microbiological purity. The analytical procedures used are stability indicating. All results met the proposed drug product specification and no out-of-specification results were obtained

Photostability studies were conducted and one batch of finished product in the commercial packaging and capsules which were removed from the primary containers were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The tested finished product in the commercial packaging remained within specification. It can be concluded that the primary container provides adequate protection against UV radiation. Capsules directly exposed to light failed Tier I dissolution testing. When tested with the Tier II dissolution method, results were within specification. Based on the results, the storage instructions of "*Store in the original container in order to protect from light"* is considered adequate.

Forced degradation studies have been conducted on the finished product. The finished product has been shown to be stable in the tested stress conditions with the exception of basic conditions, where hydrolysis was observed. The active substance is not exposed to basic conditions during finished product manufacture or in the formulation and it is therefore not necessary to control moisture levels tightly in the finished product.

Bulk stability:

A bulk stability study was conducted with bulk capsules stored in packaging representative of the packaging used during commercial manufacture. No changes in appearance, assay, related substances, dissolution, moisture content or microbiological purity were observed when stored for up to 6 months at 25°C / 60% RH.

The applicant has committed to assigning a shelf-life of the finished dosage according to CPMP/QWP/072/96 for batches of finished product destined for the market.

Food Stability Studies

A food stability study was conducted which had the objective of evaluating the stability of finished product capsule contents when mixed, at full dose with water and/or various food matrices (applesauce, chocolate milk, 2% milk, infant formula and vanilla yogurt). Storage temperatures assessed included 5±3°C and 25±2°C. When mixed at the full dose, all food-finished product matrices exhibited acceptable stability over a 24-hour period and passed the acceptance criteria for both the concentration of tecovirimat and for the absence of related substances. The five water matrices included in the study were across a relevant pH range 3.0 – 8.5. Storage temperatures assessed included 5±3°C, 25±2°C and 40±2°C. When mixed at the full dose, all drug-water matrices exhibited acceptable stability over a 72-hour period and passed the acceptance criteria for both concentrations of tecovirimat and for the related substances.

Based on available stability data, the proposed shelf-life of 5 years and the following storage conditions as stated in the SmPC (section 6.3) are acceptable:

- Store below 25°C.
- Store in the original package in order to protect from light.

For storage conditions after mixing the medicinal product (as per 6.3): Capsules that have been opened and mixed with food or liquids, should be consumed within 30 minutes.

2.4.3.5. Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

Gelatine obtained from bovine sources is used in the product. Valid TSE CEPs from the suppliers of the gelatine used in the manufacture are provided.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

During the procedure the CHMP raised five Major objections. Two Major Objections raised in relation to the active substance concerned the designation of the active substance starting materials and the discussion/control of potential and actual genotoxic impurities. In relation to the finished product, two Major Objections were raised in relation to the dissolution methods and a Major Objection was also raised on the nitrosamine risk assessment. All Major Objections were addressed in a satisfactory way and further details are provided in the relevant chapters above. Regarding the control of impurities, one minor resolve quality issue remained which has no impact on the Benefit/Risk ratio of the product. For details on the recommendation please see relevant chapter below.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied QbD principles in the development of the active substance and finished product and the manufacturing process of the finished product. However, no design space was claimed.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

Ames testing should be conducted on the impurity SG2, and if found to be Ames-positive, a more sensitive analytical procedure and as low a limit as possible be put in place in the drug substance and drug product specifications. Furthermore, if any remaining potential impurities have not been subject to ICH M7 hazard assessment, that it be conducted on them. This should be completed by Q2 2022.

2.5. Non-clinical aspects

2.5.1. Introduction

Tecovirimat SIGA is being developed for the treatment of orthopoxvirus disease (smallpox, monkeypox, cowpox, and vaccinia complications) in adults 18 years of age and older and paediatric and adolescent patients weighing at least 13 kg. Tecovirimat is active against orthopoxviruses (variola, monkeypox, cowpox, vaccinia) via targeting the viral protein, p37, and preventing the formation of egress competent enveloped virions.

GLP

Pharmacology, pharmacokinetic, and toxicology studies described by the applicant that were conducted under GLP regulations were performed in compliance with U.S. FDA and/or OECD (Organisation for Economic Co-operation and Development) Good Laboratory Practice (GLP) regulations.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

All primary pharmacodynamics studies have been reviewed in-depth in the clinical assessment report and the pivotal efficacy studies are summarised in the nonclinical report.

The nonclinical pharmacology of tecovirimat was investigated in a comprehensive set of *in vitro* and *in vivo* studies designed to assess the activity and mechanism of action of the test material. The pivotal *in vivo* efficacy studies were conducted in monkeys and rabbits under GLP conditions. Pilot studies leading to the development of the intravenous challenge MPXV/NHP and intradermal challenge RPXV/rabbit models, were mouse models (vaccinia, cowpox, ectromelia), as well as prairie dogs and golden ground squirrels infected with MPXV as potential models for human smallpox.

In vitro efficacy studies have demonstrated that tecovirimat shows antiviral specificity against multiple members of the orthopoxvirus genus (EC_{50} in the ~10 to 70 nM range) and that the antiviral activity is limited to the parent compound and not to tecovirimat metabolites. These EC_{50} values are orders of magnitude lower than Cmax values achieved with the proposed dose of 600 mg BID. Additionally, the *in vitro* studies demonstrated the ability of tecovirimat to inhibit virus replication (as demonstrated by the inhibition of plaque formation) as well as extracellular virus formation, indicating that tecovirimat can prevent cell-to-cell spread and long-range dissemination of orthopoxviruses. Furthermore, *in vitro* studies have demonstrated the ability of tecovirimat to inhibit its molecular target, the VP37 protein, from interacting with intracellular transport components thus preventing the production of enveloped egress-competent virus.

The applicant conducted numerous *in vivo* PD studies in different animal species. As described by Chapman *et al*. (2010), no single animal model recapitulates all known aspects of human Orthopoxvirus. Therefore, different animal models (NHP, rabbit, mouse, prairie dog and golden ground squirrel infected with appropriate Orthopoxvirus) chosen by the applicant are acceptable for the investigation of the efficacy of tecovirimat for treatment of human smallpox disease.

In all *in vivo* MPXV/NHP efficacy studies, cynomolgus macaques were infected on Day 0 with a lethal dose of monkeypox virus Zaire '79 strain by IV inoculation with $5x10^7$ plaque-forming units (pfu) per animal. In rabbit studies, New Zealand White rabbits were infected on Day 0 with a lethal dose of rabbitpox virus strain Utrecht by ID inoculation with 1,000 pfu per animal. In both models, oral tecovirimat treatment was initiated on or after Day 4 post-infection after the onset of clinical signs (pock lesions in NHPs and fever and viremia in rabbits). Tecovirimat was delivered by oral gavage in a vehicle comprised of 1% W/W hydroxypropyl methylcellulose (HPMC) and 0.5% Tween 80. In all studies, survival was the primary endpoint.

In the monkey orthopox model Tecovirimat at a dose of 3 mg/kg (and above) provides 90-100% protection from mortality while higher doses (10 mg/kg) additionally reduce viral load and lesion formation. The proposed human dose, 600 mg twice daily for 14 days is derived from the efficacy, safety/toxicology and pharmacokinetic studies using this model.

Pivotal *in vivo* primary pharmacology studies were conducted in monkeys infected with monkeypox virus (MPXV) and rabbits infected with rabbitpox virus (RPXV). Monkeys and rabbits are considered to be the primary models for clinical effects, mimicking certain aspects of human smallpox, following orthopoxvirus infection. Specifically, the IV administration of MPXV (5×10^7 pfu) to monkeys and the intradermal administration of RPXV (1,000 pfu) to rabbits result in uniform mortality with clear indications of disease progression prior to death.

Oral (gavage) administration of tecovirimat resulted in a reduction in the primary and secondary outcomes of orthopoxvirus infection in both species. Specifically, studies in monkeys demonstrated that administration of tecovirimat at dose levels of ≥ 3 mg/kg/day for 14 days (initiated no later than post-infection Day 4) resulted in decreases in the incidences of mortality (> 95% survival compared to < 5% survival in monkeys treated with tecovirimat at dose levels of ≥ 3 mg/kg/day and ≤ 3 mg/kg/day, respectively). Treatment of monkeys with tecovirimat at dose levels of ≥ 10 mg/kg/day for 14 days (initiated no later than post-infection Day 4) did not result in further increases in survival but did result in lower circulating MPXV DNA levels, fewer pock lesions (verifying the findings of the *in vitro* studies that tecovirimat reduces viral dissemination), and fewer clinical signs of infection (unresponsiveness, dyspnoea and fever, and lymphadenopathy). Studies in rabbits demonstrated that oral (gavage) administration of tecovirimat at dose levels of ≥ 20 mg/kg/day for 14 days (administered no later than post-infection Day 4) resulted in decreases in the incidences of mortality, blood RPXV levels, and clinical signs of infection (including dyspnoea, fever, and respiratory distress). Survival for all dose levels (ranging from 20-120 mg/kg/day) was similar and exceeded 90% while all untreated rabbits succumbed to disease. Preliminary *in vivo* primary pharmacology studies conducted in mouse, prairie dog, and squirrel models of orthopoxvirus infection showed similar protective effects following oral (gavage) tecovirimat administration.

In addition, the supportive studies in mice also revealed that use of tecovirimat did not influence an induction of protective immune response and resistance after secondary challenge with a lethal dose of virus.

In conclusion, pivotal nonclinical studies suggest that tecovirimat oral treatment was significantly effective to NHPs at minimum dose of 10 mg/kg and to rabbits at minimum dose of 20 mg/kg when treated daily for 14 days (at least 5 days are required) starting from Day 4 (delay up to maximum Day 5) post appropriate infection in animals. Survival of animals treated with effective tecovirimat doses

was 80%-100%. Increases to higher tecovirimat doses above the minimum effective dose for each species did not confer a greater benefit in either animal model. The results of primary pharmacology studies are acceptable.

2.5.2.2. Secondary pharmacodynamic studies

Studies conducted in mice and monkeys demonstrated that the oral (gavage) administration of tecovirimat to immunocompromised animals decreased the adverse effects of a smallpox vaccine when they were co-administered. In immunocompetent mice and monkeys, administration of tecovirimat with the smallpox vaccine reduced the severity of the primary vaccine lesion without compromising acquisition of full protective immunity.

The studies presented are more consistent with the primary therapeutic activity of tecovirimat, as opposed to an investigation of possible secondary "off target" effects. No secondary screening was carried out by the applicant. This was considered unnecessary by the applicant due to numerous other studies both *in vitro* and *in vivo* which showed no evidence of off target activity. The action of tecovirimat is to inhibit the function of VP37 and block the envelopment of virus, inhibiting release and slowing dissemination. While this protein has a high level of homology amongst the orthopoxviruses (~95%) it has no significant homologies with other viral or mammalian proteins. The lack of secondary pharmacodynamics studies is acceptable.

2.5.2.3. Safety pharmacology programme

Tecovirimat is negative in the hERG channel assay at concentrations up to 30 µM, this corresponds to approximately 11,830 ng/ml. The Cmax recorded in Study ST-246-008, 600 mg BID, was 2,209 ng/ml, which is 7.4 times lower than the highest concentration tested in Study 246-PH-001. In the 28-day cynomolgus monkey study (Study No. 246-TX-007), once daily dosing at 300 mg/kg was not associated with any effects on CV function.

In addition, an administration of a single oral dose of tecovirimat up to 2,000 mg/kg or multiple oral doses of tecovirimat as high as 300 mg/kg up to three months did not reveal significant cardiovascular effect of the oral administration of tecovirimat on qualitative or quantitative ECG parameters in monkeys. Just in one study in monkeys, after application of a 12-day multiple oral dose (300 mg/kg/day) there was evidence for a mild, transient, possibly tecovirimat-related, prolongation of the QT interval.

In the mouse studies neurobehavioural effects were observed at all dose levels. However, these effects were only considered adverse at the highest dose level of 2,000 mg/kg. As such the NOAEL was considered toe 1,000 mg/kg. Tecovirimat did not have any effects on respiratory parameters in Study No. 246-PH-003, and the NOAEL was considered to be 2,000 mg/kg.

2.5.2.4. Pharmacodynamic drug interactions

Pharmacodynamic drug interaction studies have been conducted with tecovirimat in monkeys and mice in order to determine the effects of co-administering tecovirimat with a smallpox vaccine. This approach was taken by the applicant as there are no other drugs approved for treatment of smallpox and as such human PK interactions using *in vitro* and *in vivo* assessments are not warranted or possible. It is likely that the approved smallpox vaccine would be deployed simultaneous to tecovirimat in a smallpox emergency and the possibility exists that they may be co-administered in "off-label" use.

In both animal species, concurrent administration of tecovirimat and ACAM2000® did not inhibit induction of immunity and provided protection against a subsequent lethal MPXV (monkeys) or VACV (mice) challenge.

2.5.3. Pharmacokinetics

The repeat-dose oral PK/TK of tecovirimat has been evaluated in a range of species including key primary species used to support the animal efficacy studies of tecovirimat (i.e., rabbits and monkeys).

The LC-MS/MS or HPLC-MS/MS methods used in pharmacokinetic and toxicokinetic GLP studies are considered appropriate and validated for determination of tecovirimat and its metabolites (M4, M5, and TFMBA) quantities in mouse, rabbit and monkey plasma. The analytical methods were validated for intra-assay and inter-assay reproducibility and if necessary, specificity, dilution effect, freeze/thaw stability and storage stability. In a number of PK and TK studies tecovirimat concentrations in rat, rabbit, dog and monkey plasma were measured using a non-validated LC-MS/MS method.

Absorption

In vivo oral bioavailability studies conducted with mice, rats, rabbits, and monkeys indicate that tecovirimat has good oral bioavailability. Following oral administration, tecovirimat rapidly appeared in plasma, as indicated by the time to reach maximum plasma concentration (Tmax) values within approximately 5.0 hours. In oral repeat-dose studies conducted in mice for up to 3 months, in rats for 12 days, in rabbits for up to 14 days, and in monkeys for up to 3 months and in EFD studies conducted in mice and rabbits, exposure parameters generally increased with dose but dose-proportionality was not always observed.

In mice and rats, the oral bioavailability following administration of a single dose of tecovirimat was noted to be highest at the lowest dose tested (30 mg/kg) with absolute bioavailability (Fabs) values of approximately 45 and 40% in male and female mice, respectively, and 90 and 33% in male and female rats, respectively. The decrease in bioavailability observed with increasing dose, represents saturation in absorption.

In rats, there was no significant difference in bioavailability between male and female animals following repeated administration.

In a single-dose study in monkeys, the bioavailability of orally administered tecovirimat increased approximately 2-fold when administered with food compared to fasted conditions (Fabs values of 50% and 28% in fed versus fasted animals, respectively). As a result, the nonclinical PK/TK studies were generally conducted under fed conditions and tecovirimat is indicated to be administered with food in humans.

The repeat-dose oral PK/TK of tecovirimat in rabbits following 7 days of administration indicated oral bioavailability values of 29% and 7.5% in males and females, respectively, on Day 1 and 15.5% and 14.1% in males and females, respectively, on Day 7 at 100 mg/kg. The TK analysis indicates that the difference in bioavailability values between male and female rabbits that were noted after the first dose was not seen after administration of the seventh dose; thus, there was no significant difference in bioavailability between male and female animals following repeated administration. In pregnant rabbits receiving tecovirimat at dose levels ranging from 10 to 1,000 mg/kg/day between gestation days (GD) 6 to 18, there was evidence of accumulation beginning at 300 mg/kg/day but not at levels of 100 mg/kg/day and below. On GD 19, at 72 hours post-dose, tecovirimat was measurable in plasma at 100 mg/kg/day; however, the mean plasma concentrations were below the lower level of quantification (LLOQ) at 10 and 30 mg/kg/day.

In a 14-day study in monkeys, a dose-proportional increase in exposure was noted over a tecovirimat dose range of 0.3 to 30 mg/kg/day. Data from repeat-dose toxicology studies, conducted over 28 and 91 days, indicated increasing exposure to tecovirimat with increasing dose levels. Additionally, the repeated administration of tecovirimat for 91 days resulted in a slight accumulation at steady state.

The repeat-dose oral PK/TK of tecovirimat in monkeys was evaluated in a 7-day TK and toxicity study, a 28-day toxicity study and a 91-day toxicity study. In addition, the oral PK of polymorph Forms I and Forms I and V were evaluated a 14-day study. There was no consistent significant difference in oral systemic exposure between Form I and V, as such, the micronised Form I was selected for advancement into the human formulation as it was the more stable and suitable for large-scale production.

Distribution

The plasma protein binding of [^{14}C]-tecovirimat was moderate to high (77.3 to 96.3%) in all species studied (mouse, rat, rabbit, dog, monkey and human), with human binding being on the low end (approximately 80%), and appears to be concentration-independent over a wide range of concentrations (0.03 to 50 µM). Specifically, the average percent binding of tecovirimat in mouse, rat, rabbit, dog, monkey, and human plasma was 87.7, 95.8, 88.7, 90.6, 87.5 and 79.7%, respectively.

Following oral administration in mice, 100 mg of [^{14}C]-tecovirimat/kg was systemically distributed with the highest concentrations noted in liver and gall bladder, respiratory tract tissues (i.e. nasal turbinates), and bone marrow. The highest tissue concentrations were observed at 24 hours post-dose and declined to near or below limit of quantitation (BLQ) in most tissues beginning at 96 hours post-dose. Elimination of radioactivity was complete and below LLOQ after 24 hours in all tissues with the exception of bone marrow and liver for which radioactivity persisted till the last sample collection time point of 168 hours post-dose.

Tecovirimat crosses the blood brain barrier, this was confirmed in studies with dogs. Also, the penetration of tecovirimat into the brain and cerebrospinal fluid (CSF) was demonstrated in monkey. Repeated oral administration of tecovirimat at a dose level of 300 mg/kg/day resulted in mean plasma, brain, and CSF tecovirimat concentrations of 1,435 ng/mL, 834 ng/g, and 143 ng/mL, respectively, in males and 2,090 ng/mL, 1,152 ng/g, and 177 ng/mL, respectively, in females.

In a placental and milk transfer study in mice, [^{14}C]-associated tecovirimat was noted to be transferred to the offspring through the placenta and the milk.

Metabolism

In vitro studies have demonstrated that [^{14}C]-tecovirimat is stable in dog, monkey, and human liver microsomes, but not in rat and mouse liver microsomes.

An *in vitro* study evaluating the potential of tecovirimat to be metabolised by human UGT enzymes revealed tecovirimat is a substrate of human recombinant UGTs (specifically of UGT1A1, 1A3, and 1A4). The percent of tecovirimat remaining after 2 hours of incubation with UGT1A1, 1A3, and 1A4 was 66%, 79%, and 59%, respectively. Tecovirimat is not an acetylcholinesterase substrate.

Clinical data reveal that tecovirimat is extensively metabolised by amide hydrolysis into metabolites M4 and TFMBA. M4 is presumably metabolised via a deamination process to form the metabolite M5. Tecovirimat and M4 are further metabolised by direct glucuronide conjugation. These metabolites were also identified in 14-day oral studies in monkeys and mice administered tecovirimat at dose levels of 300 and 1,000 mg/kg/day, respectively.

As observed in humans, the metabolite-to-parent exposure ratios in monkeys indicated that tecovirimat was extensively metabolised. However, the exposure ratios were lower in mice.

The safety of M4 and M5 is supported by nonclinical data demonstrating that the plasma M4 exposure in mice and the plasma M5 exposures in both mice and monkeys were higher than those in humans. The exposure of TFMBA was disproportionately higher in humans than in animals.

Excretion

One mass balance study was carried out in mice. The excretion profile of tecovirimat in mice indicates that faeces is the major route of elimination (71-75%) followed by urine (18-24%) at 96h post dose. In mice, approximately 95% of the administered dose was excreted by 96 hours post-dose. In faeces, tecovirimat was excreted unchanged whereas in urine, several metabolites, including TFMBA, were detected and only a trace amount of the parent compound was present.

Pharmacokinetic drug interactions

The applicant did not perform dedicated nonclinical pharmacokinetic drug interactions studies. Therefore, DDI evaluation was performed with human samples and tecovirimat interaction with bupropion, flurbiprofen, or omeprazole, repaglinide, midazolam and cytochromes P450.

Based on *in vitro* results conducted using human samples, tecovirimat does not show inhibition potentials toward major CYP enzymes and common transporters except breast cancer resistance protein (BCRP) in *in vitro* drug-drug interaction potential assays. However, it may induce certain CYP enzymes including CYP3A4, and its metabolites M4 and M5 have the potential to produce drug-drug interactions by the induction of CYP2B6.

In conclusion, the pharmacokinetic and ADME of tecovirimat have been characterised *in vitro* and *in vivo*. From the presented studies tecovirimat properties across the nonclinical species tested *in vivo* and across human and animals *in vitro* are comparable. Overall, the NC data show that oral administration of tecovirimat is likely to result in adequate exposure of substance to assure protection against smallpox and other human orthopoxviruses in humans.

2.5.4. Toxicology

The nonclinical toxicology programme for tecovirimat includes single-dose studies and repeat-dose studies up to 3 months in duration in BALB/c mice and cynomolgus monkeys, *in vitro* and *in vivo* genotoxicity studies, a fertility and early embryonic development study in CD1 mice, EFD studies in CD1 mice and New Zealand White rabbits, a pre- and post-natal development study in CD1 mice, and a phototoxicity evaluation in hairless mice.

2.5.4.1. Single dose toxicity

The pivotal single-dose toxicity studies conducted in mice and monkeys demonstrated that tecovirimat was well tolerated following oral administration of up to 2,000 mg/kg (in both species) which produced high systemic exposures to tecovirimat.

2.5.4.2. Repeat dose toxicity

Mice

In mice, oral administration of tecovirimat for 28 days and 3 months resulted in significant increases in relative liver and spleen weights at dose levels of 600 mg/kg/day and above; however, these findings were not considered to be of toxicological significance given that there were no microscopic or clinical chemistry findings and the weight changes were absent in the recovery animals. Due to the lack of tecovirimat-related effects at the highest dose levels in the 28 day and 3-month study, respectively,

the no-observed-adverse-effect levels (NOAEL) in the 28 day and 3 month mouse studies were 2,000 and 1,000 mg/kg/day, respectively.

However, in 91-day GLP-compliant study in mice (IITRI 2083-003-001 SN3) oral administration of tecovirimat resulted in significant increases in relative liver and spleen weights at dose levels of 600 mg/kg/day and above. These findings were not considered to be of toxicological significance given that there were no microscopic or clinical chemistry findings and the weight changes were absent in the recovery animals. However, statistically significant increase in absolute and relative reticulocyte counts in the high dose females was documented. But the increases were not considered toxicologically significant since they were not associated with any histopathological changes in the liver or bone marrow of these animals. The applicant showed that there is no relation between reticulocyte count and increase in spleen weight. However, the histological examination has been performed for the control group and 100 mg/kg dose group only and do not correlate with reticulocyte count. Therefore, this non-clinical data cannot completely exclude the relation of these changes with the use of tecovirimat.

The exposures achieved in mice at the 1,000 mg/kg/day dose level in the 3 month study were approximately 21- to 24-fold and 26- to 32-fold over the human clinical exposure (at 600 mg BID dosing for 14 days) for AUC and Cmax values, respectively.

Dogs

In the maximum tolerated dose (MTD) study, 246-TX-015, single oral administration of tecovirimat resulted in seizures and mortality at 300 mg/kg/day; however, no apparent seizures or changes in EEG were noted at 100 mg/kg/day. Yet in study 246-TX-014, all three high-dose dogs (100 mg/kg/day) were sacrificed in moribund condition within ~ 12 hours of tecovirimat administration on Day 1, and 2 out of 3 dogs suffered convulsions.

The Cmax of the proposed human dose 2,209 ng/ml (SIGA-246-008) is similar to the Cmax observed at the NOAEL in this study, 2,142 ng/ml (male and female combined). It is acknowledged that the Cmax of the proposed human dose is below that of the mid-dose (100 mg/kg) in the dog study 246-TX-015, where seizures were not observed, however seizures and deaths were observed in Study 246-TX-014 at 100 mg/kg and these TK data are from the same dose in 246-TX-015 albeit a different batch.

The 246-TX-015 Study report states because of toxicity seen in dogs in a previous study, (assumed to be 246-TX-014) conducted at another laboratory, this study was designed to evaluate any toxicity and the toxicokinetics in dogs using a different batch of test article. This approach was designed to discern whether the toxicity seen in the previous study was associated with only the dogs and procedures used at the other laboratory, the initial batch of test article used at that laboratory, or the dog being more sensitive to this test article than other species tested.

According to study report 246-TX-014 blood was taken for TK analysis from all animals on Day 1 up to 10h, with the exception of 1 100 mg/kg animal. Only the 30 mg/kg animals were bled at 12 and 24h, as the 100 mg/kg animals had been euthanised.

The applicant is asked to provide a detailed discussion of the differences between studies 246-TX-014 and 246-TX-015, including a comparison of toxicokinetic data from the samples taken in Study 246-TX-014 with Study 246-TX-015. A discussion of the batches used, and a rationale why convulsions and deaths were observed at 100 mg/kg in 246-TX-014 but not 246-TX-015. The applicant is asked to comment on the deaths and seizures seen at 100 mg/kg in Study 014 as the exposure margins at the same dose in Study 246-TX-015, are low compared to the human data from the pivotal Study SIGA-246-008, at 600 mg BID providing margins of only 2.1 and 0.64 for Cmax and AUC respectively. At the NOAEL in this study the margins are 0.97 and 0.31 for Cmax and AUC respectively. In these studies,

adverse events were associated with Cmax > 10,000 ng/ml, and that toxicokinetic data show that the study 014 Cmax values were ≥2 fold higher than those from the same doses in the study 015. No batch data was available for the API in study 014, so no comparison could be made between the different batches used in the two studies. However, no evidence of seizure or convulsions were noted in the 3-month toxicology studies in mouse and NHP. The mean Cmax exposure in the mouse study at the highest dose (1000 mg/kg) was 64,900 ng/mL, and that in NHP (300 mg/kg) was 5,303 ng/mL. A comparison between the 3-month toxicology study in NHP and humans, show that the mean AUC and Cmax values are 2.5 and 2.4-fold, respectively, higher in NHP compared to humans. Nonetheless, due to the adverse event in dogs, SIGA monitored the EEGs in all human subjects in the pivotal safety study (study SIGA-246-008). Following review of the EEGs the DSMB stated that the study drug appears safe and well-tolerated and any concerns about the potential risk of seizure were adequately addressed and defined by the design and outcome of the study. The EEG results which were reviewed from the SIGA-246-008 study do not present a signal of concern related to possible seizures regarding the use of tecovirimat at the 600 mg twice per day dose.

In Section 5.3 of the SmPC the applicant states exposure margins for 300 mg/kg "approximately 4 times higher than the highest observed human exposure at the recommended human dose (RHD) based on Cmax" and for 100 mg/kg "similar to the highest observed human exposure at the RHD based on Cmax". At 100 mg/kg the margin is 2x that of the RHD, it is at the NOAEL in this study (30 mg/kg) where the margin is similar to that of the RHD. The applicant was asked to revise the wording of Section 5.3 in this respect, as these margins are not considered "sufficiently in excess of the maximum human exposure".

In response to this request the applicant has reworded section 5.3 to state;

The non-clinical safety was evaluated in 28-day and 3-month studies in mice and monkeys, respectively. Cmax exposures at the no observed adverse effect level in the toxicology studies compared to the human Cmax at the recommended human dose (RHD) have safety margins of 23 based on the mouse and 2.5 based on the monkey. The dog is a more sensitive species to tecovirimat and was tested after a single dose or repeated doses. Six hours after a single dose of 300 mg/kg, one dog experienced convulsions (tonic and clonic) with electroencephalography (EEG) consistent with seizure activity. This dose produces a Cmax in the dog that was approximately 4 times higher than the highest human Cmax at the RHD. In the dog, the no observe adverse effect level was determined to be 30 mg/kg with a Cmax safety margin at the RHD of 1.

Monkeys

In the monkey, oral administration of tecovirimat for 28 days or 3 months did not result in any test article-related effects at the highest tested dose level of 300 mg/kg/day.

Tecovirimat was administered at dose levels of 30 (low), 100 (mid) and 300 (high) mg/kg/day in monkeys and the NOEL was 300mg/kg in repeated-dose studies. Meanwhile in the single dose toxicity study 246-TX-005 (monkeys) NOAEL was 2,000 mg/kg. However, according to study 246-TX-007, with the dose of 300mg/kg/day the Cmax and AUC0-24h were only 1.1-fold in monkey males higher than that observed after oral administration of a human clinical dose of 600 mg twice a day. This dose was chosen as tecovirimat absorption was approaching saturation above 300 mg/kg, according to the Cmax and AUC, when compared with the 600 mg/kg dose. Based on this data the 300 mg/kg dose was selected for a 7-day study (Phase II of 246-TX-004) and subsequently for study 246-TX-007 (28-day study) and study IITRI 2083-003-001-SN6 (3-month study). However, it was possible to achieve a higher exposure limit, using higher than 300 mg/kg dose.

In the repeat-dose toxicity studies, there were no significant tecovirimat-related findings in either mice or monkeys administered tecovirimat by the oral route.

The dose of 300 mg/kg was determined to be the NOAEL in male and female monkeys following 28 days and 3 months of oral dosing. The dose of 300 mg/kg/day for 3 months in the monkey (Study IITRI 2083-003-001 SN6) produced AUC and Cmax values of 2.5-fold and 2.4-fold over the human exposures, respectively, at a clinical dose of 600 mg BID for 14 days.

The exposures achieved in mice at the 1,000 mg/kg/day dose level in the 3 month study (IITRI 2083-003-001 SN3) were approximately 21- to 24-fold and 26- to 32-fold over the human clinical exposure (at 600 mg BID dosing for 14 days) for AUC and Cmax values, respectively

The exposure multiples in the monkey studies are quite low. However, no significant toxicities were observed in these studies.

In response to Clinical D120, the applicant submitted a new PK study, No. 246-TX-019, A Single-Dose Pharmacokinetic Study of ST-246 by Intravenous Infusion in Cynomolgus Monkeys. The IV route of administration allowed evaluation of tecovirimat at higher exposures than those achieved orally. In NHP study TX-019, NHPs received single doses of 20 mg/kg or 30 mg/kg with 4 or 6 h infusions. Exposure margins achieved based on Cmax were 6 based on total and 4 based on unbound mean Cmax, when compared to human PK data from SIGA-246-008. These margins are greater than those achieved in the oral dosing studies in NHPs and dogs.

2.5.4.3. Genotoxicity

The genotoxic potential of tecovirimat was evaluated in an *in vitro* bacterial and mammalian mutagenicity assays as well as in an *in vivo* mammalian genotoxicity study. Tecovirimat showed no mutagenic effects in *in vitro* bacterial reverse mutation and mouse lymphoma L5178Y/TK± cells assay and no genotoxic effects in an *in vivo* bone marrow micronucleus assay in mice.

The results of these studies demonstrated that tecovirimat has no mutagenic or genotoxic activity.

2.5.4.4. Carcinogenicity

There were no carcinogenicity studies performed with tecovirimat and the applicant has not provided justification for not performing carcinogenicity studies. Considering the lack of genotoxicity of tecovirimat, the indication and duration of administration (a single cycle of treatment for 14 days), in line with the ICH S1A guideline, the lack of carcinogenicity studies is acceptable.

2.5.4.5. Reproductive and developmental toxicity

In the fertility and early embryonic development study (IITRI 2083-003-001 SN7) treatment with tecovirimat did result in a dose-dependent decrease in the fertility and fecundity rates. A significant decrease was noted in the rate of viable foetuses at the high-dose level of 1,000 mg/kg/day; however, this finding was observed in the absence of a significant decrease in the fertility/fecundity rates and was attributed to a single pregnant high-dose female that was included in the calculations for fertility/fecundity indices but was not included in the group of females given a uterine exam on GD 13 (as a definitive GD 13 could not be determined for this animal). There were no other tecovirimat-related effects reported on any fertility parameters.

However, SmPC section 5.3 states: "In male mice, decreased male fertility associated with testicular toxicity (increased percent abnormal sperm and decreased sperm motility) was observed at 1,000 mg/kg/day". Meanwhile, according to study IITRI 2083-003-001 SN7 report, only the number of abnormal sperm was noted in high-dose males with no changes in sperm counts or sperm motility. These changes were not considered to be biologically meaningful. There were no group differences in

male organ weights in comparison to the control group and no abnormalities of testes in high dose animals. In response to a request in the D120 LoQ to revise this statement the applicant revised section 5.3 of the SmPC to state;

In a fertility and early embryonic development study in mice, no biologically meaningful effects of tecovirimat on male or female fertility were observed at tecovirimat exposures (AUC) approximately 24 times higher than human exposure at the RHD.

In the EFD studies conducted in mice and rabbits, oral administration of tecovirimat resulted in adverse effects on maternal rabbits when given during the period of organogenesis but no effects on EFD or teratogenicity. Maternal toxicity noted in rabbits receiving 100 mg of tecovirimat/kg/day (the highest dose tested in this species) included mortality (in 9 out of 22 rabbits) and significant decreases in body weight (due to decreases in food consumption). The weight loss impacted the number of live fetuses per doe and increased the post-implantation losses and early resorption levels. The maternal NOAELs were considered to be the highest dose level of 1,000 mg/kg/day in mice and the mid-dose level of 30 mg/kg/day in rabbits while the developmental NOAELs in mice and rabbits were determined to be the highest dose levels of 1,000 and 100 mg/kg/day, respectively.

Section 5.3 of the SmPC states "No embryo-foetal toxicities were observed at doses up to 1,000 mg/kg/day in mice (approximately 23 times higher than human exposure at the RHD)….No embryo-foetal toxicities were observed at doses up to 100 mg/kg/day in rabbits (0.4 times the human exposure at the RHD)."

It is acknowledged that no embryo-foetal toxicity was observed in either study, however, considering the disparity in the margins calculated the applicant was asked to discuss which study, and hence safety margins are most appropriate to represent the true outcome of these studies. In response the applicant notes that from the rabbit pilot developmental toxicity study MPI 1151-024, the lowest dose tested of 300 mg/kg produced maternal toxicity, so it was too high to be considered for the definitive developmental toxicity study in rabbits. The highest dose tested in the definitive developmental toxicity study in rabbits was 100 mg/kg and did not produce embryo-foetal toxicity. Pregnant mice tolerated higher doses which produced higher exposures than the rabbit.

In a pre- and post-natal development study conducted in mice, the oral administration of tecovirimat at 100, 300, or 1,000 mg/kg/day did not result in any adverse effects on pre- or post-natal development.

The applicant was also asked to revise the wordings in Section 4.6, in line with the standard statements in Appendix 3 of the guideline (EMEA/CHMP/203927/2005), and 5.3 of the SmPC regarding these studies. In response these sections were updated to read;

Section 4.6:

<u>Pregnancy</u>

There are no data from the use of tecovirimat in pregnant women.
Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).

Tecovirimat is not recommended during pregnancy.

Section 5.3 contains:

In a fertility and early embryonic development study in mice, no effects of tecovirimat on female fertility were observed at tecovirimat exposures (AUC) approximately 24 times higher than human exposure at the RHD. In a fertility and early embryonic development study in mice, no biologically

meaningful effects of tecovirimat on male or female fertility were observed at tecovirimat exposures (AUC) approximately 24 times higher than human exposure at the RHD.

Reproductive toxicity studies have been performed in mice and rabbits. Based on pilot studies, the highest dose selected for the definitive study in rabbit was 100 mg/kg and in mice was 1,000 mg/kg. No embryo-foetal toxicities were observed in rabbit at doses up to 100 mg/kg/day (0.4 times the human exposure at the RHD) and no embryo-foetal toxicities were observed at doses up to 1,000 mg/kg/day in mice (approximately 23 times higher than human exposure at the RHD).

No embryo-foetal toxicities were observed at doses up to 100 mg/kg/day in rabbits (0.4 times the human exposure at the RHD). Maternal toxicity was detected in rabbits at 100 mg/kg/day, which included decreases in body weight and mortality.

Juvenile toxicity studies

Data from studies examining juvenile animals (monkeys) are taken from repeat dose toxicology studies, as well as pharmacokinetic studies and primary pharmacodynamic studies. No separate studies in offspring or juvenile animals are provided in the application.

The proposed indication encompasses paediatric patients weighing at least 13Kg. The average two-year-old human weighs 12 Kg. The youngest monkeys used in the applicant's studies were 19 months old (Study 246-TX-007), noting that 2-year old monkeys cover 5-12-year-old humans. A 6-month old monkey is the developmental equivalent of a 2-year-old human child, and ethically the youngest age monkeys can be used in studies is 10 months. It is therefore acknowledged that studies in pre-weaning NHPs are difficult to perform and ICH S11 guidance recommends an alternative testing approach. The applicant was asked to justify based on their studies the inclusion of early age groups in their indication. In response the applicant noted that data from the segment III study showed that mouse pups were exposed to tecovirimat via transplacental transfer and milk consumption. It was found that significant exposure levels of tecovirimat were achieved in pups via transplacental transfer but not via milk consumption (Study IITRI 2083-003-001 SN9).

In the transplacental transfer study, the drug levels were measured in mouse pups at 1, 4, 8, and 24 h after dosing of the mothers. Based on our data, the average amount of transplacental transfer in the highest dose group (1000 mg/kg) at 24-hour post-dose (at the highest drug levels) is 0.47% of maternal dose. This amount is equivalent to 17052 ng/g bodyweight of pups or 17052 ng/mL (based on average mouse body density of 1 g/mL) (Miller W.H., et al., 2005). The drug concentrations at 1, 4, 8, and 24 h time points as shown in Table 1 are used in estimation of AUC0-24h which is approximately 270918 ng*h/mL. The highest concentration (17052 ng/mL) and AUC0-24h in mouse litter are approximately 11 folds and 10 folds higher, respectively, than the Cmax and AUC0-24h in human on Day 1 at clinical dose of 600 mg twice daily (SIGA-246-008). The data confirm that mouse pups can be safely exposed to tecovirimat at 10 or 11 folds above human exposure.

In addition, metabolism of tecovirimat by esterases would be unaffected by very young age as one of the major esterases, have been shown to have similar levels in children between 3 weeks and 6 years old. The justification provided can be accepted for inclusion of young age groups in the indication.

2.5.4.6. Other toxicity studies

Phototoxicity

Administration of tecovirimat at single oral gavage dose levels of up to 2,000 mg/kg followed by UV radiation did not result in the development of skin reactions indicative of phototoxicity.

Metabolites

The exposure of the three main metabolites in humans (M4, M5, and TFMBA) was observed in both mice and monkeys. The exposures to M4 and M5 exceeded that in humans at the recommended clinical dose for mice, and the exposure to M5 exceeded that in humans for monkeys. The exposures to TFMBA in mice and monkeys was less than that in humans, but lack of a toxicological signal in either mice or monkeys, the lack of genotoxicity for TFMBA, and a minimal adverse event profile in humans, demonstrate that this metabolite does not represent a meaningful risk to humans.

Data showed that the TFMBA area under the plasma concentration time curve (AUC) constitutes the highest level in plasma (63% on Day 1 and 70% on Day 14) whereas the M4 AUC was 13% and 10% of total drug-related exposures on Day 1 and Day 14, respectively. M5 AUC constitutes only a minor fraction of total exposures (1% and 6% of the total drug-related exposures on Day 1 and Day 14, respectively).

The safety of M4 and M5 is supported by nonclinical data demonstrating that the plasma M4 exposure in mice and the plasma M5 exposures in both mice and monkeys were higher than those in humans. The exposure of TFMBA was disproportionately higher in humans than in animals.

TFMBA was negative for potential genotoxicity, no adverse effects were seen in monkeys after three months of testing, tecovirimat has a relatively short clinical dosing schedule with an excellent safety profile, and no unexpected adverse events were seen in clinical studies in those with severe renal or hepatic impairment. Plasma protein binding of TFMBA was low in mouse (50.0% bound) and high in monkey and humans (97.1 and 98.6% bound, respectively). Furthermore, the FDA concluded that although the TFMBA metabolite does not meet the standards of current guidance (ICH M3(R2)), considering the serious nature of the disease, the FDA QSAR computer modelling team has estimated that TFMBA's structure has no potential for genotoxicity. Genotoxicity has been evaluated by the applicant in a micronucleus test with mice at doses of tecovirimat up to 2,000 mg/kg, which based on exposure to tecovirimat provides a margin of ~28.

Impurities

Impurities and degradation products identified and monitored during the development of tecovirimat include SG1, SG2, Impurity A, SG1 Exo-isomer, SG2 Dimer, ST-246 Exo-isomer, Hydrazine, trifluoromethyl benzoic acid (TFMBA), and an unknown impurity designated Unknown 1.

SG1 and SG2 are starting materials in the production process of tecovirimat. These are controlled in the intermediate manufacturing process of the drug substance. Impurity A, SG1 Exo-isomer, SG2 Dimer, and ST-246 Exo-isomer are potential impurities or by-products of the drug substance starting materials. They are well characterised and controlled by specified impurity testing.

Hydrazine is used in the process to produce the starting material SG2 and is a potential degradation product of the drug substance. According to the application of the principles of the ICH M7 (R1) guideline (EMA/CHMP/ICH/83812/2013) hydrazine is mutagenic/genotoxic *in vitro* and *in vivo* and it is classified as Group 2B, or possibly carcinogenic to humans.

The applicant presented assessment of the SG2 structure (possibility of monoacylhydrazine) and mutagenic potential according to DEREK NEXUS and SARAH NEXUS methodology. The conclusion of this assessment is that SG2 is an impurity of Class 3 with respect to mutagenic and carcinogenic potential. It means that SG2 should be controlled at or below acceptable limits (appropriate threshold of toxicological concern, TTC) or a bacterial mutagenicity assay should be conducted with SG2. The applicant did not carry out mutagenicity assay tests with SG2. The quality control of SG2 presented by the applicant was considered insufficient. Following assessment of the applicant's response to D120 MO2b, in principle it can be agreed that an SG2 level above 120 µg/day can be justified based on the

principles of ICH M7 and taking the indication into account, however it also follows that the risk should be reduced as much as possible. In response to the D180 Quality MO the applicant has provided batch data for the batch of tecovirimat used in genotoxicity testing, where SG2 was present at 0.08%. All genotoxicity tests were negative. Nonetheless the applicant has committed to carrying out an Ames test on SG2 as a PAC.

In conclusion, the results of the nonclinical toxicology studies conducted to date can be considered to suggest an acceptable safety profile to support administration of Tecovirimat in humans.

2.5.5. Ecotoxicity/environmental risk assessment

At present, only Phase I data is available for assessment. Until the results of the Phase II assessment are complete, the available data do not allow to conclude definitively on the potential risk of tecovirimat to the environment. The applicant commits to complete Phase II of the Environmental Risk Assessment and provide the updated ERA including all study reports, by February 2023.

Table 1: Summary of main study results

Substance (INN/Invented Name): Tecovirimat			
CAS-number (if available): 869572-92-9			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	3.13	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	3.13	not B
	BCF		
Persistence	DT50 or ready biodegradability		
Toxicity	NOEC or CMR		
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	Present day prevalence 3.5×10^{-6} Hypothetical smallpox endemic 0.0058 (optimistic) 0.16 (medium) 4.6 (pessimistic)	µg/L	> 0.01 threshold (Y)
Other concerns (e.g. chemical class)			(N)

2.5.6. Discussion on non-clinical aspects

Pharmacology

The nonclinical pharmacology of tecovirimat was investigated in a comprehensive set of *in vitro* and *in vivo* studies designed to assess the activity and mechanism of action of the test material. The Majority of nonclinical studies conducted were not-GLP compliant. However, pivotal primary pharmacodynamics studies in monkeys and rabbits, safety pharmacology studies and majority of pharmacodynamic drug interaction studies were carried out in accordance with GLP. This is in line with appropriate guidelines on nonclinical studies.

Collectively, the *in vitro* pharmacology data demonstrated that tecovirimat shows antiviral specificity against all species/strains within the orthopoxvirus genus that have been tested (including the human pathogens variola, monkeypox, vaccinia, and cowpox viruses, as well as animal host-adapted ectromelia and RPXV), and that the antiviral activity is limited to the parent compound (and not to tecovirimat metabolites). The EC_{50} of tecovirimat is very similar for all the orthopoxvirus species, and ranges from ~10-70 nM. Tecovirimat targets the viral VP37 protein, which is highly conserved amongst all the orthopoxviruses. Tecovirimat prevents the interaction of VP37 with cellular proteins that are likely involved in the envelopment process.

Pivotal *in vivo* pharmacology data indicate that the administration of tecovirimat to monkeys infected with MPXV, and rabbits infected with RPXV, resulted in decreases in the incidence of mortality, circulating viral DNA, and clinical signs of infection. Based on these studies the monkey model was determined to be the most conservative model for estimation of the human dose.

Pivotal nonclinical studies suggest that tecovirimat oral treatment was significantly effective to NHPs at minimum dose of 10 mg/kg and to rabbits at minimum dose of 20 mg/kg when treated daily for 14 days (at least 5 days are required) starting from Day 4 (delay up to maximum Day 5) post appropriate infection in animals. Survival of animals treated with effective tecovirimat doses was 80%-100%. Increases to higher tecovirimat doses above the minimum effective dose for each species did not confer a greater benefit in either animal model. The primary pharmacology *in vivo* studies revealed the efficacy of tecovirimat in treating of orthopoxvirus related diseases in animals. Considering that monkeys and rabbits are the primary models for clinical effects, supportive studies in prairie dogs and squirrels did not give any additional value and from 3Rs point of view should not be encouraged.

In vitro and *in vivo* safety pharmacology studies indicate that tecovirimat is not expected to pose a significant CNS, respiratory, or CV risk.

Pharmacodynamic drug interaction studies showed that tecovirimat does not have a significant negative effect on vaccination efficacy when co-administered with appropriate smallpox vaccine in monkeys or mice.

No secondary pharmacology screening of tecovirimat was carried out. The applicant has provided a robust justification for the lack of secondary pharmacology studies. Tecovirimat has high specificity for its target, VP37. Both *in vitro* and *in vivo* testing demonstrated little evidence for off-target activity. Mortality was observed in dogs; however, this species appears to be very sensitive to tecovirimat, and mortality was not observed in either mice or monkeys.

Pharmacokinetics

The absorption, distribution, biotransformation and excretion of tecovirimat was investigated in *in vitro* and *in vivo* studies with rabbits, monkeys, mice, rats and dogs. The data submitted are in accordance with legal requirements, guidelines and scientific advice.

Methods of analysis (LC-MS/MS or HPLC-MS/MS) used to quantify tecovirimat and its metabolites in plasma were appropriately validated for intra-assay and inter-assay reproducibility.

In vivo oral bioavailability studies conducted with mice, rats, rabbits, and monkeys indicate that tecovirimat has good oral bioavailability. In oral repeat dose studies carried out in mice, rats, rabbits and monkeys, exposure parameters generally increased with dose but dose-proportionality was not always observed.

Following oral administration in mice, tecovirimat was systemically distributed with the highest concentrations noted in liver and gall bladder, respiratory tract tissues, and bone marrow. The highest tissue concentrations were observed at 24 hours post-dose. Tecovirimat was demonstrated to cross the blood brain barrier as it was measured in the brains of mice, dogs and monkeys. In a placental and

milk transfer study in mice, tecovirimat was noted to be transferred to the offspring through the placenta and the milk.

Clinical data reveal that tecovirimat is extensively metabolised by amide hydrolysis into metabolites M4 and TFMBA. M4 is presumably metabolised via a deamination process to form the metabolite M5. Tecovirimat and M4 are further metabolised by direct glucuronide conjugation. These metabolites were also identified in oral studies in monkeys and mice. As observed in humans, the metabolite-to-parent exposure ratios in monkeys indicated that tecovirimat was extensively metabolised. However, the exposure ratios were lower in mice and the exposure of TFMBA was disproportionately higher in humans than in animals.

Tecovirimat was excreted unchanged in faeces, the main route of elimination, whereas in urine, several metabolites, including TFMBA, were detected and only a trace amount of the parent compound was present.

Based on *in vitro* DDI study results conducted using human samples, tecovirimat does not show inhibition potentials toward major CYP enzymes and common transporters except breast cancer resistance protein (BCRP), but it is a substrate of human recombinant UGTs (specifically UGT1A1, 1A3 and 1A4). However, it may induce certain CYP enzymes including CYP3A4, and its metabolites M4 and M5 have the potential to produce drug-drug interactions by the induction of CYP2B6.

From the presented studies tecovirimat properties across the nonclinical species tested *in vivo* and across human and animals *in vitro* are comparable. Overall, the NC data show that oral administration of tecovirimat is likely to result in adequate exposure of substance to assure protection against smallpox and other human orthopoxviruses in humans.

Toxicology

The non-clinical safety of tecovirimat has been established in acute and repeated dose oral toxicity studies in mice, rats, dogs, and monkeys, and the genotoxic potential has been assessed *in vitro* and *in vivo*. In addition, reproductive toxicity has been evaluated in mouse and rabbit models.

In the key repeat-dose toxicity studies, oral administration of tecovirimat was not associated with any significant tecovirimat-related findings in either the mouse or the monkey.

In repeat-dose toxicity studies, there were no significant tecovirimat-related findings in either mice or monkeys administered tecovirimat by the oral route.

In repeated-dose toxicity study, statistically significant increase in absolute and relative reticulocyte counts in the high dosed females was documented. But the increases were not considered toxicologically significant since they were not associated with any histopathological changes in the liver or bone marrow of these animals. However, the histological examination was been performed for the control group and 100 mg/kg dose group only and do not correlate with reticulocyte count. Therefore, this non-clinical data cannot completely exclude the relation of these changes with the use of tecovirimat.

The exposures achieved in mice at the 1,000 mg/kg/day dose level in the 3 month study were approximately 21- to 24-fold and 26- to 32-fold over the human clinical exposure (at 600 mg BID dosing for 14 days) for AUC and Cmax values, respectively .

The dose of 300 mg/kg/day for 3 months in the monkey produced AUC and Cmax values of 2.5-fold and 2.4-fold over the human exposures, respectively, at a clinical dose of 600 mg BID for 14 days.

Regarding the dog studies, the applicant was asked to comment on the deaths and seizures seen at 100 mg/kg in Study 014 as the exposure margins at the same dose in Study 015, are low compared to the human data from the pivotal Study SIGA-246-008, at 600 mg BID providing margins of only 2.1

and 0.64 for Cmax and AUC respectively. At the NOAEL in this study the margins are 0.97 and 0.31 for Cmax and AUC respectively. Dogs appear to be very sensitive as a species to tecovirimat. Nonetheless due to the adverse event in dogs, SIGA monitored the EEGs in all human subjects in the pivotal safety study (study SIGA-246-008). The EEG results which were reviewed from the SIGA-246-008 study do not present a signal of concern related to possible seizures regarding the use of tecovirimat at the 600 mg twice per day dose.

The applicant revised the wording in section 5.3 of the SmPC with respect to these studies.

In addition, the applicant provided a new PK study (TX-019) where NHPs were dosed intravenously, thereby achieving higher exposures than that achieved orally. The maximum unbound tecovirimat Cmax in NHPs derived from 246-TX-019 at which no CNS toxicity was observed (1922 ng/mL) is considerably higher than the calculated maximum unbound Cmax in healthy adults dosed to steady state with 600 mg BID (from SIGA-246-008 [892 ng/mL]).

Tecovirimat is not genotoxic. Considering the lack of genotoxicity, the indication and duration of administration the lack of carcinogenicity studies is acceptable.

In the reproductive and developmental toxicity studies, oral gavage administration of tecovirimat to male and female mice was not associated with any adverse effects on male or female fertility, implantation or early embryonic development. However, it is stated in the SmPC section 5.3., that in male mice, decreased male fertility associated with testicular toxicity was observed.

No embryo-foetal toxicity was observed in either a mouse or rabbit EFD study. However, considering the disparity in the margins calculated, 27 and 0.4 respectively, the applicant was asked to discuss which study, and hence safety margins are most appropriate to represent the true outcome of these studies. The applicant is also asked to revise the wordings in Sections 4.6 and 5.3 of the SmPC regarding these studies.

In response sections 4.6 and 5.3 of the SmPC were updated with respect to clarifications regarding these studies.

No specific juvenile toxicity studies were carried out. The proposed indication encompasses paediatric patients weighing at least 13Kg. Data from pre/post-natal development mouse studies helps support the safety of tecovirimat administered at earlier ages.

Tecovirimat did not result in the development of skin reactions indicative of phototoxicity in mice. There was no carcinogenicity, antigenicity, immunotoxicity and dependence studies performed with tecovirimat.

Data obtained from mouse, monkey and human PK studies indicate that the main metabolites M4 and M5 have been qualified in accordance with the guidelines. The AUC for TFMBA was disproportionately higher in humans than in the animals tested, but it is believed that the formation of TFMBA does not contribute to any safety issue and additional nonclinical safety studies for TFMBA may not be necessary if the applicant can determine the pharmacokinetics of the major metabolites in renal and hepatic impairment trials.

Impurities and degradation products identified and monitored during the development of tecovirimat. According to DEREK NEXUS and SARAH NEXUS methodology SG2 is an impurity of Class 3 with respect to mutagenic and carcinogenic potential and should be controlled at or below acceptable limits or a bacterial mutagenicity assay should be conducted with SG2. The applicant did not provide mutagenicity assay tests with SG2 and has not performed an Ames test with SG2 following the D120 LoQ. In principle it is agreed that a level above 120 µg/day can be justified based on the principles of ICH M7 and taking the indication into account, however it also follows that the risk should be reduced as much as possible. In the absence of a negative Ames test result, the limit of SG2 has been set to NMT 0.05%

in the drug substance and NMT 0.05% in the drug product as it is a process impurity as well as a potential degradation product. The limit of NMT 0.05% allows the lifetime exposure to be under 38.3 mg. Additionally, SG2 is infrequently detected above the LOQ during 84 months of stability. Nonetheless, the applicant proposes to perform the Ames test for SG2 as a post authorisation measure.

At present, only Phase I Environmental Risk Assessment data is available for assessment. The available data do not allow to conclude definitively on the potential risk of tecovirimat to the environment.

Overall, the nonclinical toxicology studies conducted to date are considered acceptable and suggest a favourable safety profile of Tecovirimat in humans.

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points to be addressed:

To complete Phase II of the Environmental Risk Assessment and provide the updated ERA including all study reports.

2.5.7. Conclusion on the non-clinical aspects

The applicant has provided adequate responses to the concerns raised regarding the pharmacology and toxicology studies. In addition, a new PK study was provided in support of an IV formulation and allowed evaluation of tecovirimat at higher exposure than oral administration.

The non-clinical studies are adequate to support the Marketing Authorisation Application for tecovirimat.

In addition, until the results of the Phase II Environmental Risk Assessment are complete, no final conclusions on the environmental risk assessment is currently possible.

The CHMP considers the following measures necessary to address the non-clinical issues:

The applicant commits to complete Phase II of the Environmental Risk Assessment and provide the updated ERA including all study reports.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Study No.	Type of Study	N[a]	Objective(s)
SIGA-246-008	Pivotal Phase 3, proposed clinical dose of oral tecovirimat 600 mg or placebo twice daily for 14 days	419	Safety, tolerability, and PK in fed and fasted healthy subjects
SIGA-246-015	Phase 1 multiple-dose (600 mg tecovirimat twice daily for 15 days); DDI study	77	Safety, tolerability, and effect of repeated doses of tecovirimat on single-dose PK of probe substrates flurbiprofen, omeprazole, midazolam, repaglinide, and bupropion
SIGA-246-002	Phase 1 multiple-dose (250, 400, or 800 mg tecovirimat or placebo once daily for 21 days)	19	Safety, tolerability, and PK in fed state
SIGA-246-004	Phase 2 multiple-dose (400 mg or 600 mg tecovirimat or placebo once daily for 14 days)	101	Safety, tolerability, and PK in fed state
SIGA-246-001	Phase 1 single-dose (500, 1000, or 2000 mg tecovirimat or placebo)	37	Safety, tolerability, and PK in fed and fasted state
SIGA-246-PO-005	Phase 1 single-dose, bioavailability of 2 forms (I and V) of tecovirimat (400 mg)	11	Safety, tolerability, and PK of 2 forms (I and V) of tecovirimat in fed state
SIGA-246-009	Phase 1 single-dose (600 mg tecovirimat and 100 µCi of [^{14}C]-tecovirimat), mass balance	6	Safety, tolerability, mass balance, and routes of elimination of [^{14}C]
SIGA-246-010	Phase 1 single supratherapeutic dose (1000 mg tecovirimat), effects of tecovirimat; thorough ECG study	48	ECG, safety, tolerability, and PK of single doses of tecovirimat 1000 mg, moxifloxacin 400 mg, and placebo in the fed state
SIGA-246-012	Phase 1 single-dose (600 mg tecovirimat), effect of renal impairment	37	PK, safety, and tolerability in subjects with varying degrees of renal impairment including end-stage renal disease requiring HD; effect of HD on the removal of tecovirimat from the bloodstream
SIGA-246-013	Phase 1 single-dose (600 mg tecovirimat), effect of hepatic impairment	32	PK, safety, and tolerability in subjects with varying degrees of hepatic impairment
SIGA-246-018	Phase 1 single-dose (100, 200, or 600 mg tecovirimat), effect of mixing capsule contents with food or liquid	47	PK, safety, and tolerability after administration of a single dose as capsule contents mixed with a food or liquid compared to a single dose as intact capsules
SIGA-246-006	Phase 1 single-dose (600 mg tecovirimat), palatability and drug-masking	21	Palatability/taste assessment in foods; drug was not ingested

[a]N is the number of subjects completing the study.
KEY: DDI = drug-drug interaction; ECG = electrocardiogram; HD = hemodialysis; N = sample size; PK = pharmacokinetics

Tecovirimat can exist as different crystalline polymorphs of which the major Forms are I, III and V. All forms of tecovirimat are chemically the same and behave similarly once they reach the systemic circulation. The only difference between Form I and Form V concerns their solubility, which impacts on absorption. Form V is a hemihydrate and was used in the earlier clinical studies (Phase 1, single- and multiple-dose clinical trials SIGA-246-001 and 002) but it could not be manufactured consistently at larger scales. Therefore, the applicant switched to Form I, which is a monohydrate and was used in all other clinical studies with some small changes in capsule formulation over time. SIGA-246-005 (see below) demonstrated that single oral doses of Form V and Form I administered as 400 mg (2 x 200 mg capsules) in the fed state were not bioequivalent.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Absorption

The absolute bioavailability of tecovirimat has not been determined in humans. In mice and rats, the oral bioavailability after a single dose of tecovirimat was highest at the lowest dose tested (30 mg/kg). Absolute bioavailability was 40-45% in male and female mice and ~15% in male and female rabbits on Day 7 of dosing at 100 mg/kg/day. In a single-dose study in monkeys, the absolute bioavailability of tecovirimat was 50% in fed and 28% in fasted animals.

In SIGA-246-001, using single ascending doses of 500, 1,000 and 2,000 mg given in the fasted state and 1000 mg after a standard breakfast, tecovirimat was detectable in plasma from 0.5 h.

When dosing in the fasted state, plasma Cmax was proportional from 500 to 1000 mg but less than proportional between 1000 and 2000 mg. AUC_{inf} was slightly more than dose proportional between 500 and 1000 mg but less than dose proportional between 1000 and 2000 mg. Plasma clearance (CL) was independent of dose for the 500 and 1000 mg levels but was increased for the 2000 mg dose level. At the 1000 mg dose level, non-fasted subjects had greater apparent Cmax, Tmax and AUCinf than fasted subjects with a shorter t1/2 and a lower CL. The amount of tecovirimat that appeared in urine over 24 h was <1 mg in all groups.

In SIGA-246-002, using once daily dosing for 21 days (250, 400 and 800 mg) and dosing after a standard light meal (400-450 kcal and ~25% fat) on PK sampling days, steady state had been achieved by Day 6. The accumulation factors (Day 21) ranged from 1.16 to 1.21. The fraction excreted unchanged in urine (expressed as % of dose) was very low, with mean values from 0.02% to 0.03%.

In SIGA-246-004, with once daily dosing for 14 days at 400 and 600 mg after standard light meals (as above), steady state was achieved by Day 5 for the 400 mg group and by Day 6 for the 600 mg group.

On Day 1, the mean Cmax and AUC_{last} values increased by 25% and 26%, respectively, in response to a 50% increase in dose. On Day 14, the mean Cmax values increased by 18% in response to a 50% increase in dose and were increased by 10% and 4% relative to the Day 1 in the 400 mg and 600 mg groups, respectively. Mean AUC_{tau} values increased by 23% in response to a 50% increase in dose and the Day 14 vs. Day 1 accumulation factors were 1.31 and 1.33 for the 2 treatment groups.

Table 2: Summary of Days 1 and 14 ST-246 Plasma Pharmacokinetic Variable Estimates (PK Population)

	C_{max} (ng/mL)	C_{min} (ng/mL)	T_{max} (h)	AUC_{last} (ng·h/mL)	AUC_{τ} (ng·h/mL)	λ_z (1/h)	$t_{1/2}$ (h)	CL/F (L/h)	V_z (L)	RAC	C_{avg} (ng/mL)	Fluctuation (%)
Day 1												
ST-246 400 mg												
N	43	—	43	43	22	—	—	—	—	—	—	—
Mean (SD)	1170 (429)	—	4 (1)	9926 (4044)	11329 (4945)	—	—	—	—	—	—	—
Median	1100	—	4	8527	11589	—	—	—	—	—	—	—
Range	449-2560	—	2-6	3889-20692	3889-20606	—	—	—	—	—	—	—
ST-246 600 mg												
N	44	—	44	44	23	—	—	—	—	—	—	—
Mean (SD)	1467 (626)	—	4 (1)	12469 (5280)	13895 (5702)	—	—	—	—	—	—	—
Median	1350	—	4	12212	12762	—	—	—	—	—	—	—
Range	410-3670	—	2-6	3090[a]-29790	5602-29784	—	—	—	—	—	—	—
Day 14												
ST-246 400 mg												
N	41	41	41	41	40	24	24	40	24	41	40	40
Mean (SD)	1286 (449)	174 (80)	4 (1)	17183 (7708)	12026 (4255)	0.03 (0.02)	26 (11)	38 (14)	1248 (588)	1.3 (0.5)	501 (177)	226 (58)
Median	1210	177	4	15923	10769	0.03	24	37	1176	1.3	449	220
Range	534-2420	0-437	2-6	4787-37908	4829-21263	0.02-0.08	8-46	19-83	464-2537	0.6-3.1	201-886	85-378
ST-246 600 mg												
N	42	41	41	42	40	26	26	40	26	41	40	40
Mean (SD)	1523 (607)	201 (112)	3 (1)	19448 (9800)	14791 (5712)	0.05 (0.04)	24 (15)	48 (25)	1356 (790)	1.3 (0.6)	616 (238)	225 (51)
Median	1635	177	4	19592	14333	0.04	20	42	1120	1.3	597	229
Range	0-3120	0-461	2-6	0[b]-41664	3793-34966	0.01-0.23	3-58	17-158	286-3341	0.6-4.1	158-1457	54-330

The dose proportionality analysis showed that the ratios of dose normalised Cmax and AUC_{tau} values ranged from 80% to 85%, and the 90% confidence intervals did not include 1.0. Therefore, dose proportionality could not be concluded.

SIGA-246-008

This was a double-blind study designated as pivotal by the applicant since it compared the final dose regimen of tecovirimat (600 mg BID for 14 days) vs. placebo in adult subjects. There were two parts – Lead-in and Expanded portions. Randomisation was stratified by age in the latter cohort only.

The Lead-in cohort of 40 subjects compared tecovirimat PK when dosing was in the fed (within 30 min of a meal of ~ 600 kcal and 25 g fat) and fasted (no food or drink 2 h before or 2 h after dosing) states. Another 382 subjects were to be enrolled into the Expanded portion, of which 40 in the tecovirimat group were to be assessed for PK. Dosing of this cohort was in the fed state. Blood sampling was conducted to determine plasma concentrations of tecovirimat, M4, M5 and 4-trifluoromethyl-benzoic acid [TFMBA].

There were 452 subjects randomised and 449 were treated, of which 419 (93.3%) completed assigned treatment but 426 completed study (last visit). The study population comprised more female vs. male subjects (59% vs. 41%) with a mean age of ~40 years and range from 18-80 years. In the PK subpopulation (n=81; 65 tecovirimat), 52.4% of subjects were female and the mean age was ~37 years with a range of 18-72 years. Disposition and analysis populations are shown below.

Table 3: Subject Disposition (Safety Population)

	Placebo (N = 90) n (%)	Tecovirimat 600 mg (N = 359) n (%)	Total (N = 449) n (%)
Enrolled[a]			851
Randomized	91	361	452
Received at least 1 dose of study drug	90 (100)	359 (100)	449 (100)
Completed dosing	85 (94.4)	334 (93.0)	419 (93.3)
Discontinued dosing	5 (5.6)	25 (7.0)	30 (6.7)
Reason for dosing discontinuation			
Adverse event	2 (2.2)	6 (1.7)	8 (1.8)
Subject's request	0	4 (1.1)	4 (0.9)
Inability to complete study procedures	1 (1.1)	1 (0.3)	2 (0.4)
Lost to follow-up	0	6 (1.7)	6 (1.3)
Protocol violation	1 (1.1)	4 (1.1)	5 (1.1)
Other	1 (1.1)	4 (1.1)	5 (1.1)
Completed study[b]	85 (94.4)	341 (95.0)	426 (94.9)
Discontinued study	5 (5.6)	18 (5.0)	23 (5.1)
Reason for study discontinuation			
Lost to follow-up	0	3 (0.8)	3 (0.7)
Other	0	1 (0.3)	1 (0.2)
Did not attend Day 28 Follow-up Visit, did not complete dosing	4 (4.4)	14 (3.9)	18 (4.0)
Did not attend Day 28 Follow-up Visit, completed dosing	1 (1.1)	0	1 (0.2)

Source: Table 14.1.1

Notes: All percentages were based on the Safety Population.

[a] Subjects were considered to be enrolled if they provided written consent.

[b] Subjects who completed the Day 28 (+ 2 days) Follow-up Visit were considered to have completed the study.

Table 4: Analysis Populations

	Placebo (N = 90) n (%)	Tecovirimat 600 mg (N = 359) n (%)	Total (N = 449) n (%)
Enrolled Population			851
ITT Population (randomized)	91	361	452
Safety Population	90 (100)	359 (100)	449 (100)
PP Safety Population	85 (94.4)	336 (93.6)	421 (93.8)
PK Population	0	63 (17.5)	63 (14.0)
Age at randomization (actual strata)[a]			
18–30 years	24 (26.7)	102 (28.4)	126 (28.1)
31–45 years	25 (27.8)	97 (27.0)	122 (27.2)
46–64 years	22 (24.4)	92 (25.6)	114 (25.4)
65–80 years	11 (12.2)	36 (10.0)	47 (10.5)
Age at randomization (planned strata)[a]			
18–30 years	24 (26.7)	104 (29.0)	128 (28.5)
31–45 years	25 (27.8)	96 (26.7)	121 (26.9)
46–64 years	22 (24.4)	92 (25.6)	114 (25.4)
65–80 years	11 (12.2)	35 (9.7)	46 (10.2)

Source: Table 14.1.1
Key: ITT = intent-to-treat; PK = pharmacokinetic; PP = per-protocol.
Notes: All percentages were based on the Safety Population.
Analysis populations were defined as follows: Enrolled – provided consent; ITT – randomly assigned to treatment; Safety – received any study drug; PP Safety – took at least 80% of study drug; PK – all subjects in the PP Safety Population who took at least the last 2 doses of study drug in sequence, had sufficient plasma concentration data, and had no protocol deviations or other circumstances that would have excluded them from analysis.

Fasted vs. fed in the Lead-in cohort:

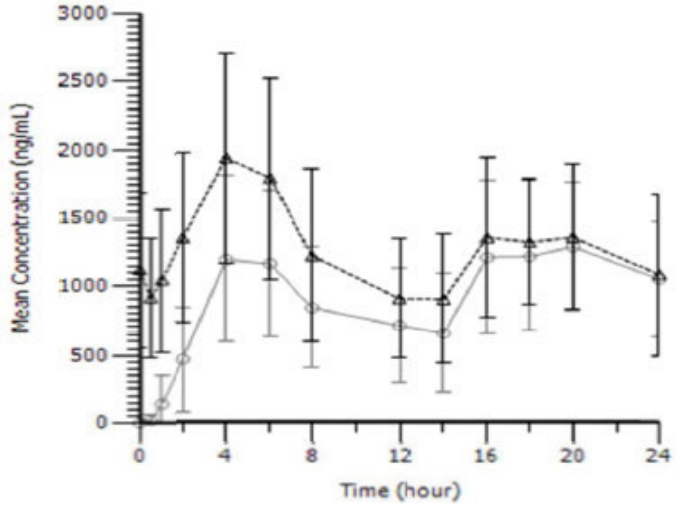
The mean Cmax and AUC_{0-24} values for fed subjects were approximately 1.4-fold higher vs. fasted subjects while mean $t_{1/2}$ values were comparable (19.3 vs. 23.1 h, respectively).

Table 5: Mean (±SD) Plasma Pharmacokinetic Parameters at Days 1 and 14 for the Lead-in Cohort Grouped by Fed and Fasted for Tecovirimat (Lead-in Cohort)

	Day 1		Day 14	
	Fed (N = 16)	Fasted (N = 15)	Fed (N = 16)	Fasted (N = 15)
C_{max} (ng/mL)				
Arith Mean (SD)	1559.1 (623.74)	1261.2 (475.00)	2473.8 (958.11)	1714.4 (768.37)
C_{min} (ng/mL)				
Arith Mean (SD)	393.25 (195.008)	204.72 (146.510)	678.16 (304.847)	414.07 (267.140)
C_{avg} (ng/mL)				
Arith Mean (SD)	868.875 (321.5305)	609.146 (244.7234)	1354.434 (591.7730)	981.042 (470.4023)
C_{tau} (ng/mL)				
Arith Mean (SD)	608.75 (323.174)	206.95 (145.630)	1046.1 (568.81)	415.9 (270.45)
T_{max} (h)				
Med (Min, Max)	6.042 (4.00, 20.00)	20.000 (14.00, 23.92)	3.917 (0.00, 18.00)	14.000 (1.00, 18.00)
AUC_{0-24} (h·ng/mL)				
Arith Mean (SD)	23561.064 (9137.2693)	17242.018 (6754.1219)	32506.409 (14202.5530)	23545.462 (11289.6707)
AUC_{last} (h·ng/mL)				
Arith Mean (SD)	20789.960 (7691.0369)	14582.391 (5859.9682)	50625.435 (21008.1083)	39582.586 (21207.3871)
AUC_{tau} (h·ng/mL)				
Arith Mean (SD)	20789.960 (7691.0369)	14582.391 (5859.9682)	32506.409 (14202.5530)	23551.616 (11289.8026)
$AUC_{0-\infty}$ (h·ng/mL)				
Arith Mean (SD)	—	—	50974.571 (21166.0652)	40718.267 (22203.0984)
$t_{1/2}$ (h)				
Arith Mean (SD)	—	—	19.294 (5.6023)	23.094 (15.9760)
CL_{ss}/F (L/h)				
Arith Mean (SD)	—	—	20.812 (6.3233)	29.616 (11.3495)
V_Z/F (L)				
Arith Mean (SD)	—	—	572.324 (246.1923)	916.982 (504.1979)
R_{ac} AUC_{tau}				
Arith Mean (SD)	—	—	1.593 (0.4046)	1.691 (0.4919)
% Fluctuation				
Arith Mean (SD)	—	—	139.125 (45.7909)	135.534 (28.3496)

Fed state data from Lead-in and Expanded cohorts (n=48)

After multiple dosing in fed subjects, tecovirimat reached a mean Cmax of 2208.8 ng/mL in ~4 h. The tecovirimat mean Cmin estimated from all fed subject data on Day 1 was 560 ng/mL with a median of 490 ng/mL and range from 143-2020 ng/mL (CV% 65). On day 14 the mean Cmin was 690 ng/mL, with median at 694 ng/mL, range from 2.5-1360 ng/mL and CV% 37.6.



Notes: Day 1 = grey (n = 48); Day 14 = black (n = 48).

Figure 2: Mean ± SD Plasma Concentration -Time Profile of Tecovirimat in Fed Subjects on Day 1 and Day 14 (PK Population)

The metabolites M4, M5 and TFMBA reached Cmax in ~6 to 16 h. Plasma exposures to tecovirimat and metabolites in the fed population were higher on Day 14 compared with Day 1. The accumulation ratios from AUC_{0-24} values were 1.18 for tecovirimat, 1.7 for M4, 14.1 for M5 and 2.4-fold for TFMBA.

Table 6: Plasma Exposure (C_{max} and AUC_{0-24}) for Tecovirimat and Metabolites (M4, M5, and TFMBA) in Fed Subjects at Day 1 and Day 14

	C_{max} (ng/mL)		AUC_{0-24} (h·ng/mL)			
	Day 1	Day 14	Day 1	% of Total Exposure	Day 14	% of Total Exposure
Tecovirimat	1591.00	2208.75	25875.94	24.0	30632.18	13.5
M4	906.96	1289.52	13634.28	12.6	23486.76	10.4
M5	109.11	665.48	929.11	0.9	13066.87	5.8
TFMBA	5135.63	7955.83	67597.04	62.6	159582.68	70.4

Source: Listing 16.2.5.2.2; WinNonlin 6.4 report
Key: AUC_{0-24}= area under the plasma concentration-time curve from time 0 to 24 hours; C_{max} = maximum observed drug concentration in plasma; TFMBA = 4-(trifluoromethyl)-benzoic acid.
Note: Total exposure was a summation of the AUC_{0-24} values for tecovirimat and all metabolites.

SIGA-246-PO-005 compared 400 mg single doses as I and V forms, each administered as 2 x 200 mg capsules (the excipients were identical between I and V formulations) within 30 min of completing a standard light meal (400-450 kcal and 25% fat).

Table 7: Summary of ST-246 Plasma PK Parameter Estimates (PK Population)

Form Group	Statistics	AUC_{0-t} (ng.hr/mL)	$AUC_{0-\infty}$ (ng.hr/mL)	$AUC_{(extrap)}$ (%)	$t_{1/2}$ (hr)	C_{max} (ng/mL)	T_{max} (hr)
Form I	N	12	11	11	11	12	12
	Mean	15624.5	19922.02	17.444	27.446	1068.9	3.8
	SD	5449.188	6543.563	7.84	13.109	294.3	1.5
	CV%	34.876	32.846	44.947	47.763	27.5	39.6
	Geometric Mean	14816.26	19049.63	15.748	24.746	1026.9	3.5
	Median	14151.15	17201.75	13.214	25.12	1170	3.5
	Minimum	8053.5	13959.18	5.7	10.94	525	2
	Maximum	26596.58	31058.8	30.4	56.48	1590	8
	Missing	0	1	1	1	0	0
Form V	N	11	8	8	8	11	11
	Mean	20065.32	21982.71	15.275	29.18	1230.2	3.8
	SD	6744.974	9330.953	10.811	21.992	348.6	1.6
	CV%	33.615	42.447	70.78	75.365	28.3	41.9
	Geometric Mean	19020.83	20409.17	12.369	23.083	1185	3.6
	Median	19398.5	19465.47	12.465	16.647	1180	4
	Minimum	10398.53	11946.95	4.53	11.48	732	2
	Maximum	30974	39058.28	37.51	69.45	1940	8
	Missing	0	3	3	3	0	0

NOTE: For a given variable and drug form, geometric mean was not calculated if any of the values was 0
KEY: $AUC_{0-\infty}$ = Area under the plasma concentration-time curve from time zero to infinity; AUC_{0-t} = Area under the drug concentration-time curve from time zero to time t where t is the last timepoint with a drug concentration ≥ lowest obtainable quantification; $AUC_{(extrap)}$ =Area under the curve extrapolated $t_{1/2}$ = Terminal half-life; C_{max} = maximum plasma concentration; CV% = Coefficient of variance; h = hours; N = Number of subjects; PK = Pharmacokinetics; SD = Standard deviation; T_{max} =Time to maximum plasma concentration

The two formulations were not bioequivalent based on $AUC_{0-\infty}$ and AUC_{0-T} values, i.e. values were lower for the I Form. The bioequivalence criteria were met for Cmax but the upper 90% CI was < 1.00.

Table 8: Bioequivalence Analysis of ST-246 Plasma Pharmacokinetic Parameter Estimates (PK Population)

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TABLE 21.4
BIOEQUIVALENCE ANALYSIS OF ST-246 PLASMA PHARMACOKINETIC PARAMETER ESTIMATES
(PK POPULATION)

Variable CV%	Geometric Mean [1] Test N=12	Geometric Mean [1] Reference N=11	Ratio (%) [2] (Test/Ref)	90% CI [3] Lower	90% CI [3] Upper	Power	ANOVA
ln(Cmax (ng/mL))	1026.869	1161.847	88.383	80.602	96.914	0.9851	11.820
ln(AUC(0-t) (ng.hr/mL))	14816.260	18865.366	78.537	67.764	91.022	0.6336	19.103
ln(AUC(0-inf) (ng.hr/mL))	19305.414	21945.342	87.970	73.903	104.716	0.4039	16.590

SIGA-246-018

This was a randomised partial crossover study to further investigate the effect of foods that had been selected from the palatability study SIGA-246-006. Capsule contents were opened and mixed with 2% fat milk or with apple sauce. All subjects received their assigned doses 30 min after a standard breakfast of 600 kcal and 25 g fat. In each dosing group Tmax occurred at 3.5-4 h except after intact capsules in cohort 3 (5 h). The comparisons made within cohorts 3 and 4 after 600 mg doses (3 x 200 mg capsules) indicated slightly higher Cmax and AUC values for the opened capsules mixed with milk or apple sauce vs. intact capsules, with a more notable effect of milk than apple sauce. As shown below, the 80, 125% limits were slightly exceeded for several of the comparisons made.

Table 9: Statistical Analysis of Pharmacokinetic Parameters for Tecovirimat 600 mg (Pharmacokinetic Population)

Parameter (unit)	Treatment	Cohort	Period	N	Geometric Mean	Treatment Comparison	Ratio (%) of Geometric Mean	90% CI of the Ratio (%)	Intrasubject Variability (CV)
AUC_{0-t} (h*ng/mL)	Tecovirimat 600 mg in 2% milk	3	1	12	20856.1	Cohort 3, Period 1/ Cohort 3, Period 2	113.96	(98.81, 131.44)	18.69
	Tecovirimat 600 mg in capsules	3	2	11	18301.2				
	Tecovirimat 600 mg in applesauce	4	1	12	17536.0	Cohort 4, Period 1/ Cohort 4, Period 2	112.52	(101.91, 124.22)	13.56
	Tecovirimat 600 mg in capsules	4	2	12	15585.3				
AUC_{0-24h} (h*ng/mL)	Tecovirimat 600 mg in 2% milk	3	1	12	16634.4	Cohort 3, Period 1/ Cohort 3, Period 2	117.17	(102.02, 134.57)	18.12
	Tecovirimat 600 mg in capsules	3	2	11	14196.8				
	Tecovirimat 600 mg in applesauce	4	1	12	13804.9	Cohort 4, Period 1/ Cohort 4, Period 2	113.64	(106.10, 121.72)	9.38
	Tecovirimat 600 mg in capsules	4	2	12	12147.7				
AUC_{0-inf} (h*ng/mL)	Tecovirimat 600 mg in 2% milk	3	1	11	24424.7	Cohort 3, Period 1/ Cohort 3, Period 2	105.91	(92.24, 121.60)	18.02
	Tecovirimat 600 mg in capsules	3	2	11	23062.3				
	Tecovirimat 600 mg in applesauce	4	1	11	22319.5	Cohort 4, Period 1/ Cohort 4, Period 2	113.88	(99.36, 130.52)	15.70
	Tecovirimat 600 mg in capsules	4	2	10	19599.4				
C_{max} (ng/mL)	Tecovirimat 600 mg in 2% milk	3	1	12	2017.7	Cohort 3, Period 1/ Cohort 3, Period 2	116.02	(106.31, 126.62)	11.39
	Tecovirimat 600 mg in capsules	3	2	11	1739.1				
	Tecovirimat 600 mg in applesauce	4	1	12	1654.4	Cohort 4, Period 1/ Cohort 4, Period 2	101.99	(93.02, 111.84)	12.62
	Tecovirimat 600 mg in capsules	4	2	12	1622.1				

Abbreviations: ANOVA, analysis of variance; CI, confidence interval; CV, coefficient of variation; MSE, mean square error.
Notes: Cohort 3 = tecovirimat 600 mg in 2% milk/tecovirimat 600 mg in capsules, Cohort 4 = tecovirimat 600 mg in applesauce/tecovirimat 600 mg in capsules.
A linear mixed effect model with treatment as a fixed effect and subject as a random effect was fitted to the natural log-transformed pharmacokinetic parameters.
Ratio of geometric means and 90% CI for ratio of geometric means are expressed as percent.
Intra-subject CV = Square root of [exp (MSE of ANOVA) –1] × 100.

Based on linear regression, the applicant considered there was a relatively good correlation between dose and AUC (AUC_{0-t} shown below). However, the AUCs after 100 mg in 2% milk vs. 600 mg in 2% milk were ~6-fold higher only for AUC_{0-t} and increased ~4-fold for AUC_{0-24} and AUC_{0-inf}. For the comparison between 200 mg and 600 mg mixed in apple sauce, the increases were by ~2-fold for each value. Thus, in general, 100 mg and 200 mg doses would provide higher than predicted exposures based on the values for 600 mg doses when each is delivered in the same media.

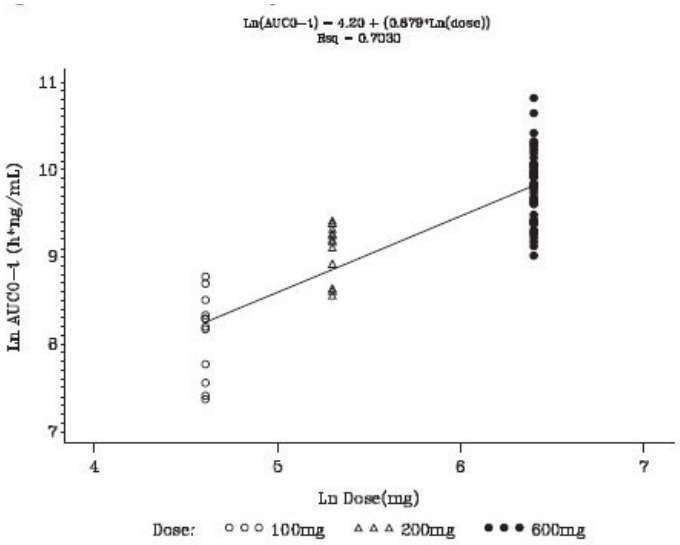


Figure 3: Relationship between AUC_{0-t} ad Dose for Tecovirimat

Distribution

The in-vitro plasma protein binding of [14C]-tecovirimat was moderate to high (77.3 to 96.3%) in all species studied (mouse, rat, rabbit, dog, monkey and human), with human binding at ~80%. Protein binding appeared to be concentration-independent over the range of 0.03 to 50 µM. Of the 3 major metabolites of tecovirimat in humans, TFMBA has the highest plasma protein binding (98.6% bound in human plasma) whereas the plasma protein binding of M4 is in a range of 4.6 to 20.7% and that for M5 ranges from 6.6 to 33.0% in mouse, monkey and human plasma.

In SIGA-246-009 (see below), total radioactivity levels were approximately 10% to 40% lower in whole blood compared to plasma, demonstrating limited partitioning into blood cells.

Excretion

SIGA-246-009 was a mass balance study in which 6 male subjects received 600 mg tecovirimat (3 x gelatin capsules containing 200 mg tecovirimat powder) and 100 µCi of [14C]-tecovirimat after a meal (667 kcal and 24 g of fat). Mean Cmax for radiolabelled tecovirimat (in solution) was twice that for unlabelled drug (in granular form), which may also reflect the 2-h interval between 4 and 6 h samples.

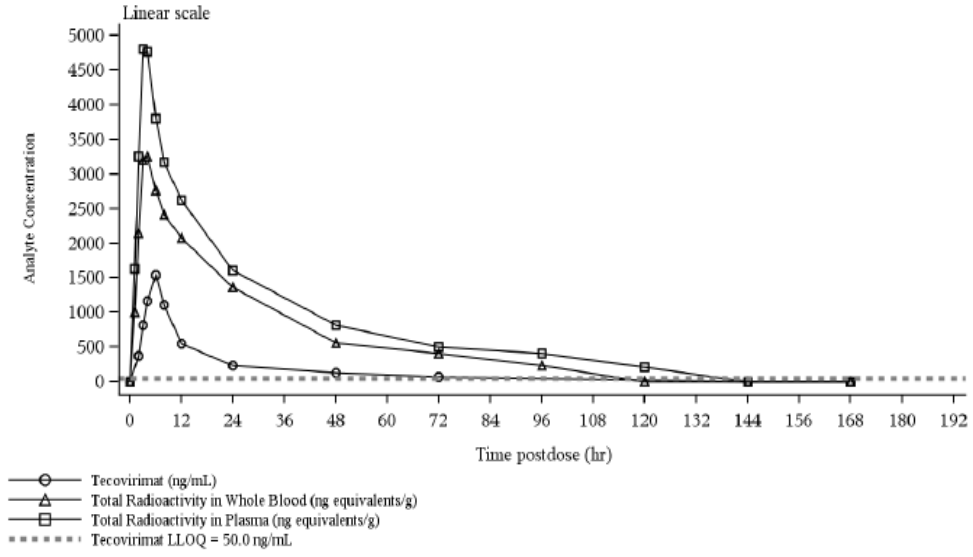


Table 10: Summary of the pharmacokinetic parameters of tecovirimat in plasma, total radioctivity in plasma, and total radioactivity in whole blood following a single oral dose of [^{14}C]-Tecovirimat

Parameter (units)	Tecovirimat in Plasma, N=6 Geometric Mean (CV%)	Total Radioactivity in Plasma, N=6 Geometric Mean (CV%)	Total Radioactivity in Whole Blood, N=6 Geometric Mean (CV%)
AUC_{0-24} (ng*h/mL)[a]	14200 (33.2)	62200 (27.8)	47200 (26.1)
AUC_{0-t} (ng*h/mL)[a]	21600 (35.9)	122000 (23.6)	81700 (43.3)
$AUC_{0-\infty}$ (ng*h/mL)[a]	25400 (38.1)	141000 (22.4)	116000 (9.9)[e]
$AUC_{0-\infty}$ Blood/Plasma Ratio	NA	NA	0.696 (23.8)[f]
C_{max} (ng/mL)[b]	1550 (43.8)	4930 (27.8)	3350 (26.5)
t_{max} (h)	6[c] 6.00 (3.00-6.25)[d]	3[c] 3.50 (3.00-4.03)[d]	4[c] 3.50 (3.00-4.03)[d]
$t_{½}$ (h)	28.9 (90.1)	39.5 (25.8)	33.2 (30.3)
CL/F (L/h)	23.6 (38.1)	NA	NA
V_z/F (L)	986 (58.7)	NA	NA

Abbreviations: AUC_{0-24} = area under the concentration-time curve from Hour 0 to the time of the 24 hour collection; AUC_{0-t} = area under the concentration-time curve from Hour 0 to the time of the last measurable concentration; AUC0-∞ = area under the concentration-time curve extrapolated to infinity; CL/F = apparent total clearance; C_{max} = maximum observed concentration; CV = coefficient of variation; N = number of subjects studied; NA = not applicable; $t_{½}$ = apparent terminal elimination half-life; t_{max} = time to maximum concentration; V_z/F = apparent volume of distribution.
[a] Units for total radioactivity: ng-Eq*h/g.
[b] Units for total radioactivity: ng-Eq/g.
[c] Timepoint at which maximum mean concentration was observed.
[d] Median (minimum-maximum) of individual subjects' t_{max} values.
[e] N = 5.
[f] For Subject 102 blood/plasma ratio calculated using AUC_{0-t} since area by extrapolation for $AUC_{0-\infty}$ was > 30%.

Approximately 95% of the radiolabelled material was recovered in urine and faeces over 192 h post-dose, with approximately 73% recovered in urine and 23% in faeces.

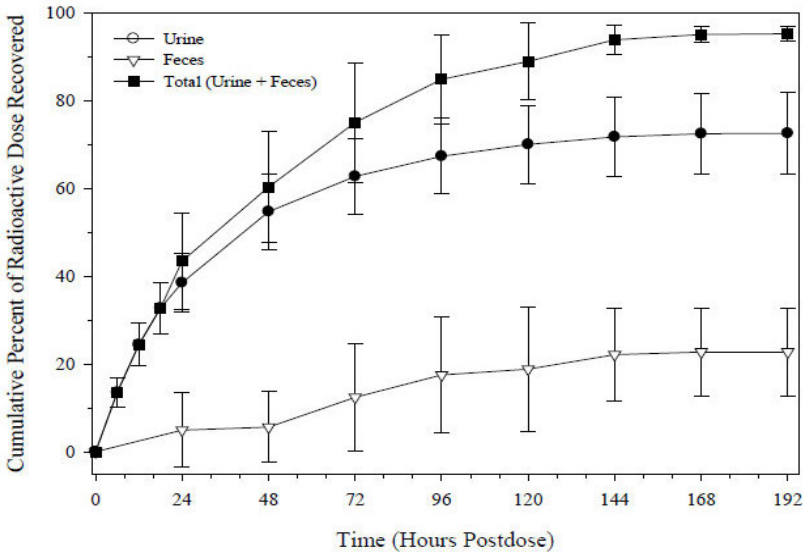


Figure 4: Arithmetic Mean (±SD) Cumulative Excretion of Total Radioactivity in Urine and Faeces Following a Single Oral Dose of [^{14}C]-Tecovirimat

Tecovirimat accounted for less than 0.02% of the 73% of the administered dose excreted in urine. Faecal excretion of total radioactivity (23%) was lower than faecal excretion of tecovirimat (35.6%) at all collection intervals.

Table 11: Summary of the cumulative urinary and fecal excretion of total radioactivity and tecovirimat following a single oral dose of [^{14}C] -Tecovirimat

Total Radioactivity			
Parameter (Units)	Urine, N=6 Arithmetic Mean (SD)	Feces, N=6 Arithmetic Mean (SD)	Total Excreta, N=6 Arithmetic Mean (SD)
%Excreted over 0-192 hours (%)	72.5 (9.30)	22.7 (9.96)	95.2 (1.56)
Tecovirimat			
Parameter (Units)	Urine, N=6 Arithmetic Mean (SD)	Feces, N=6 Arithmetic Mean (SD)	Total Excreta, N=6 Arithmetic Mean (SD)
%Excreted over 0-144 hours[a] (%)	0.0197 (0.00779)	35.6 (11.1)	NA
CL_R (mL/h)	4.36 (27.9)[b]	NA	NA

CL_R = renal clearance; N = number of subjects; NA = not applicable; SD = standard deviation.
[a] 0-144 hour data presented as this is the last timepoint for which data are summarized for all 6 subjects.
[b] Geometric mean (CV%) presented.

Metabolism

In SIGA-246-009, only those metabolites containing radiolabel were analysed, so the most abundant metabolite TFMBA (see SIGA-246-008) was not captured in the profiling. Radiolabelled tecovirimat underwent extensive biotransformation to produce 9 identified metabolites.

In plasma, tecovirimat was the only compound detected at 1 h post-dose, accounting for 96% of total radioactivity. By 2 h, tecovirimat accounted for 79% of radioactivity, with M4 and M7 accounting for 14% and 3% of total radioactivity, respectively. By 6 h post-dose, M4 was the most abundant component, accounting for 49% of total radioactivity compared to 38% for tecovirimat. M4 also accounted for 63-66% of total radioactivity at 8, 12 and 24 h post-dose.

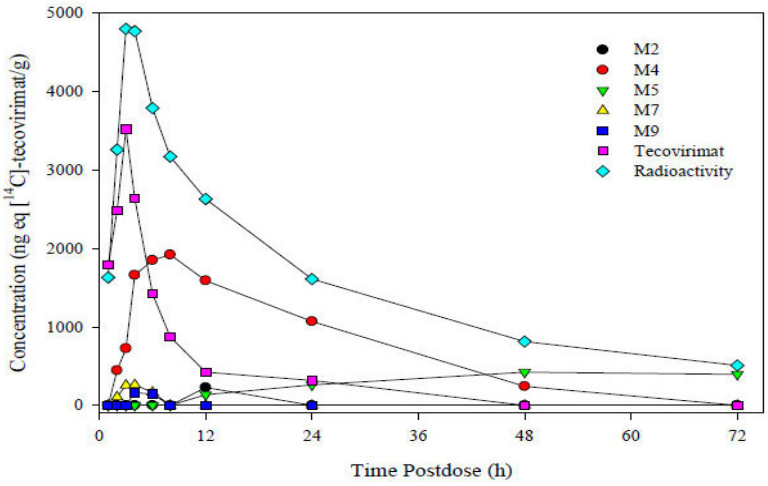


Figure 5: Concentration of Tecovirimat and metabolites in male human plasma following a single oral dose of [^{14}C]-Tecovirimat

Based on AUCs, M4 was the most abundant circulating radioactive component (44% of total radioactivity AUC), followed by tecovirimat (20.5%) and M5 (19%). The glucuronide conjugates of M4 (M2) and tecovirimat (M7 and M9) accounted for 1.6% of AUC.

Table 12: Pharmacokinetic parameters for [^{14}C] -Tecovirimat and metabolites in plasma following a single oral dose of [^{14}C] -Tecovirimat

Metabolite Designation	T_{max} (Hours)	C_{max} (ng eq/g)	Half-life (Hours)	$AUC_{(0-t)}$ (h•ng eq/g)	$AUC_{(0-\infty)}$ (h•ng eq/g)	% AUC Extrapolated to Infinity	% AUC of Total Radioactivity[a]
M2	12	227	NC	454	NC	NA	0.410
M4	8	1920	12.9	48000	52500	8.58	43.8
M5	48	423	NC	20700	NC	NA	18.9
M7	4	261	NC	918	NC	NA	0.840
M9	4	163	NC	386	NC	NA	0.350
Tecovirimat	3	3520	7.28[b]	22500	25800[b]	12.9	20.5
Total Radioactivity	3	4800	28.8	110000	131000	16.2	NA

Abbreviations: AUC = area under the concentration-time curve; AUC_{0-t} = area under the concentration-time curve from 0 hour to last quantifiable timepoint (72 hours postdose); $AUC_{0-\infty}$ = area under the concentration-time curve from 0 hour to infinity; C_{max} = maximal concentration observed; eq = equivalents [^{14}C]-tecovirimat; h = hours; NC = not calculated; NA = not applicable; T_{max} = time to reach C_{max}.
[a] % AUC of total radioactivity calculated as follows: AUC_{0-72}/total radioactivity AUC_{0-72} * 100.
[b] The elimination rate constant (λ_z) determined by linear regression of logarithmic-transformed concentration versus time data had an adjusted R^2 value of <0.7. Therefore, extrapolated data should be interpreted with caution.

In urine, the primary tecovirimat glucuronide conjugate M9 and the M4 glucuronide conjugate M2 were the most abundant radioactive components accounting for means of 24.4% and 30.3% of radioactivity dose, respectively. The primary tecovirimat glucuronide conjugate M8 and the M4 glucuronide conjugate M3 were minor metabolites in urine, accounting for means of 5.66% and 3.43% of radioactivity dose, respectively. In total, glucuronide conjugates accounted for approximately 95% of urine radioactivity or approximately 64% of the radioactivity dose. Metabolite M4 and its oxidised metabolite M1 were minor urine metabolites and unchanged tecovirimat was not detected in urine.

In faeces, tecovirimat was the predominant radioactive component and accounted for a mean of 15.9% of the dose across all subjects. The metabolites M6, M8 and M9 accounted for very small percentages of the radioactivity dose.

Pharmacokinetics in target population

The applicant conducted a POPPK analysis of data from healthy subjects in SIGA-246-004. There was no POPPK analysis using data from SIGA-246-008 since there was intensive sampling in the PK subset.

SIGA-RAS-003 describes the POPPK analysis of the human PK data obtained in SIGA-246-004, in which there was once daily administration of 400 mg or 600 mg for 14 days. Overall, 88 subjects and 1511 plasma concentrations, including 116 BLQ plasma concentrations, were used in this human POPPK analysis.

A 2-compartment model with mixed error, correlation between CL/F and Vc/F, and IIV on all PK parameters was retained as the structural model for healthy humans. Based on PK parameters derived from the structural model, typical values of CL/F and Vc/F were 41.18 L/h and 254.83 L, respectively.

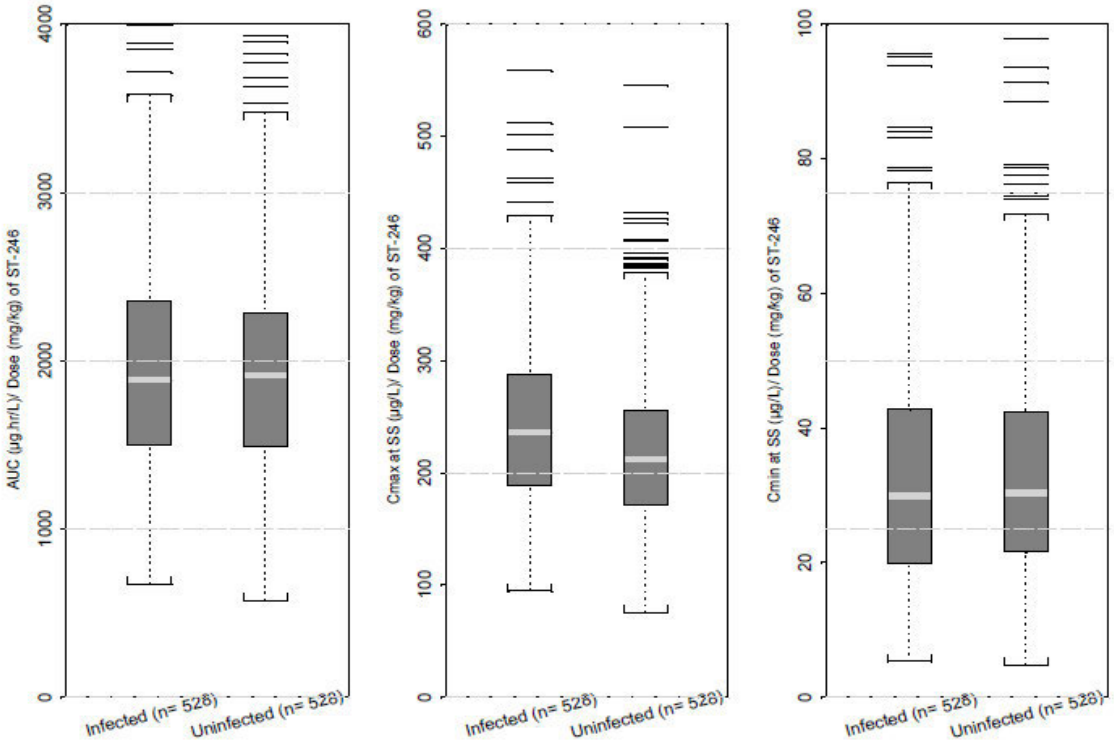
Initially, exploratory analyses were performed to visually assess the effect of key covariates (WT, sex) on PK parameters. The effects of SEX on CL/F, Vc/F as well as DOSE on Ka, CL/F and Vc/F were selected for the formal covariate analysis. In the covariate analysis the effect of SEX on Vc/F remained statistically significant after the backward elimination.

For a healthy human with body weight of 78.4 kg, the typical values of CL/F would be 41.15 L/h (987.6 L/day) and Vc/F in female and male subjects would be 281.51 L and 217.44 L, respectively. The terminal half-life in male and female subjects is almost similar (16.7 h in males vs. 17.4 h in females).

Consequently, there was no clinically significant sex effect on plasma exposure and terminal half-life.

Tecovirimat was well absorbed in healthy humans with a typical absorption rate of 1.06 h-1 and a lag-time of 1.46 h. Inter-individual variability of PK parameter estimates was relatively high, with values ranging from 16.74 to 54.39%.

Individual exposure to tecovirimat for infected humans was simulated using the final human POPPK model with typical population parameters (Ka, CL/F and Vc/F) that were adjusted using the ratios of parameters obtained from infected and uninfected monkeys. Simulations were performed to determine the systemic exposure of tecovirimat following daily oral administrations of 400 or 600 mg. For each dose level, two subgroups of 264 subjects were included according to the infection status (infected/uninfected) but having the same demographic characteristics as subjects in SIGA-246-004. From the box plots of dose-normalised exposure at steady state, the applicant concluded that the dose-normalised AUC and Cmin values were comparable but Cmax values were 1.12-fold higher in infected humans as compared to uninfected ones.

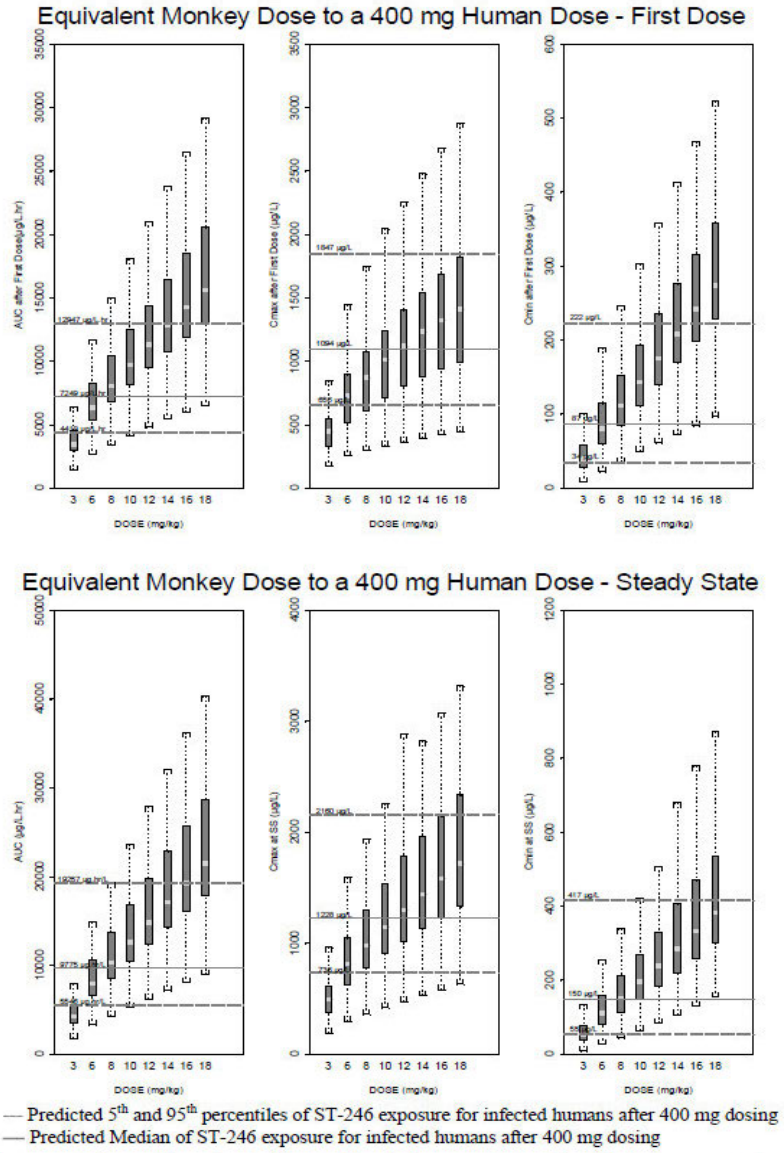


AUC: Area under the concentration profile under steady state; C_{max}: Peak concentration; C_{min}: Minimum concentration; SS: Steady-state

Figure 6: Dose-normalied simulated exposure of ST-246 under steady state conditions in uninfected and infected humans

Simulations were conducted to determine the tecovirimat dose in monkey that is equivalent to human doses of 400 - 600 mg once daily. The median AUC and Cmax in infected monkeys after the first dose and at steady-state after 8 to 10 mg/kg/day dosing were equivalent to median AUC and Cmax values predicted in infected humans receiving a dose of 400 mg. Median Cmin values for infected monkeys

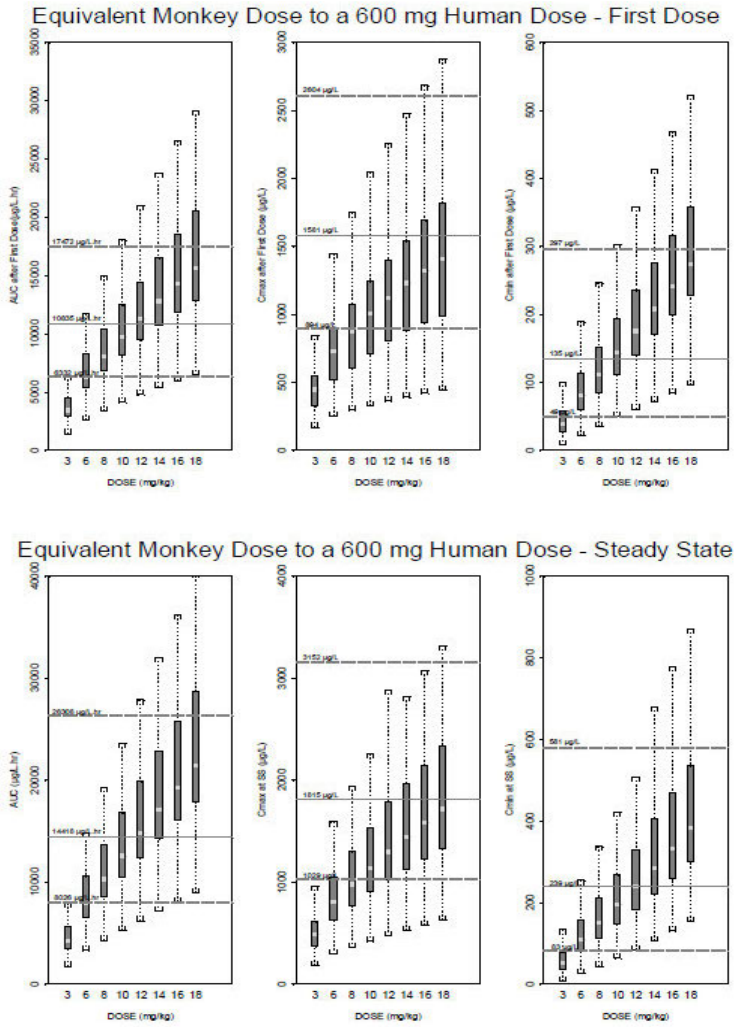
were slightly higher than those predicted in infected humans but they remained within the acceptable range of the targeted Cmin values in infected humans.



AUC: Area under the concentration profile under steady state; C_{max}: Peak concentration; C_{min}: Minimum concentration; SS: Steady-state

Figure 7: Simulated ST-246 exposure in infected humans following different dosing after the first dose and at steady-state and boundaries of typical exposure in infected monkeys following 400 mg dosing

Similarly, a tecovirimat dose of 12 to 14 mg/kg administered to infected monkeys resulted in similar exposure as the 600 mg dose administered to infected humans.



AUC: Area under the concentration profile under steady state; C_{max}: Peak concentration; C_{min}: Minimum concentration; SS: Steady-state

Figure 8: Simulated ST-246 exposure in infected humans following different dosing after the first dose and at steady-state and boundaries of typical exposure in infected monkeys following 600 mg dosing

SIGA-PCS-106

This report describes the comparison of tecovirimat PK in humans at 600 mg BID dose as documented in the Lead-in cohort of SIGA-246-008 and in NHPs at 10 mg/kg. This exercise was conducted to support continuation of dosing with 600 mg BID in the Expanded portion of SIGA-246-008. Plasma exposures in humans were compared to:

i) Those derived in NHPs who received an efficacious dose of 10 mg/kg (Cmin or Cavg);

ii) The upper exposure derived in dogs for safety (Cmax levels linked to dog seizures).

The figure shows the day 14 human data (600 mg BID in fed and fasted states) compared to NHP exposures when dosing with 10 mg/kg.

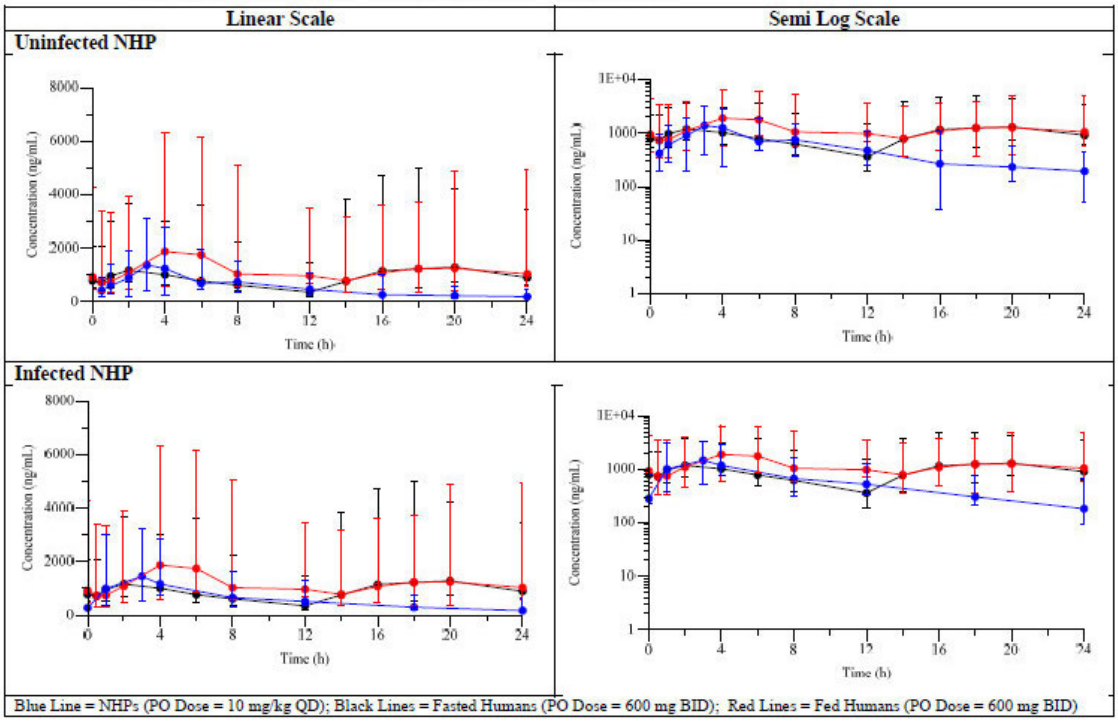


Figure 9: Median [90%CI] Tecovirimat levels in NHPs (PO Dose = 10 mg/kg QD; Blue Line) and humans (PO Dose = 600 mg BID; Black Lines = Fasted, Red Lines = Fed) on Day 14

Results from the non-compartmental analysis (NCA) of exposures of infected and non-infected NHPs at 10 mg/kg QD and of fed and fasted humans at 600 mg BID are presented below.

Table 13: Noncompartmental exposures in NHPs at the 10 mg/kg QD PO dose

	Infected				Non-Infected			
Statistics	C_{max} (ng/mL)	C_{min} (ng/mL)	AUC_{0-t} (ng.h/mL)	C_{avg} (ng/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)	AUC_{0-t} (ng.h/mL)	C_{avg} (ng/mL)
Day 1 (N)	**6**	**6**	**6**	**6**	**12**	**12**	**12**	**12**
Mean	809	193	8110	338	1081	180	10826	451
Min	378	37	4578	191	435	60	3269	136
Median	743	188	7441	310	1047	185	11467	478
Max	1320	339	13294	554	1650	344	17537	731
Geometric Mean	749	158	7629	318	1022	154	9871	411
CV% Geometric Mean	46.1	93.2	39.6	39.6	38.3	66.4	51.1	51.1
25th Percentile	545	102	5507	229	844	95	7435	310
75th Percentile	1133	297	10888	454	1358	265	14212	592
Day 14 (N)	**6**	**6**	**6**	**6**	**6**	**6**	**6**	**6**
Mean	1444	169	14352	598	1400	187	12701	529
Min	936	56	6975	291	1000	106	9346	389
Median	1460	149	14827	618	1495	192	12701	529
Max	2010	344	18615	776	1750	256	15954	665
Geometric Mean	1403	143	13650	569	1374	181	12488	520
CV% Geometric Mean	27.2	72.4	38.2	38.2	21.9	29.9	20.5	20.5
25th Percentile	1112	81	11209	467	1083	156	10259	427
75th Percentile	1725	258	18342	764	1600	216	15192	633

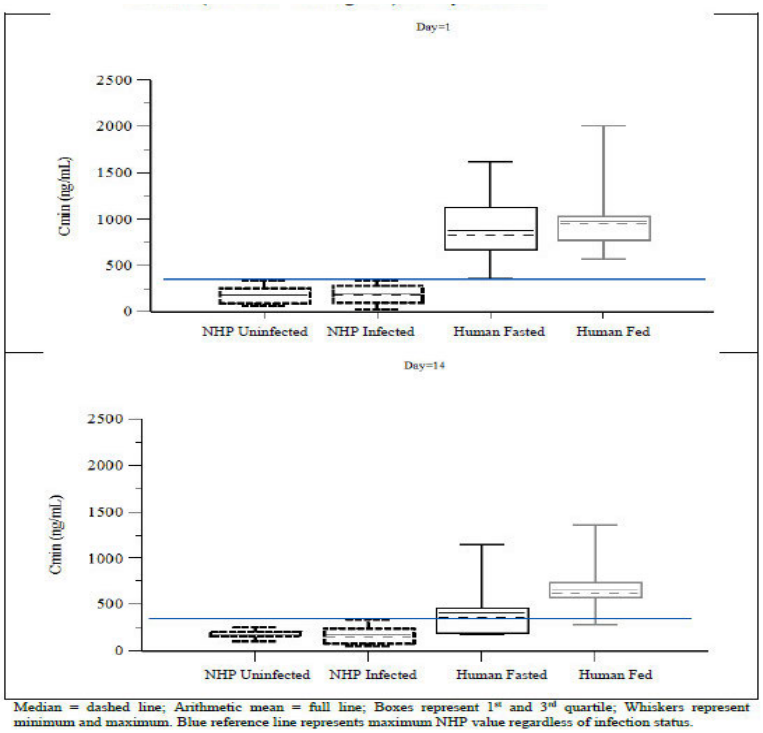
$C_{avg} = C_{ss} = AUC_{0-t}/24$; C_{min} after the 1st dose = C_{last}

Table 14: Noncompartmental exposures in humans at the 600 mg BID PO dose

Statistics	Fed				Fasted			
	C_{max} (ng/mL)	C_{min} (ng/mL)	AUC_{0-t} (ng.h/mL)	C_{avg} (ng/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)	AUC_{0-t} (ng.h/mL)	C_{avg} (ng/mL)
Day 1 (N)	**16**	**16**	**16**	**16**	**16**	**16**	**16**	**16**
Mean	1559	979	21126	880	1285	873	14932	622
Min	956	572	11445	477	581	360	6736	281
Median	1470	953	19521	813	1330	828	15828	660
Max	3290	2010	44195	1841	2480	1620	24087	1004
Geometric Mean	1468	936	19918	830	1203	814	13744	573
CV% Geometric Mean	35.2	30.5	35.3	35.3	40.1	41.5	45.9	45.9
25th Percentile	1100	780	15071	628	900	683	8770	365
75th Percentile	1510	1034	23120	963	1553	1123	19962	832
Day 14 (N)	**16**	**16**	**16**	**16**	**15**	**15**	**15**	**15**
Mean	2474	664	32706	1363	1714	409	23545	981
Min	1500	282	18529	772	766	170	9853	411
Median	2155	623	27825	1159	1530	359	19679	820
Max	4460	1360	73569	3065	3770	1140	58318	2430
Geometric Mean	2322	623	30621	1276	1581	353	21709	905
CV% Geometric Mean	37.2	38.5	36.4	36.4	42.4	58.1	41.5	41.5
25th Percentile	1750	586	25911	1080	1170	205	18104	754
75th Percentile	3163	733	32617	1359	2040	467	25019	1042

$C_{avg} = C_{ss} = AUC_{0-t}/24$; C_{min} after the 1st dose = C_{last}

In terms of minimum and average concentrations, fed humans displayed consistently higher exposures vs. NHPs at steady state with more overlap on Day 1. Cmax values observed in humans dosed with 600 mg BID were consistently lower than the safety threshold for seizure observed in dogs (~5600 ng/mL). Maximum values recorded were 3290 ng/mL on Day 1 and 4460 ng/mL on Day 14. The lowest observed Cmin in fed humans (282 ng/mL) corresponded to the 75th percentile of values in infected NHPs (258 ng/mL) and was greater than the maximum in uninfected NHPs (256 ng/mL).



Median = dashed line; Arithmetic mean = full line; Boxes represent 1st and 3rd quartile; Whiskers represent minimum and maximum. Blue reference line represents maximum NHP value regardless of infection status.

Figure 10: Tecovirimat Exposure (C_{min}) in NHPs (PO Dose = 10 mg/kg QD) and humans (PO dose = 600 mg BID) on Days 1 and 14

In summary:

Tecovirimat 600 mg BID taken with meals provided a greater exposure margin relative to the effective 10 mg/kg dose in NHPs.

- On Day 1, the median Cmin values were 5.1 x those in infected NHPs. On Day 14, the median minimal levels were 4.2x those in infected NHPs.
- On Day 1, the median average exposure and AUC values were 2.6 x those in infected NHPs. On Day 14, the median average exposure and AUC values were 1.9 x those in infected NHPs.
- On Day 1, the median Cmax values were 2.0 x those in infected NHPs. On Day 14, the median Cmax values were 1.5x those in infected NHPs.

Based on the above, the 600 mg BID dose administered with meals was selected for the Expanded portion of the study since it provided plasma exposures that exceeded by several fold those achieved in NHPs at the efficacious dose of 10 mg/kg.

SIGA-PCS-104

This report provided a triangulation of tecovirimat PK in rabbits and non-human primates given fully effective tecovirimat doses vs. human PK when dosing with 600 mg BID. The intent was to determine whether a comparison between human and NHP exposures was more or less conservative than a comparison with rabbit exposures. A parametric (model-based) and non-parametric (non-compartmental) approach was used to contrast the exposures and determine the most conservative animal model (i.e. the model that requires the highest tecovirimat exposures for maximal survival).

Based on finalSIGA-PCS-104, which reports a POPPK and PK-PD analysis of rabbit data, recursive ROC analysis identified Cavg 185 ng/mL as the best predictor of RPXV survival in rabbits. This corresponded to a 30 mg/kg QD dose, with which >95% of rabbits reached Cavg >185 ng/mL. The prior PK model in uninfected rabbits was used to simulate plasma concentrations of tecovirimat at steady state for 30 mg/kg QD (100 replicates). In NHPs, the 10 mg/kg QD dose provided maximum survival after MPXV challenge. The prior PK model in uninfected NHPs was used to simulate the plasma concentration of tecovirimat at steady state at the dose of 10 mg/kg QD (100 replicates).

Using parametric model-based approaches, the results indicated that the NHP was the most conservative animal model as it would result in the highest predicted dose in humans for achieving efficacy against smallpox.

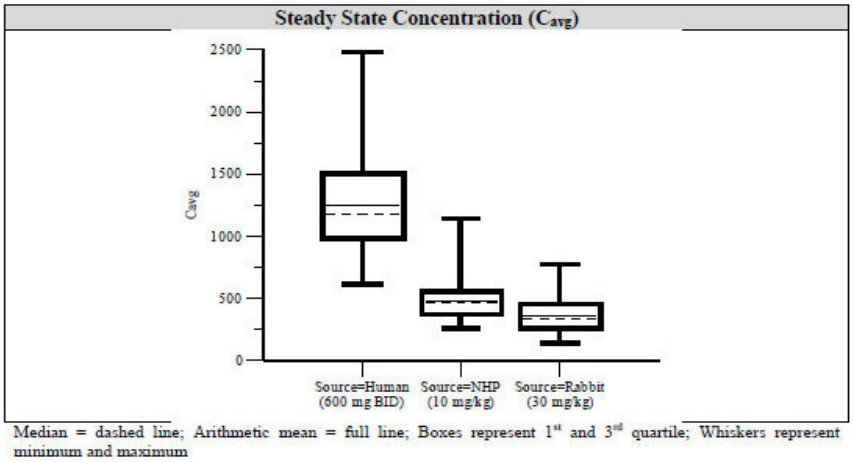


Figure 11: Tecovirimat exposure in NHPs (Dose = 10 mg/kg; N = 100), rabbits (dose = 30 mg/kg; N = 100) and humans (Dose = 600 mg BID; N = 100)

Using non-parametric (non-compartmental) based approaches, the comparisons were made with a higher rabbit dose of 40 mg/kg. PK/PD modelling in NHPs and rabbits indicated that Cmin and Cavg, respectively, are the parameters best correlated to efficacy and increased survival. With repeated administrations to rabbits dosed at 40 mg/kg and NHPs dosed at 10 mg/kg, the rabbit Cavg was ~25% of the NHP value (95% Confidence interval = 11.2 – 52.8) and the difference between these exposures was statistically significant (p<0.001). For Cmin, rabbit values were 17.2% of the NHP value (95% Confidence interval = 6.9 – 43.1), also a statistically significant difference (p<0.001). It was concluded that the NHP is the most conservative animal model as it would result in the highest predicted dose in humans for achieving efficacy against smallpox.

Special populations

Renal impairment

SIGA-246-012 evaluated the effect of varying degrees of renal function (mild, moderate, severe, ERSD) on PK of tecovirimat and the three major metabolites.

Table 15: Study Cohort Summary

Cohort	Renal Function Classification	Estimated CL_{CR} or eGFR	Cohort Size
1	Normal	$CL_{CR} \geq 90$ mL/min	7
2	Mild Impairment	eGFR ≥ 60 to < 90 mL/min/1.73 m^2	8
3	Moderate Impairment	eGFR ≥ 30 to < 60 mL/min/1.73 m^2	8
4	Severe Impairment	eGFR < 30 mL/min/1.73 m^2	7
5	ESRD	HD required (average of 3 sessions/week)	8

Abbreviation: CL_{CR} = creatinine clearance; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; HD = hemodialysis.

Subjects received 600 mg tecovirimat within 30 min of completing a meal of 600 kcal and 25 g fat. Subjects in Cohort 5 received 600 mg post-HD on Day 1 and 600 mg pre-HD on Day 8. The PK analysis showed reductions in tecovirimat AUC in severe RI and ESRD subjects.

Table 16: Summary of ANCOVA Analysis of Tecovirimat Pharmacokinetic Parameters

Parameter	Cohort	Geometric Mean	Ratio of Geometric Mean	90% CI for Ratio
AUC_{0-24} (h*ng/mL)	Cohort 4 (Test)	7950	73.1	52.25 - 102.13
	Cohort 1 (Reference)	10900		
AUC_{0-last} (h*ng/mL)	Cohort 4 (Test)	18400	107	76.87 - 148.32
	Cohort 1 (Reference)	17300		
$AUC_{0-\infty}$ (h*ng/mL)	Cohort 4 (Test)	13700	67.4	39.51 - 115.11
	Cohort 1 (Reference)	20400		
C_{max} (ng/mL)	Cohort 4 (Test)	766	65.6	48.57 - 88.73
	Cohort 1 (Reference)	1170		
AUC_{0-24} (h*ng/mL)	Cohort 5 (Test)	6190	56.8	40.38 - 80.03
	Cohort 1 (Reference)	10900		
AUC_{0-last} (h*ng/mL)	Cohort 5 (Test)	9490	55.0	39.31 - 76.91
	Cohort 1 (Reference)	17300		
$AUC_{0-\infty}$ (h*ng/mL)	Cohort 5 (Test)	10500	51.6	35.65 - 74.72
	Cohort 1 (Reference)	20400		
C_{max} (ng/mL)	Cohort 5 (Test)	767	65.8	48.35 - 89.46
	Cohort 1 (Reference)	1170		

Renal impairment increased M4 and TFMBA AUCs, with the maximum increases in ESRD. An increase in M5 AUC values was only observed in moderate RI subjects.

Table 17: Summary of the pharmacokinetic parameters of M4 following single oral doses of tecovirimat 600 mg in subjects with varying degrees of renal function

Cohort	PK Parameter						
	AUC_{0-24} (h*ng/mL)	AUC_{0-last} (h*ng/mL)	$AUC_{0-\infty}$ (h*ng/mL)	C_{max} (ng/mL)	$t_{½}$ (h)	λ_z (1/h)	t_{max} (h)
Normal	7010 (47.5) (n = 7)	12200 (42.9) (n = 7)	13800 (40.2) (n = 6)	421 (46.1) (n = 7)	24.8 (79.7) (n = 7)	0.0279 (79.7) (n = 7)	12.00 (6.00, 12.02) (n = 7)
Mild	8170 (18.8) (n = 8)	15400 (24.3) (n = 8)	13800 (10.5) (n = 6)	471 (16.8) (n = 8)	18.5 (74.9) (n = 7)	0.0374 (74.9) (n = 7)	12.00 (8.00, 18.00) (n = 8)
Moderate	10300 (31.3) (n = 8)	21100 (44.5) (n = 8)	22400 (46.8) (n = 7)	615 (32.9) (n = 8)	26.4 (66.5) (n = 8)	0.0263 (66.5) (n = 8)	10.00 (4.00, 24.03) (n = 8)
Severe	7590 (52.4) (n = 7)	19900 (48.6) (n = 7)	22600 (49.6) (n = 4)	414 (57.4) (n = 7)	55.4 (40.2) (n = 6)	0.0125 (40.2) (n = 6)	8.00 (6.00, 12.00) (n = 7)
ESRD (Period I)	8010 (34.8) (n = 8)	28000 (41.8) (n = 8)	29500 (39.4) (n = 4)	460 (28.2) (n = 8)	31.1 (59.6) (n = 6)	0.0223 (59.6) (n = 6)	8.01 (6.00, 48.00) (n = 8)
ESRD (Period II)	6140 (21.5) (n = 8)	23100 (37.3) (n = 8)	NC (n = 2)	347 (19.0) (n = 8)	NC (n = 2)	NC (n = 2)	7.01 (2.00, 72.00) (n = 8)

Table 18: Summary of the Pharmacokinetic Parameters of TFMBA Following Single Oral Doses of Tecovirimat 600 mg in Subjects with Varying Degrees of Renal function

Cohort	PK Parameter						
	AUC_{0-24} (h*ng/mL)	AUC_{0-last} (h*ng/mL)	$AUC_{0-\infty}$ (h*ng/mL)	C_{max} (ng/mL)	$t_{½}$ (h)	λ_z (1/h)	t_{max} (h)
Normal	37600 (60.2) (n = 7)	73100 (64.1) (n = 7)	77700 (62.4) (n = 7)	2410 (58.1) (n = 7)	27.5 (50.2) (n = 7)	0.0252 (50.2) (n = 7)	8.00 (4.00, 18.00) (n = 7)
Mild	48700 (15.6) (n = 8)	98200 (29.3) (n = 8)	92900 (23.5) (n = 7)	2810 (14.4) (n = 8)	20.8 (56.3) (n = 8)	0.0333 (56.3) (n = 8)	12.00 (8.00, 12.05) (n = 8)
Moderate	51900 (34.4) (n = 8)	110000 (49.4) (n = 8)	117000 (49.7) (n = 8)	3170 (30.5) (n = 8)	26.7 (40.0) (n = 8)	0.026 (40.0) (n = 8)	8.00 (4.00, 24.03) (n = 8)
Severe	35600 (41.0) (n = 7)	109000 (52.7) (n = 7)	NC (n = 1)	2090 (42.3) (n = 7)	98.2 (117.1) (n = 6)	0.00706 (117.1) (n = 6)	8.00 (6.00, 24.00) (n = 7)
ESRD (Period I)	39700 (29.1) (n = 8)	161000 (37.2) (n = 8)	NC (n = 1)	2340 (30.2) (n = 8)	84.7 (45.9) (n = 6)	0.00819 (45.9) (n = 6)	8.00 (4.00, 18.00) (n = 8)
ESRD (Period II)	50200 (30.8) (n = 8)	184000 (36.6) (n = 8)	NC (n = 1)	2950 (22.5) (n = 8)	88.5 (52.2) (n = 5)	0.00783 (52.2) (n = 5)	6.00 (4.00, 8.00) (n = 8)

Haemodialysis did not have a significant impact on tecovirimat, M5 or TFMBA exposures, but did significantly remove M4 from plasma.

Table 19: Summary of ANOVA analysis of M4 pharmacokinetic parameters for Cohort 5

Parameter	Period	Geometric Mean	Ratio of Geometric Mean	90% CI for Ratio
AUC_{0-24} (h*ng/mL)	Period II (Test)	6140	76.7	65.00 - 90.47
	Period I (Reference)	8010		
AUC_{0-last} (h*ng/mL)	Period II (Test)	20100	68.2	27.30 - 170.22
	Period I (Reference)	29500		
$AUC_{0-\infty}$ (h*ng/mL)	Period II (Test)	23100	82.3	69.74 - 97.23
	Period I (Reference)	28000		
C_{max} (ng/mL)	Period II (Test)	347	75.3	63.81 - 88.98
	Period I (Reference)	460		

Hepatic impairment

SIGA-246-013 enrolled subjects with CP-A, B or C impairment or normal function. All subjects received a single dose of 600 mg within 30 min of a meal of 600 kcal and 25 g fat. The ANCOVA did not indicate a consistent trend in tecovirimat exposure according to hepatic impairment. There was a modest impact of moderate to severe hepatic impairment on exposures to the inactive metabolites M4, M5 and TFMBA. In severe hepatic function impairment, the increases in AUCs of M4, M5 and TFMBA were up to 2-, 1.6- and 1.6-fold, respectively. The M4 exposure was 4- to 5-fold below the level shown to be safe in mice after 14 days of daily dosing.

Table 20: Summary of the pharmacokinetic parameters of Tecovirimat following single oral doses of 600 mg in subjects with varying degrees of hepatic function

	PK Parameter								
Cohort	C_{max} (ng/mL)	t_{max} (hr)	AUC_{0-24} (hr*ng/mL)	AUC_{0-last} (hr*ng/mL)	$AUC_{0-\infty}$ (hr*ng/mL)	t½ (hr)	λz (1/h)	Cl/F (L/hr)	Vz/F (L)
Cohort 1	1070 (20.5) (n = 8)	4.00 (4.00, 6.03) (n = 8)	9280 (16.1) (n = 8)	16200 (22.1) (n = 8)	16300 (19.6) (n = 7)	24.4 (54.1) (n = 7)	0.0284 (54.1) (n = 7)	36.8 (19.6) (n = 7)	1290 (37.1) (n = 7)
Cohort 2	862 (50.7) (n = 8)	4.00 (1.00, 6.00) (n = 8)	7590 (52.0) (n = 8)	10900 (63.2) (n = 8)	11300 (62.3) (n = 8)	14.8 (27.2) (n = 8)	0.0469 (27.2) (n = 8)	53.3 (62.3) (n = 8)	1140 (57.4) (n = 8)
Cohort 3	1220 (23.6) (n = 8)	4.00 (4.00, 18.00) (n = 8)	11400 (30.0) (n = 8)	17700 (46.4) (n = 8)	18200 (47.8) (n = 8)	14.5 (45.7) (n = 8)	0.0479 (45.7) (n = 8)	33 (47.8) (n = 8)	689 (54.6) (n = 8)
Cohort 4	1150 (17.7) (n = 8)	4.00 (2.00, 8.00) (n = 8)	13300 (25.8) (n = 8)	18300 (39.9) (n = 8)	18600 (39.2) (n = 8)	10.1 (16.8) (n = 8)	0.0688 (16.8) (n = 8)	32.3 (39.2) (n = 8)	469 (37.4) (n = 8)

Table 21: Summary of the pharmacokinetic parameters of M4 following single oral doses of Tecovirimat 600 mg in subjects with varying degrees of hepatic function

	PK Parameter						
Cohort	C_{max} (ng/mL)	t_{max} (hr)	AUC_{0-24} (hr*ng/mL)	AUC_{0-last} (hr*ng/mL)	$AUC_{0-\infty}$ (hr*ng/mL)	t½ (hr)	λz (1/hr)
Cohort 1	382	8.00	6210	11700	11700	21.4	0.0324
	(19.6)	(6.00, 8.00)	(18.7)	(17.4)	(12.4)	(46.4)	(46.4)
	(n = 8)	(n = 8)	(n = 8)	(n = 8)	(n = 7)	(n = 7)	(n = 7)
Cohort 2	419	7.00	6800	11100	11300	12.9	0.0536
	(47.1)	(4.00, 12.03)	(50.3)	(66.4)	(65.4)	(26.9)	(26.9)
	(n = 8)	(n = 8)	(n = 8)	(n = 8)	(n = 8)	(n = 8)	(n = 8)
Cohort 3	549	6.00	8830	16500	17000	15.5	0.0447
	(31.9)	(4.00, 24.00)	(21.7)	(43.0)	(43.2)	(44.6)	(44.6)
	(n = 8)	(n = 8)	(n = 8)	(n = 8)	(n = 8)	(n = 8)	(n = 8)
Cohort 4	662	18.00	11800	29700	30200	16.4	0.0423
	(34.6)	(8.00, 48.00)	(29.5)	(48.9)	(50.3)	(20.9)	(20.9)
	(n = 8)	(n = 8)	(n = 8)	(n = 8)	(n = 8)	(n = 8)	(n = 8)

Elderly

In SIGA-246-008, the entire tecovirimat group had a mean age of 40.4 years. There were 35 and 11 subjects assigned to tecovirimat and placebo, respectively, who were aged from 65-79 years but it is unclear how many were in the PK subset.

Weight

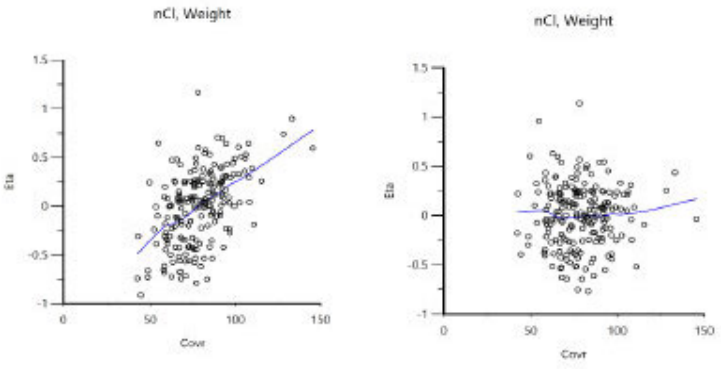
In SIGA-246-008, the entire tecovirimat group had a mean weight of 88.6 kg, with median at 85.4 kg, and a range from 49-188 kg. The mean BMI for all tecovirimat recipients was 31 kg/m^2.

Children

The doses for subjects of 13-<40 kg are based on a POPPK model that used adult data from:

- SIGA-246-004 - fed subjects administered 400 or 600 mg QD for 14 days;
- SIGA-246-018 - fed subjects administered single doses of 100, 200 and 600 mg;
- SIGA-246-008 - fed and fasted subjects administered 600 mg BID for 14 days.

A two-compartment with mixed error model was selected as the base structural model. In the final base model, the effects of age and gender were removed based on visual inspection of covariate plots and minimal effect size. Body weight (BWt) was a relevant covariate due to its effect on CL/F and V/F.



KEY: BWt is not retained as covariate (left) and retained as covariate (right) in POP-PK model (BWt in X-Axis and Between Subject Variabilities of CL/F in Y-Axis)

Figure 12: Bodyweight (BWt) effect as a covariate on clearance of Tecovirimat

The final base model also included a food effect on Ka and relative bioavailability (F1). Due to the difference between studies 018, 004 and 008, a study effect of study 018 was added to F1. The model estimated F1 was 24% higher in study 018 compared to that in 004 and 008 and CL/F at 600 mg was ~1.22- and 1.51-fold higher than that at 100 and 200 mg, respectively. The dose normalised median AUC values (AUC-D) at 100 and 200 mg doses combined was approximately 1.3-fold higher vs. the 600 mg dose indicating higher relative bioavailability at 100 and 200 mg.

The allometric coefficients of body weight on CL/F and V/F were fixed at 0.75 and 1, respectively. For doses ≤200 mg, the relative bioavailability was increased by 1.3 due to higher relative bioavailability at lower doses (as above). The AUC, Cmax and Cmin before third dose and at pre-dose at steady-state were simulated and plotted against the body weights. Doses were selected based on body weight ranges to obtain plasma levels comparable to those observed in adults and within the accepted safety and efficacy boundary (safety limit of 5575 ng/mL and minimum efficacy level at multiple folds above 169 ng/mL). Simulations were done for 50, 100, 200, 400 and 600 mg BID for the body weight ranges of 3 to <6, 6 to <13, 13 to <25, 25 to <40, and 40 to 45 kg, respectively. Simulations were replicated (n=250) for each body weight to generate a distribution of values.

The highest 95th percentile of simulated $Cmax_{ss}$ were obtained at 3, 6, 13, 25 and 40 kg, which were the lower end of each body weight range. The highest simulated values (5178 – 5945 ng/mL) were comparable to or lower than 5575 ng/mL.

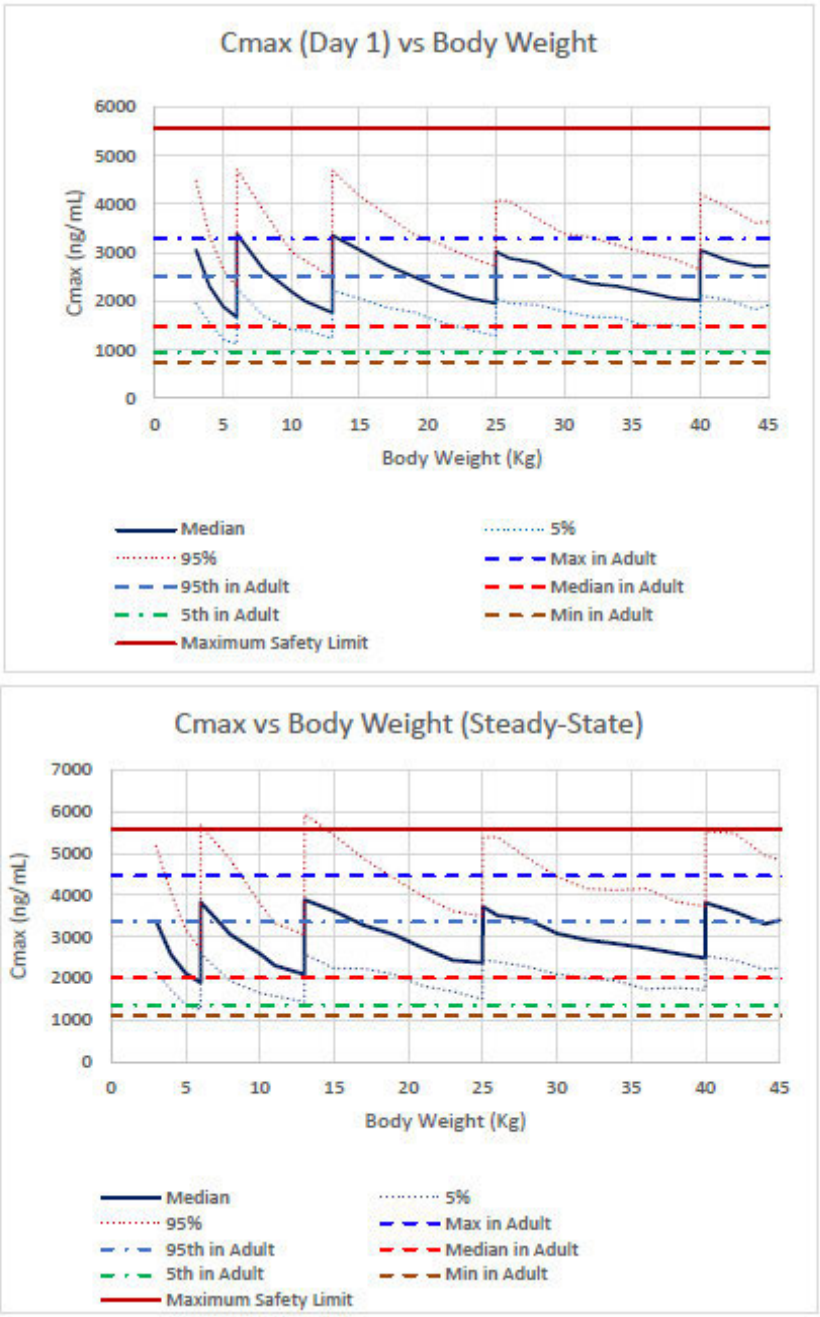


Figure 13: C_{max} vs body weights (Day 1 and steady-state)

The 5th percentile of simulated $Cmin_{ss}$ at 5.99, 12.99, 24.99 and 39.99 kg, which were the upper end of each body weight range, were 259, 248, 355 and 456 ng/mL, respectively. The lowest simulated Cmin values were comparable or higher than the 5th percentile Cmin values at steady state observed in adults receiving 600 mg BID and are multiple folds above the 169 ng/mL minimum efficacy level.

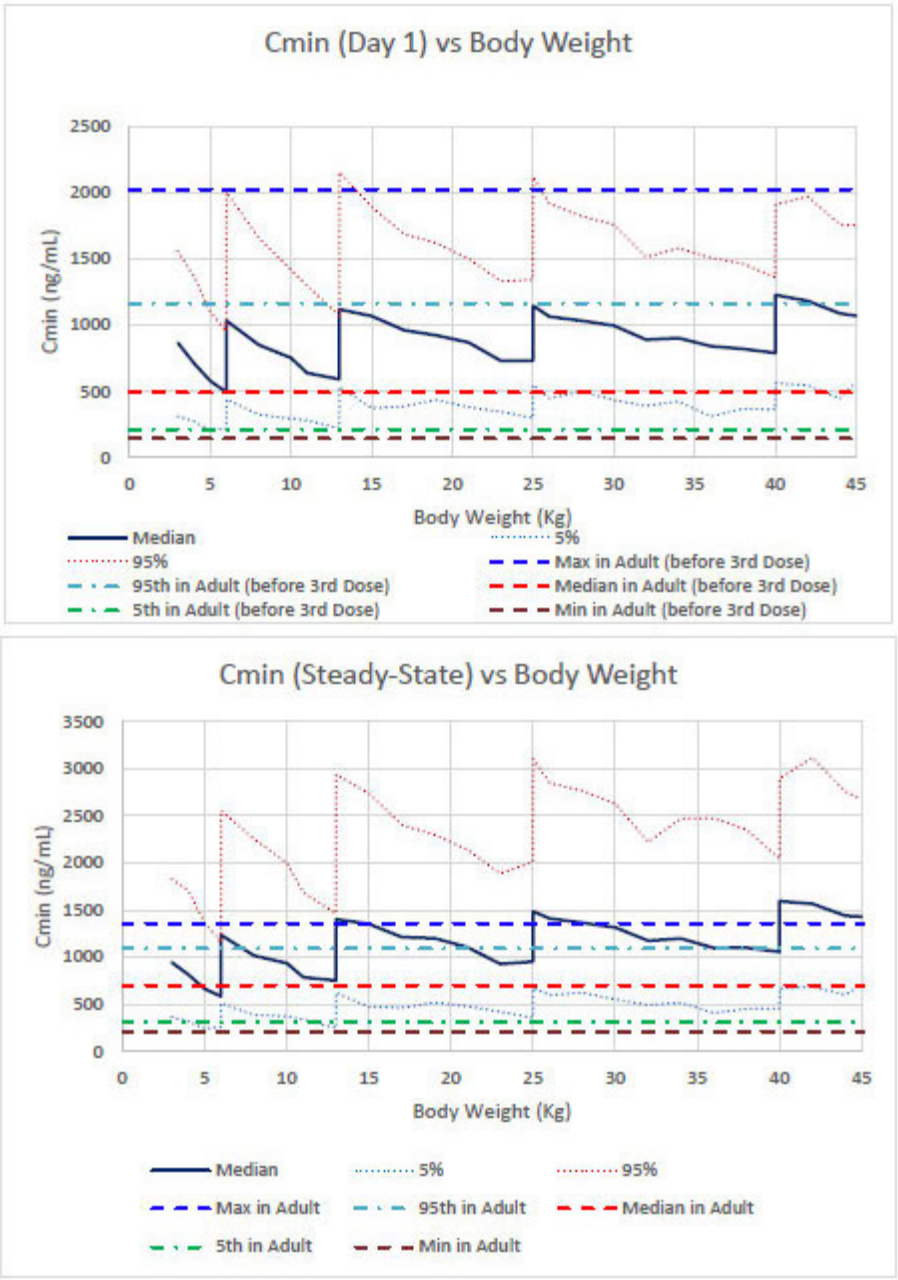


Figure 14: C_{min} vs body weights (Day 1 and steady-state)

Based on the simulation results, the BID dosing regimen of 50, 100, 200, 400 and 600 mg was selected for the body weight ranges of 3 to <6, 6 to <13, 13 to <25, 25 to <40, and ≥40 kg, respectively. Since the capsules contain 200 mg, they are suitable only for subjects from 13 kg to avoid having to open and adjust capsule contents to achieve lower doses.

Interactions

Cytochrome P450 (CYP) Enzymes

Tecovirimat is not a substrate for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4.

It tecovirimat weakly inhibits CYP2C8 and CYP2C19 but does not inhibit CYP1A2, CYP2D6, CYP2E1, CYP3A4, CYP2B6 or CYP2C9. It weakly induces CYP3A4 but does not induce CYP1A2, CYP2B6 or CYP2C9.

M4 does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A. M4 strongly induces CYP2B6 at ≥10.4 µM and significantly induces CYP3A4 at >10.4 µM.

M5 does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A. M5 strongly induces CYP2B6 at ≥7.93 µM and weakly induces CYP3A4 at ≥79.3 µM.

TFMBA does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A and does not induce CYP1A2, CYP2B6 or CYP3A4.

UGT Enzymes

Tecovirimat

Tecovirimat is a substrate of UGT1A1, UGT1A3 and UGT1A4.

M4, M5 and TFMBA

None of the metabolites gives important UGT inhibition.

Transporter Systems

Tecovirimat does not significantly inhibit P-gp and is not a P-gp substrate. Tecovirimat is not a substrate for BCRP but it significantly inhibits BCRP. It is not a significant inhibitor of OATP1B1 and OATP1B3, OAT1, OAT3 or OCT2.

M4, M5 and TFMBA do not inhibit P-gp, BCRP, OATP1B1 or OATP1B3, OAT1, OAT3 or OCT2.

SIGA-246-015 was a 3-arm drug-drug interaction study in healthy subjects to evaluate the effect of repeated doses of tecovirimat on the PK of probe substrates for CYP2C9, CYP2C19, CYP3A4, CYP2B6 and CYP2C8. Dosing on Day 1 provided a baseline for each probe substrate and the washout period was at least approximately 5 half-lives for each. Tecovirimat dosing duration (600 mg BID from days 8-22) was selected to provide a steady-state level of CYP induction. There were 78 healthy subjects randomly assigned to one of the following parallel arms:

Arm 1 (CYP2C9 + CYP2C19 + CYP3A4), n=24

The probe substrates flurbiprofen 50 mg tablet, omeprazole 20 mg capsule and midazolam 2 mg oral syrup were given alone and in combination with tecovirimat 600 mg BID. Subjects received a single oral dose each of the three substrates on Day 1, followed by a washout period from Days 2-7. Tecovirimat 600 mg BID was given for 15 days (Days 8 through 22) and single doses of each substrate drug were given with the morning dose of tecovirimat on Day 22.

Arm 2 (CYP2C8), n=30

Repaglinide 2 mg tablet was given alone on Day 1, followed by a washout period from Days 2-7. Tecovirimat 600 mg BID was given for 15 days (Days 8 through 22) and another single dose of repaglinide was co-administered with the morning dose of tecovirimat on Day 22.

Arm 3 (CYP2B6), n=24

Bupropion 150 mg tablet was given alone on Day 1, followed by a washout period from Day 2-7. Tecovirimat 600 mg BID was given for 15 days (Day 8 through Day 22) and another single dose of bupropion was co-administered with the morning dose of tecovirimat on Day 22.

All subjects were fed a meal (600 kcal and 25 g fat) 30 minutes prior to drug administration and fasted for 2 hours after taking study drug.

The tecovirimat Ctrough levels on days 20, 21 and 22 were in the range 1240-1330 ng/mL.

Co-Administered Drug	Dose of Co-Administered Drug (mg)	N	Mean Ratio (90% CI) of Co-Administered Drug PK With/Without TPOXX No Effect = 1.00	
			C_{max}	AUC_{inf}
Flurbiprofen + omeprazole + midazolam[b]	omeprazole 20 single dose	24	1.87 (1.51, 2.31)	1.73 (1.36, 2.19)
	midazolam 2 single dose		0.61 (0.54, 0.68)	0.68 (0.63, 0.73)
Repaglinide	2 single dose	30	1.27 (1.12, 1.44)	1.29 (1.19, 1.40)
Bupropion	150 single dose	24	0.86 (0.79, 0.93)	0.84 (0.78, 0.89)

[a]All interaction studies conducted in healthy volunteers with tecovirimat 600 mg twice daily.
[b]Comparison based on exposures when administered as flurbiprofen + omeprazole + midazolam.

The table and plots below summarise the findings:

- There was no effect of tecovirimat on flurbiprofen Cmax or AUCs.
- Tecovirimat increased AUCs and Cmax of omeprazole by 1.7-fold to 1.9-fold and increased AUCs and Cmax of 5-hydroxyomeprazole by 1.3-fold to 1.5-fold. The ratios of metabolite to parent were lower with co-administration. The increase in metabolite levels was unexpected and the applicant does not have an explanation for the finding.
- Tecovirimat decreased Cmax and AUCs of midazolam by 30-40% but increased AUCs of 1-hydroxymidazolam by ~3.5-fold, with a lesser effect on Cmax (~2.3-fold). The ratios for metabolite to parent were higher on co-administration.
- Tecovirimat increased Cmax and AUCs of repaglinide by ~1.3-fold.
- Tecovirimat decreased the Cmax and AUCs of bupropion by ~20%.

The applicant's conclusions were as follows:

- Tecovirimat has no clinical effect on CYP2C9 and no clinically important effect on CYP2B6. Tecovirimat is a weak inhibitor of CYP2C8 and CYP2C19.
- Tecovirimat is a weak inducer of CYP3A4.

These conclusions are based on FDA criteria (<2-fold increases in AUC being weak inhibition and decreases in AUC by 20-50% being weak induction).

Table 22: Statistical analysis of the effect of Tecovirimat on the pharmacokinetic of 1-hydroxymidazolam (Pharmacokinetic population)

Parameter	Treatment	N	Geometric Means	Treatment Comparison	Ratio (%) of Geometric Means	90% Confidence Intervals of the Ratio (%)	Intrasubject Variability (CV)
AUC_{0-t} (ng•h/mL)	FOM	24	10.44				
	FOM+T	24	37.25	(FOM+T) / FOM	357.00	(329.35, 386.97)	16.40
AUC_{0-inf} (ng•h/mL)	FOM	24	11.13				
	FOM+T	18	39.47	(FOM+T) / FOM	354.76	(321.92, 390.95)	17.23
AUC_{0-24h} (ng•h/mL)	FOM	24	10.99				
	FOM+T	24	36.76	(FOM+T) / FOM	334.59	(309.39, 361.84)	15.93
C_{max} (ng/mL)	FOM	24	3.03				
	FOM+T	24	6.91	(FOM+T) / FOM	227.92	(201.44, 257.88)	25.36

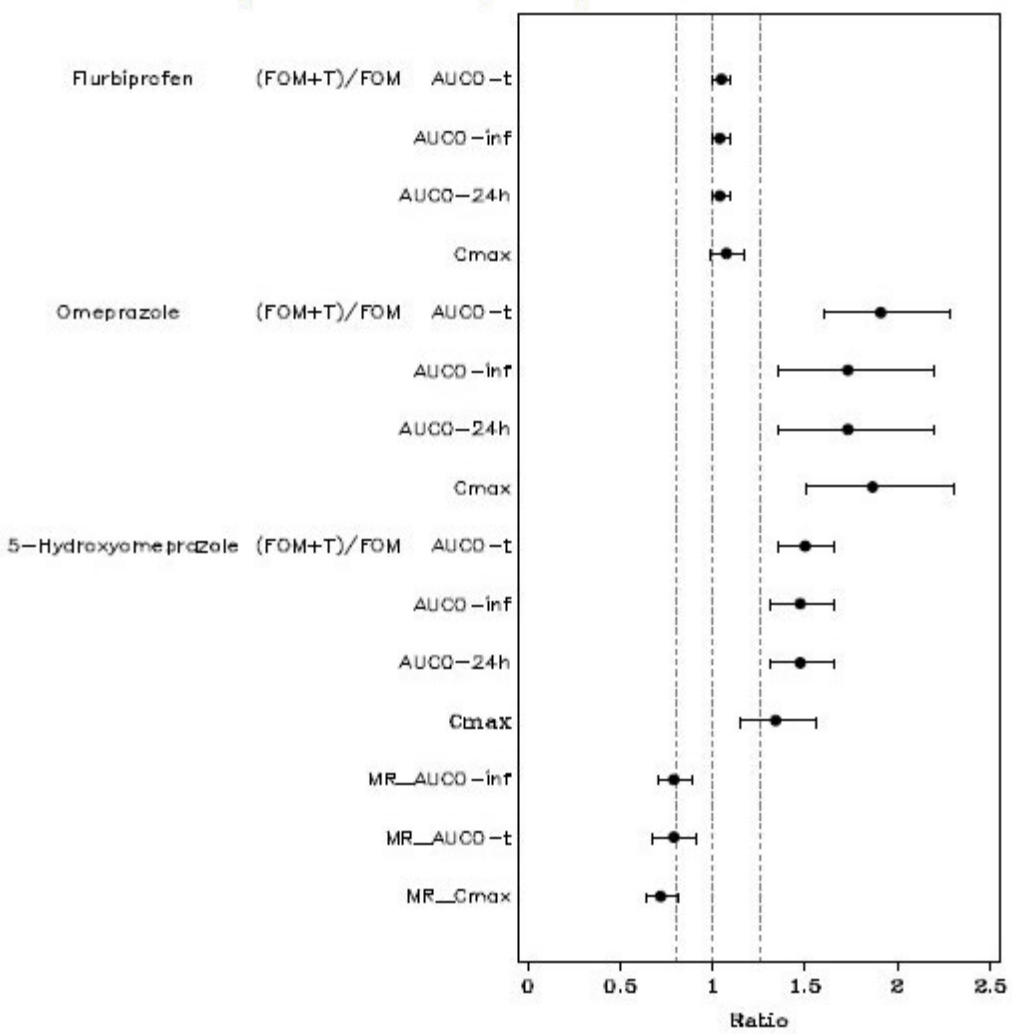
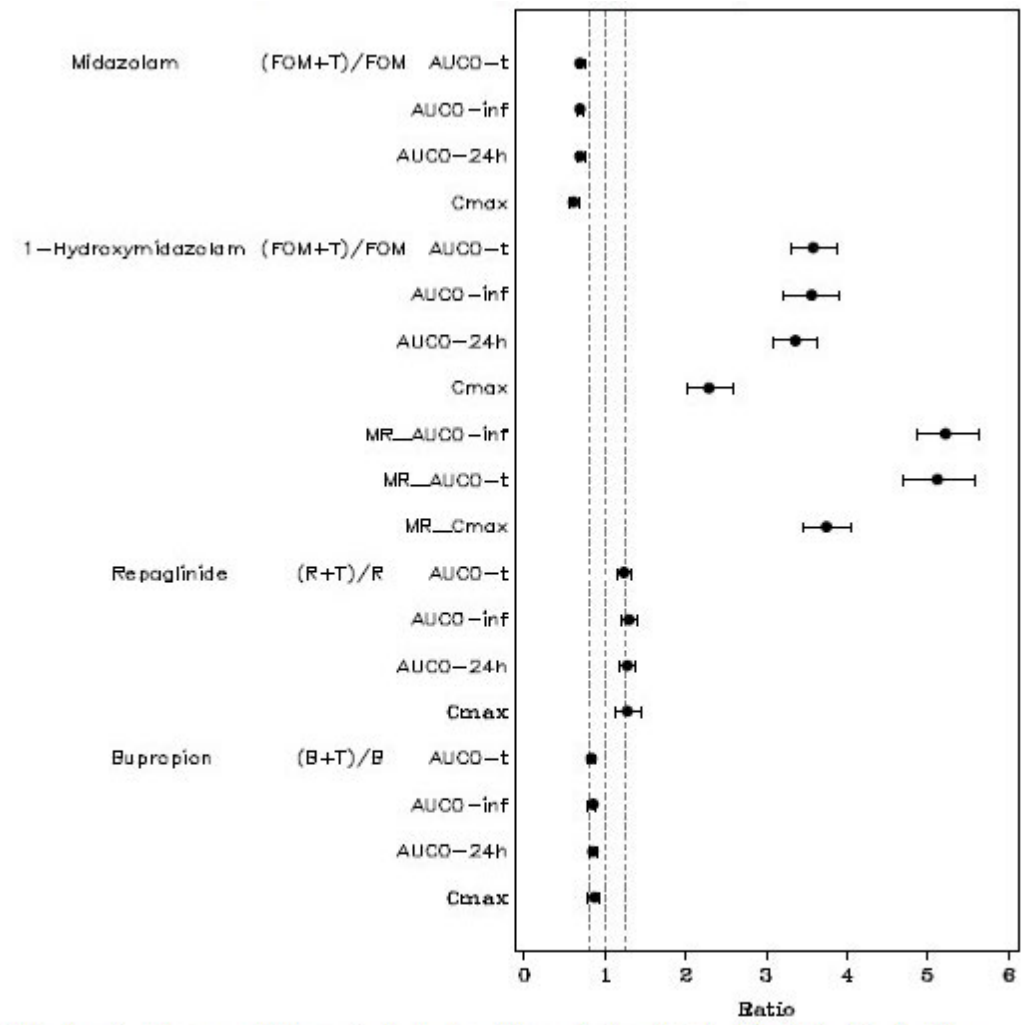


Figure 15: Forest plot for all analytes/parameters comparisons (pharmacokinetic population)



Note: In each study arm, subjects received a single oral dose of probe substrates (Arm 1: flurbiprofen 50 mg, omeprazole 20 mg, midazolam 2 mg [FOM]; Arm 2: repaglinide 2 mg [R]; Arm 3: bupropion 150 mg [B]) on Day 1, followed by a washout period (Day 2 through Day 7). Subjects received tecovirimat 600 mg [T] twice daily for 15 days (Day 8 through Day 22). A single oral dose of probe substrates was co-administered with the morning dose of tecovirimat on Day 22.

Figure 15: Forest plot for all analytes/parameters comparisons (pharmacokinetic population) (continued)

2.6.2.2. Pharmacodynamics

Since clinical efficacy studies are not possible, the evidence for the anticipated antiviral effect of tecovirimat in humans comes from the in-vitro and in-vivo nonclinical studies, together with PK-PD analyses to support the clinical dose regimen. The initial studies used Form V while later studies used Form I, which is that intended for the market.

The applicant designates the 6 studies shown in the table, all of which used Form I, as being pivotal. These pivotal in-vivo studies are described below, following a summary of in-vitro data. The pivotal studies formed the basis of the human dose selection process based on animal and human POPPK models, identification of nonclinical PDTs and consideration of margins for human exposure vs. safe and effective animal exposures.

Study No.	Type of Study	N	Objective(s)
Nonhuman Primate (cynomolgus monkey)			
FY10-087	PK in NHPs infected with MPXV; tecovirimat doses of 3, 10, and 20 mg/kg	24	PK and efficacy in NHPs who received 14 daily doses of tecovirimat or placebo from 4-17 days post-infection with MPXV
AP-09-026G	Repeat-dose efficacy study to determine the minimum effective therapeutic dose in NHPs infected with MPXV; tecovirimat doses of 0.3, 1, 3, and 10 mg/kg	27	Minimum effective dose of tecovirimat Form I for the treatment of MPXV in the lesional NHP model of smallpox, with tecovirimat or placebo treatment beginning on the day of onset of pox lesions in each animal and continuing for 14 days
SR10-037F	Efficacy of delayed tecovirimat treatment following lethal MPXV challenge in NHPs; tecovirimat dose of 10 mg/kg	21	Maximum delay post–MPXV challenge at which 14 daily doses of tecovirimat is effective at preventing mortality in NHPs
SR10-038F	Efficacy of 3, 5, 7, and 10 daily doses of tecovirimat 10 mg/kg in NHPs infected with MPXV	25	Minimum dose duration post–MPXV challenge at which tecovirimat is effective at preventing mortality in NHPs
Rabbit (New Zealand White rabbit)			
SR13-025F	PK in rabbits infected with RPXV; tecovirimat doses of 40, 80, and 120 mg/kg	24	PK and efficacy in rabbits who received 14 daily doses of tecovirimat from 4-17 days post-infection with RPXV
SR14-008F	Dose-response relationship in rabbits infected with RPXV; tecovirimat doses of 20, 40, 80, and 120 mg/kg	50	Minimum efficacious dose that provides maximal survival benefit in rabbits infected with RPXV receiving 14 daily doses of tecovirimat or placebo

KEY: MPXV = monkeypox virus; N = sample size; NHP = nonhuman primate; PK = pharmacokinetics; RPXV = rabbitpox virus

In-vitro studies

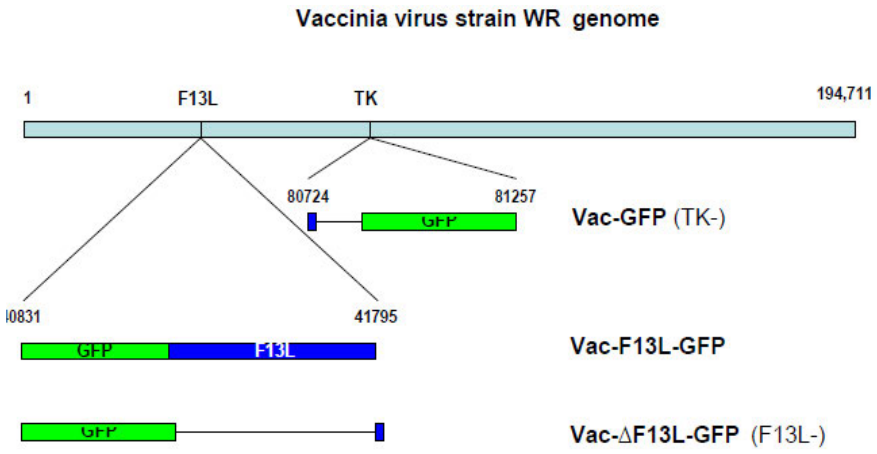
Mechanism of action

Tecovirimat (previously designated ST-246) inhibits the activity of the orthopoxvirus VP37 protein, which is encoded by and highly conserved in all members of the orthopoxvirus genus. Tecovirimat blocks the interaction of VP37 with cellular Rab9 GTPase and TIP47, which prevents the formation of egress-competent enveloped virions necessary for cell-to-cell dissemination of virus. The applicant conducted a series of in-vitro and in-vivo nonclinical studies to document the antiviral effects of tecovirimat, some of which also investigated the mechanism of antiviral activity.

In cell culture vaccinia virus results in the formation of four types of infectious virus particles: Intracellular mature virus (IMV), Intracellular enveloped virus (IEV), Cell associated enveloped virus (CEV) and Extracellular enveloped virus (EEV). Efficient plaque formation by vaccinia virus in permissive cells requires production of extracellular virus. Virus yield assays were conducted to determine whether tecovirimat inhibited intracellular and/or extracellular virus production using vaccinia virus IHD-J.

Tecovirimat reduced extracellular virus titres by approximately 10-fold at 24 h post-infection but it had little effect on intracellular virus titres relative to untreated controls.

Vaccinia virus plaque formation in permissive cells requires production of extracellular virus and variants that contain deletions in genes required for production of extracellular virus particles form small plaques. The applicant conducted a study using 2 cowpox strains (CPX strain Brighton Red and a tecovirimat-resistant variant of Brighton Red plus 3 recombinant strains derived from the WR vaccinia virus strain (Vac-GFP: expresses the GFP gene from the TK locus; Vac-F13L-GFP: expresses the GFP gene as a c-terminal fusion protein with F13L; Vac-ΔF13L-GFP: expresses GFP from the F13L locus.



- Tecovirimat inhibited plaque formation and virus-induced CPE caused by wild-type cowpox virus. Tecovirimat did not inhibit plaque formation by the resistant cowpox virus variant, which had a glycine to cysteine change at amino acid position 277 within F13L, such that the tecovirimat-treated and control (untreated) plates showed similar CPE.
- Against the recombinant vaccinia viruses derived from the WR strain, tecovirimat reduced the size of GFP-positive foci in cells infected with Vac-GFP and Vac-F13L-GFP but not Vac-ΔF13L-GFP relative to untreated control samples. However, the foci formed by Vac-ΔF13L-GFP were smaller than the foci formed by virus that expressed wild-type F13L in the absence of tecovirimat.
- Plaques were visible in cells infected with Vac-ΔF13L-GFP in the presence and absence of tecovirimat although they were noticeably smaller than plaques formed by wild-type Vac-GFP infected cells in the absence of drug. No plaques were observed in cells infected with viruses expressing F13L (Vac-GFP, Vac-F13L-GFP) in the presence of drug.

It was concluded that tecovirimat inhibits virus spread and plaque formation in cells infected with viruses expressing functional F13L but not in cells infected with Vac-ΔF13L-GFP, which contains a deletion of the F13L gene. Since the F13L gene encodes the envelope protein p37 required for production of extracellular virus, the findings supported the conclusion that p37 is the target of tecovirimat. Specifically, the F13L protein participates in the envelopment of IMV particles in virus-modified membranes derived from the trans Golgi or late endosome compartments to produce an egress-competent form of virus particle. F13L co-localises to the trans Golgi, plasma and endosomal membranes. The protein shuttles between these various compartments through a clathrin-mediated endosomal pathway.

In-vitro activity

Tecovirimat showed dose-dependent inhibition of orthopoxvirus-induced cytopathic effects with EC_{50} values of 0.009 µM for vaccinia virus and 0.050 for cowpox virus. Based on the CC_{50}, the therapeutic index was estimated to be > 4000. While there was no significant correlation between human serum concentration and tecovirimat EC_{50}, there was a trend to increasing EC_{50} values as a function of human serum. This trend was used to calculate an apparent EC_{50} value in 100% human serum of 0.028 µM for vaccinia virus strain WR.

The tecovirimat EC_{50} values against a range of orthopoxviruses were of the same order, including two smallpox (variola) viruses from two different sources. The in-vitro activity of tecovirimat was also assessed against a panel of 14 variola viruses of 7 haplotypes. The tecovirimat EC_{50} values ranged from 0.011 µM to 0.067 µM.

Table 23: Spectrum of antiviral activity

Virus	EC_{50} (µM)
Cowpox (Brighton Red)	0.050
Cowpox CDV[r] (Brighton Red)	0.030
Ectromelia	0.068
Camelpox	0.012
Monkeypox (Zaire '79)	0.014
Variola (BUT)	0.016
Variola (BSH)	0.046

Tecovirimat was active *in vitro* against a cidofovir-resistant cowpox variant and was more active than cidofovir alkoxy alkylester derivatives that were designed to increase its activity in cell culture, indicating that the antiviral target for tecovirimat is different from that of cidofovir.

Table 24: Antiviral activity of ST-246 compared to CDV and CDV analogues

Compound	EC_{50} (µM)	CC_{50} (µM)	TherapeuticIndex
ST-246	0.009	> 40	> 4400
CDV	80	600	8
HDP-CDV	1.2	36	30
ODE-CDV	2.2	59	26

The antiviral specificity of tecovirimat was further assessed by determining its in-vitro activity against a range of RNA and DNA viruses using cell lines as appropriate to the virus under study. Results supported the specificity of tecovirimat for orthopoxviruses.

Table 25: Spectrum of antiviral activity

Virus	Family	Classification	EC_{50} (µM)
Vaccinia	Orthopoxviridae	Double stranded DNA	0.009
Herpes Simplex virus type-1	Herpesviridae	Double stranded DNA	> 40[a,b]
Cytomegalovirus	Herpesviridae	Double stranded DNA	> 40[a,b]
Respiratory syncytial virus	Paramyxoviridae	Negative single strand RNA	> 40[a,b]
Rotavirus	Reoviridae	Double stranded RNA	> 40[a,b]
Rift Valley Fever virus	Bunyaviridae	Negative single strand RNA	> 40[a,b]
Tacaribe virus	Arenaviridae	Ambisense RNA	> 40[a,b]
Lymphocytic choriomeningitis virus	Arenaviridae	Ambisense RNA	> 40[a,b]

[a]Each value represents 2 independent determinations.
[b]Assessment limited by solubility of ST-246 at > 40 µM

Resistance to tecovirimat

The CPX strain Brighton Red (10^7 pfu) was plated on Vero cell monolayers in the presence of 10 µM tecovirimat and virus was isolated from plaques that formed at day 3 post-infection. The EC_{50} value of the resistant variant was shifted from 0.01 µM for wild-type virus to greater than 40 µM. Sequence analysis of the tecovirimat-resistant allele identified a single base change resulting in a glycine residue being replaced by cysteine at amino acid position 277in the protein encoded by the V061 gene. This change was re-engineered back into wild-type cowpox and vaccinia virus genomes and the resulting recombinants were found to be resistant to tecovirimat. Results suggest that the cowpox virus V061 gene product, which is homologous to vaccinia virus F13L, is the target of tecovirimat.

Tecovirimat-resistant vaccinia virus variants were selected by direct plating of wild-type virus stocks in the presence of inhibitory concentrations of drug or by introducing random point mutations in the viral gene target and isolating virus from plaques that arise under selection.

Fluctuation analysis was used to determine whether tecovirimat resistance was the result of pre-existing mutations in the virus population or was induced by exposure to the compound. The resistance frequency was 1.2 resistant plaques per 1 x 10^6 plaques for wild-type vaccinia virus strain WR. The

ratio of the variance to the mean was 2.8 for the bulk population and 6.8 for the 10 plaque isolates, suggesting that mutations that confer tecovirimat resistance likely pre-existed in the virus population.

The F13L alleles from each resistant variant were amplified by PCR and sequenced to ascertain whether amino acid changes that correlate with drug resistance were present. To confirm that the observed changes correlated with resistance, the F13L gene was transferred into the wild-type viral genome by marker rescue and the level of resistance to tecovirimat measured. The EC_{50} values for most variants were >50 µM, which was the upper limit of the assay based upon the solubility of tecovirimat in tissue culture media. Results suggested that mutations in at least 7 positions within F13L can confer resistance and that resistance associated mutations cluster within a 64 amino acid domain spanning amino acid 238 to amino acid position 302 in the p37 protein of vaccinia virus.

Antiviral activity of metabolites of tecovirimat

M4, M5 and TFMBA were evaluated for antiviral activity against rabbitpox virus (RPXV). None of the three metabolites tested showed inhibition of CPE up to the maximum tested compound concentration of 5 µM nor were they cytotoxic.

In-vivo studies

In-vivo studies with Monkeypox virus in cynomolgus macaques

ap-09-026g aimed to identify the minimum effective dose of tecovirimat Polyform I by starting treatment with 0.3, 1, 3 or 10 mg/kg when each individual monkey first developed lesions and continuing for up to 14 days. In the placebo and 1 mg/kg groups no monkeys (0/7 and 0/5, respectively) survived to day 42 post-treatment compared to 1/5 in the 0.3 mg/kg group and 4/5 in each of the 3 and 10 mg/kg groups. The mean number of days from treatment start to day of death were 10.4 for placebo and 16.6, 12.6, 31.4 and 31.8 days for the tecovirimat ascending dose groups. The two deaths that occurred in the 3 and 10 mg/kg groups were not attributed to typical MPXV disease and were thought due to complications of gavage.

Table 26: Survival post-infection up to Day 42 following 14-day treatment with ST-246

ST-246 Dose (mg/kg)	Number Started Study	Number Completed Study	Day Post-Infection of Unscheduled Death[a]
Placebo	7	0	9, 14 (2), 15 (2), 17 (2)
0.3	5	1	12, 15, 16, 18
1	5	0	11, 14, 15, 16, 27
3	5	4	5
10	5	4	11

[a] Number in parentheses indicates the number of animals necropsied on that day.

Whole blood viral DNA levels and total pox lesions measured as time-weighted average, rate of increase, and maximum number all exhibited dose-related decreases, generally with statistical significance in the 3 and 10 mg/kg groups. All whole blood viral DNA parameters in the 3 and 10 mg/kg groups exhibited a statistically significant difference compared to placebo.

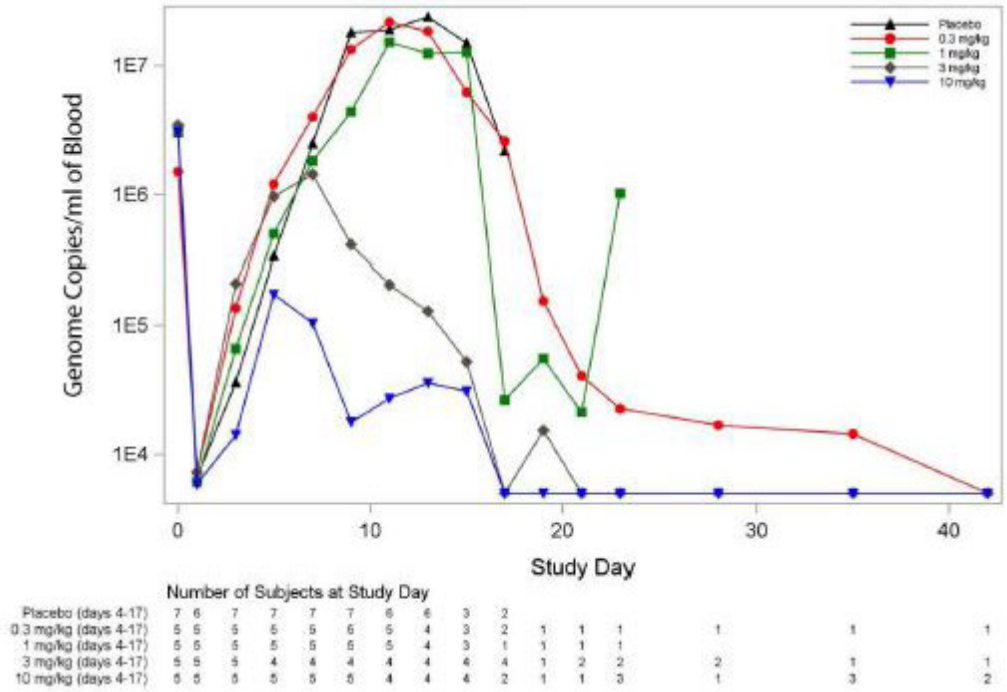


Figure 16: Study AP-09-026G: Geometric mean viral load

The rate of increase of pox lesions over the treatment period was significantly decreased at both 3 and 10 mg/kg doses compared to placebo, but there were significantly fewer skin pox lesions (time-weighted average and maximum number) only in the 10 mg/kg group.

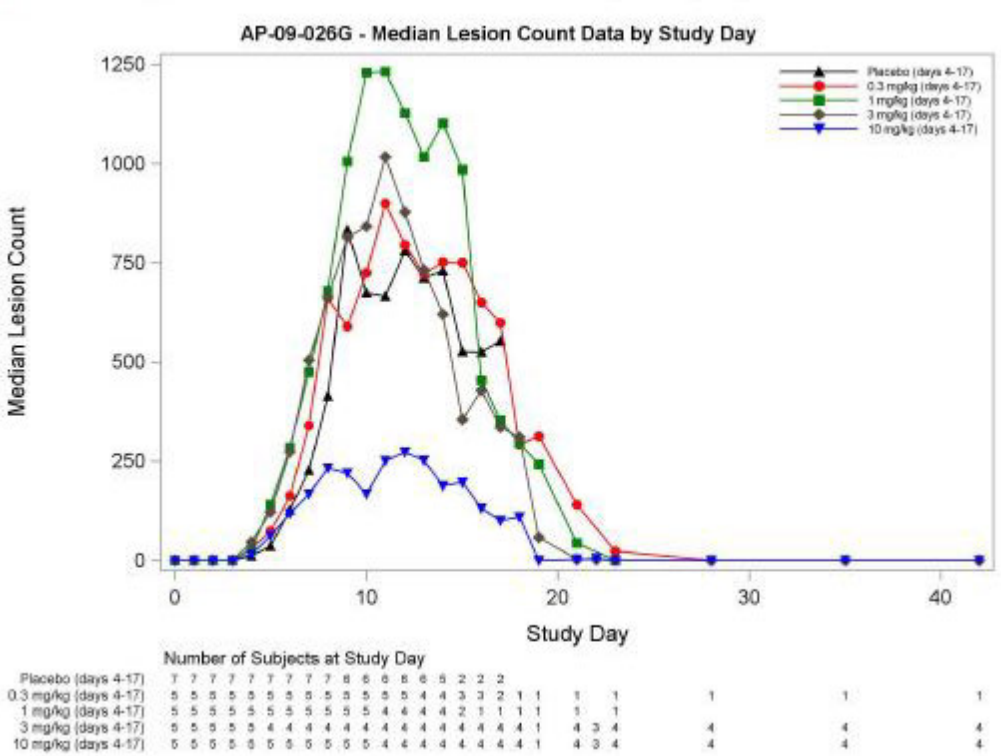


Figure 17: Study AP-09-026G: Median lesion count by study day

Plasma concentrations of tecovirimat were dose-proportional across the 0.3 to 10 mg/kg groups and from pre-dose to 4 h after each dose. It was concluded that the minimum effective dose of tecovirimat Polyform I when started on the day of onset of lesions was 3 mg/kg (36 mg/m^2), with corresponding plasma levels of approximately 250 ng/mL at 4 h post-dose sr10-037f aimed to determine the maximum delay that could be applied when using Polyform I tecovirimat 10 mg/kg. Tecovirimat was commenced on Day 4, 5 or 6 (groups 2, 3 and 4) after IV challenge and was continued for 14 days. Group 1 received vehicle. None of the 3 animals in the vehicle group survived to post-infection Day 56 while 5/6 in the Day 4 and Day 5 groups and 3/6 in the Day 6 group survived to scheduled euthanasia.

Table 27: Number of animals surviving to scheduled termination

Group	Number of Animals		Statistics[a]
	Study Start	Study End	
Placebo	3	0 (0%)	--
ST-246 Day 4	6	5 (83%)	p = 0.0476[c]
ST-246 Day 5	6	5 (83%)	p = 0.0476[c]
ST-246 Day 6	6	3 (50%)	p = 0.4643
All ST-246 Treated[b]	18	13 (72%)	p = 0.0421[c]

[a]P-value obtained using Fisher's Exact Test (2-sided) vs. Placebo
[b]Day 4, Day 5, and Day 6 groups combined
[c]Significant at $p \leq 0.05$

The mean time-weighted averages of log_{10} viral DNA for treatment Days 1-16 and post-infection Days 3-24 were reduced by tecovirimat but the decreases were not statistically significant ($p \geq 0.0888$) for any active group vs. placebo group comparison. On Day 4, all animals had skin lesions. There were no significant differences in mean time-weighted average of total lesion counts for treatment Days 1-16 and post-infection Days 3-24 in any tecovirimat group vs. vehicle.

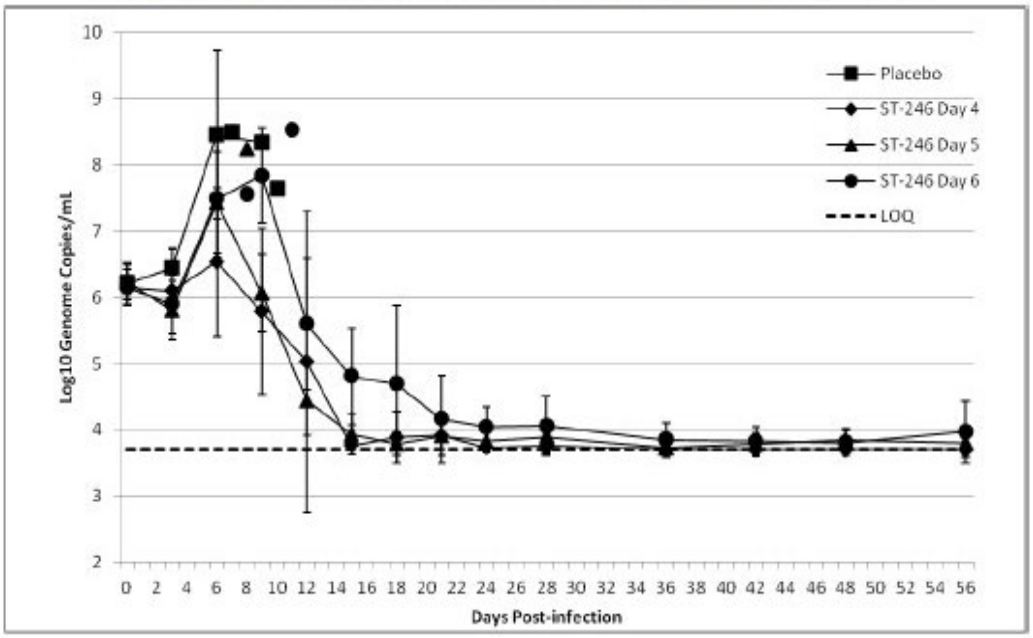


Figure 18: Mean whole blood monkeypox viral load from inoculation through Day 56

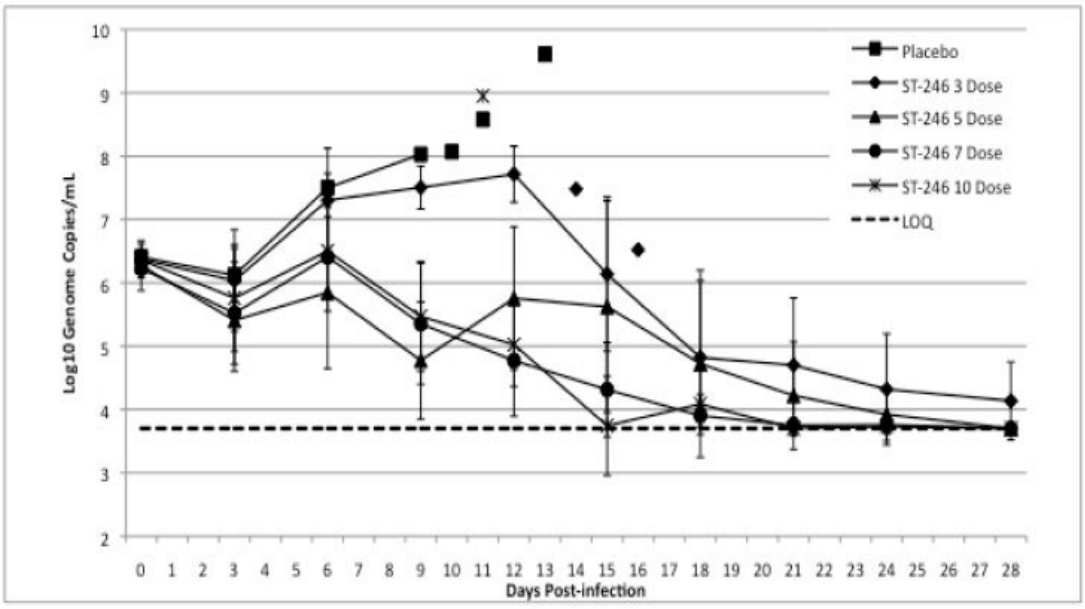
SR10-038f aimed to determine the minimum duration of dosing that could be applied when using Polyform I tecovirimat 10 mg/kg. Tecovirimat was commenced on Day 4 post-challenge (challenge as in prior studies) and was given for 3, 5, 7 or 10 days. Group 1 received vehicle. One of the 4 animals in the vehicle group survived compared to 2/4 treated with tecovirimat 3 doses, 6/6 given 5 or 7 doses and 4/5 given 10 doses.

Table 28: Study SR10-038F: Survival and time to death analysis

Dose (Regimen)	No. of Animals/ Sex	Survival Rate		Time to Death		
		Survival (n [%])	P-value[a]	Median Time to Death (Days)	Mortality Day (No., Sex)	P-value[b]
Placebo (Days 4–13)	2M/2F	1 (25)	--	8.0	Day 10 (1F) Day 11 (1M) Day 13 (1M)	--
Tecovirimat 10 mg/kg (Days 4–6)	2M/2F	2 (50)	0.3643	18.0	Day 14 (1M) Day 16 (1F)	0.1000
Tecovirimat 10 mg/kg (Days 4–8)	3M/3F	6 (100)	0.0141[c]	24.0	--	0.0333
Tecovirimat 10 mg/kg (Days 4–10)	3M/3F	6 (100)	0.0141[c]	24.0	--	0.0333
Tecovirimat 10 mg/kg (Days 4–13)	2M/3F	4 (80)	0.0972	24.0	Day 11 (1M)	0.1270

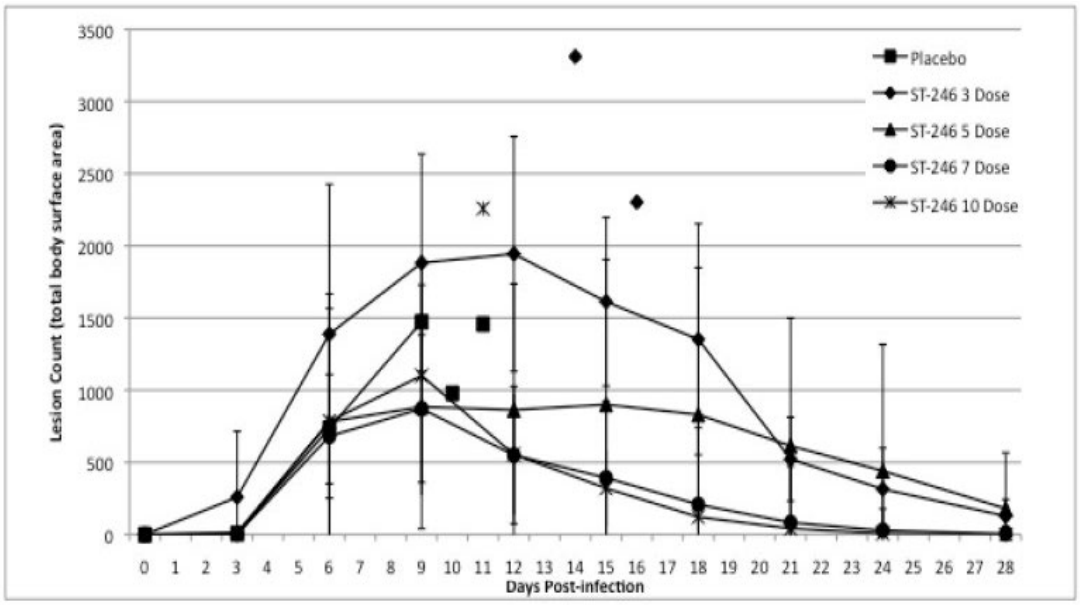
[a]P-value is based on a Boschloo Test (with Berger-Boos modification of gamma = 0.001) compared with placebo.
[b]P-value is from an exact Wilcoxon test compared with placebo.
[c]Denotes statistical significance at the 0.025 level.

Trends in blood viral DNA levels and pock lesion counts were consistent with improved efficacy when tecovirimat was given for more than 3 days.



NOTES: Symbols connected by lines indicate the mean of each group at each scheduled sampling, with error bars indicating standard deviations. Stand-alone symbols not connected by lines indicate individual animal data collected off-schedule at the time of euthanasia Symbols for individual animals are the same as the treatment group to which they belong.
KEY: LOQ = limit of quantitation (dashed line)

Figure 19: Whole blood viral load (log10 genomes/ml) from inoculation Through Day 28



NOTES: Symbols connected by lines indicate the mean of each group at each scheduled counting interval, with error bars indicating standard deviations. Stand-alone symbols not connected by lines indicate individual animal lesion counts performed off-schedule at the time of euthanasia. Symbols for individual animals are the same as the treatment group to which they belong.

Figure 20: Total lesion count (excluding injection site) from inoculation through Day 28

Fy10-087 documented the effect of infection on tecovirimat PK in the IV challenge model when using $5x10^7$ pfu as the challenge dose and starting treatment with tecovirimat 3, 10 or 20 mg/kg once daily on Day 4 post-infection. PK on days 4, 10 and 17 post-challenge was compared with PK after dosing on Day -10 pre-challenge. There was no consistent effect of the infectious process on tecovirimat PK and also no gender-related difference.

With a mean post-challenge viral load of 3.11 x 10^6 copies/mL, there was a decrease to 1.11 x 10^5 copies/mL at day 3. Loads increased in the placebo group (1001-1006) to terminal or near-terminal levels of 5.57 x 10^6 to 8.32 x 10^7 copies/mL. Animals given tecovirimat (groups 2-4 shown in the other 3 panels) had gradual declines in viral loads that were not dose dependent.

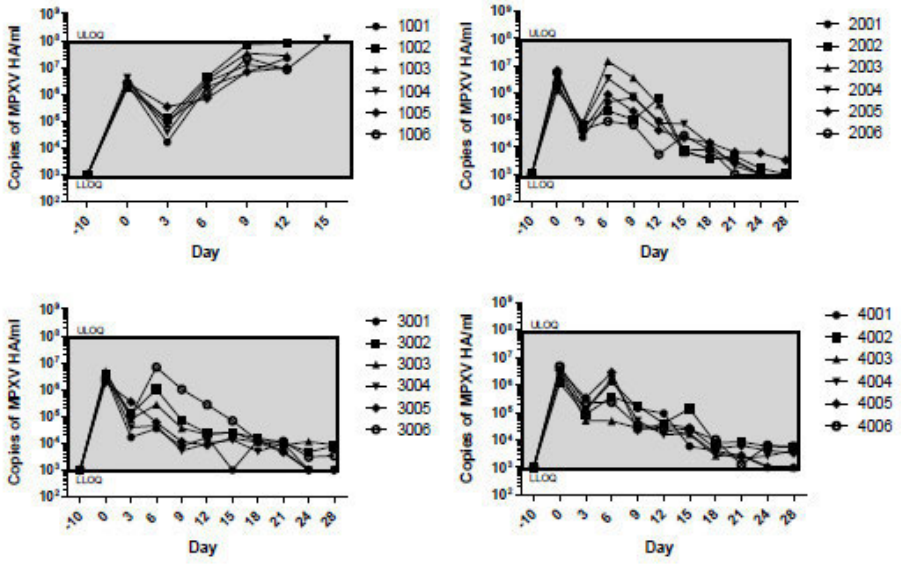


Figure 21: Quantified copies of MPXV HA gene in whole blood for all study groups

In parallel there was resolution of MPXV lesions from macule to desquamation in the tecovirimat-treated animals.

In-vivo studies with rabbitpox virus in New Zealand White (NZW) rabbits

SR14-008F evaluated protection by tecovirimat at various doses against lethal intradermal challenge.

Tecovirimat 20, 40, 80 or 120 mg/kg was orally administered once daily for 14 days starting on Day 4 after intradermal challenge with rabbitpox Utrecht strain at ~1000 pfu. All rabbits had a fever at the time of starting treatment. All 10 rabbits who received placebo died before or on Day 10. In the tecovirimat groups, 90% treated with 20 or 40 mg/kg and 80% treated with 80 or 120 mg/kg survived. Thus, the tecovirimat dose level did not have an effect on the survival rate.

There was a significant correlation between Day 4 tecovirimat levels and survival (P = 0.01) where the plasma tecovirimat concentration from samples collected at 2 h post-dose at a 95% probability of survival was 746.00 (484.83-2853.00 95% CI) ng/mL. There was no significant correlation between Day 5, 10 and 11 tecovirimat plasma levels and survival (P >0.05).

Table 29: Study SR14-008F: Survival and time to death analysis

Dose (Regimen)	No. of Animals/ Sex	Survival Rate		Time to Death	
		Survival (n [%])	P-value[a]	Mortality Day (No., Sex)	P-value[b]
Placebo (Days 4–17)	5M/5F	0 (0)	--	Day 5 (1F) Day 6 (2M) Day 7 (1M/2F) Day 8 (1M/1F) Day 9 (1F) Day 10 (1M)	--
Tecovirimat 20 mg/kg (Days 4–17)	5M/5F	9 (90)	0.0010[c]	Day 14 (1M)	< 0.0001[c]
Tecovirimat 40 mg/kg (Days 4–17)	5M/5F	9 (90)	0.0010[c]	Day 12 (1M)	< 0.0001[c]
Tecovirimat 80 mg/kg (Days 4–17)	5M/5F	8 (80)	0.0011[c]	Day 9 (1F) Day 13 (1F)	< 0.0001[c]
Tecovirimat 120 mg/kg (Days 4–17)	5M/5F	8 (80)	0.0011[c]	Day 9 (1F) Day 12 (1M)	< 0.0001[c]

[a]P-value is based on a Boschloo Test (with Berger-Boos modification of gamma = 0.001) compared with placebo.
[b]P-value is from an exact Wilcoxon test compared with placebo.
[c]Denotes statistical significance at the 0.025 level.

Rabbits treated with placebo (Group 1) exhibited high levels of viral DNA in the blood whereas levels were much lower in the tecovirimat groups.

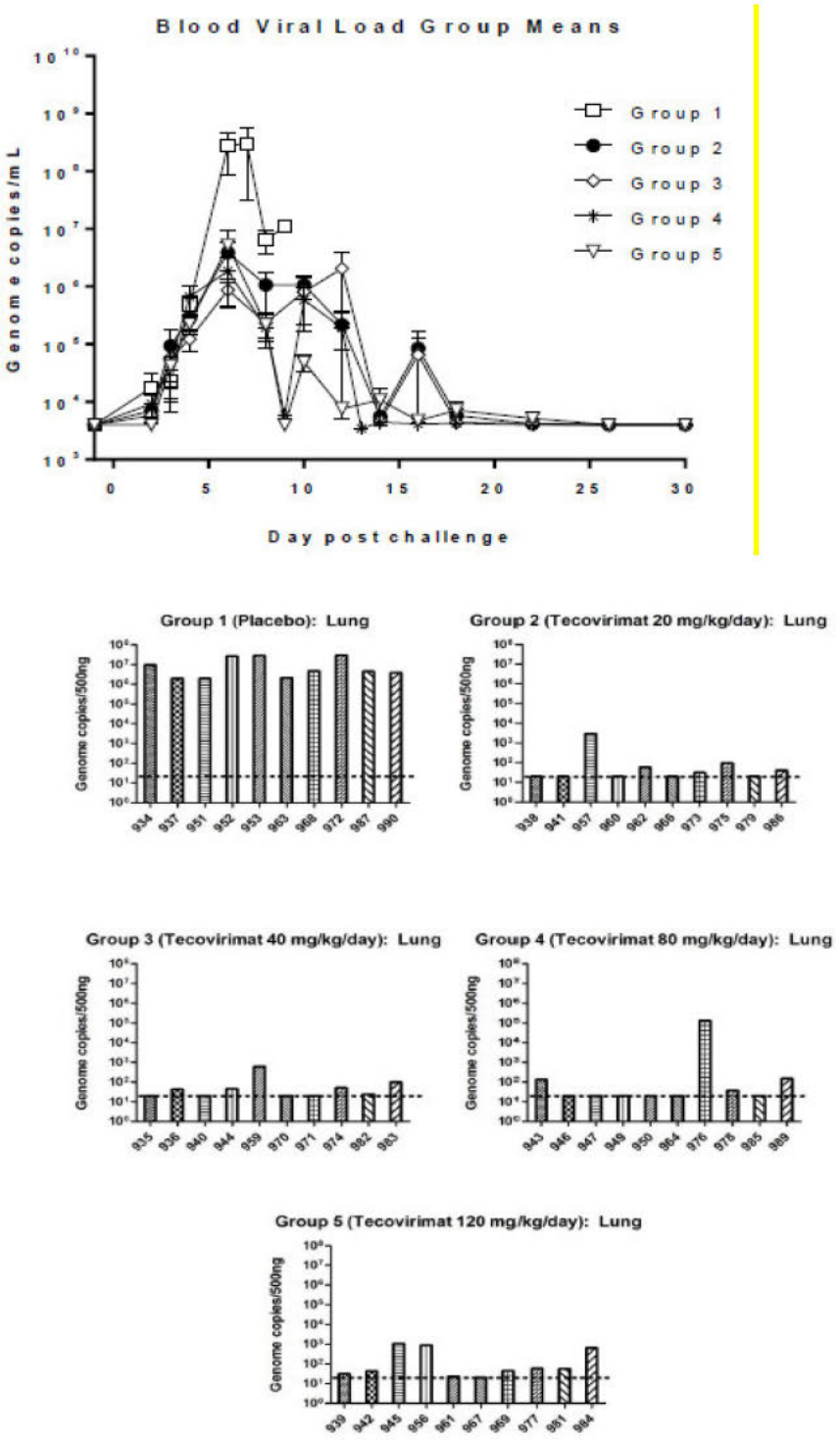


Figure 22: Viral load in lungs of rabbits following RPXV challenge via intradermal route. NZW rabbits were challenged with a target dose of 1000 PFU RPXV on Study Day 0 and received placebo (Group 1) or 20, 40, 80, 120 mg/kg tecovirimat (Groups 2-5) once daily beginning of Day 4 and continuing for 14 consecutive days. Shown are measurements of viral load (genome copies/mL) by qPCR in tissue samples at unscheduled (moribund) and scheduled euthanasia (Day 30-31 post-challenge). The LLOQ of the assay is 20 genome copies/500 ng of total tissue DNA, which is represented by the dotted line.

SR13-025F evaluated the effect of time of initiation of tecovirimat treatment on protection against lethal intradermal challenge.

The applicant first conducted a pilot study (SR13-007F) in which 80 mg/kg tecovirimat orally once daily for 14 days commenced on Days 2, 3, 4, 5 or 6 post-challenge with 300 pfu Utrecht strain. All 18 animals that started tecovirimat on days 2-4 survived, as did 4/5 that started on Day 5. All 5 animals that started tecovirimat on Day 6 and all 12 treated with vehicle died.

Early treatment with tecovirimat afforded better control of viraemia.

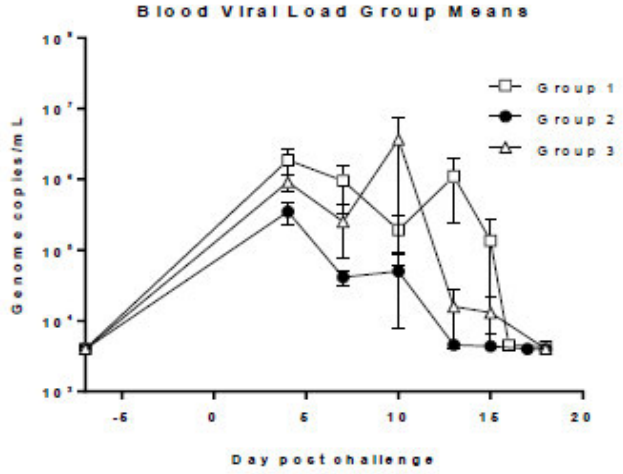
- Tecovirimat treatment initiation on Day 2 post-challenge provided complete control of viraemia in 4/6 to <LLOQ through Day 20.
- When tecovirimat treatment was initiated 3 days after challenge, significantly lower peak viraemia levels were measured on Day 6.
- When treatment was initiated on Days 4 and 5 post-challenge, viraemia peaked in all animals on Day 6 and was significantly reduced afterwards.
- All rabbits that started treatment on Day 6 had high levels of viraemia until the time of death/euthanasia by Days 6 and 7.

In SR13-025F, 24 NZW rabbits were randomised into 3 groups. On Day -7 (7 days prior to challenge), all animals received a single dose of tecovirimat at 40 mg/kg (Group 1), 80 mg/kg (Group 2) and 120 mg/kg (Group 3) to determine tecovirimat PK in the uninfected state. On Day 0, all animals received intradermal challenge with a target dose of 1,000 PFU. On Day 4 post-challenge, all animals started once daily tecovirimat at their assigned group dose for 14 days. Across the 3 tecovirimat groups, 22/24 survived and the other two were not thought to have died from the infection.

Table 30: Study SR13-025F: Survival and time to death details

Dose (Regimen)	No. of Animals/ Sex	Survival Rate	Time to Death
		Survival (n [%])	Mortality Day (No., Sex)
Tecovirimat 40 mg/kg (Days 4–17)	4M/4F	7 (87.5)	Day 16 (1F)
Tecovirimat 80 mg/kg (Days 4–17)	4M/4F	7 (87.5)	Day 17 (1M)
Dose (Regimen)	**No. of Animals/ Sex**	**Survival Rate**	**Time to Death**
		Survival (n [%])	**Mortality Day (No., Sex)**
Tecovirimat 120 mg/kg (Days 4–17)	4M/4F	8 (100)	--

The blood viral load peaks showed no statistically significant differences between dose groups.



The rate and extent of exposure to tecovirimat, as measured by AUC_{0-t} and Cmax, generally increased in a dose-proportional manner in uninfected and infected rabbits and were not significantly impacted by infection. The mean tecovirimat Cmin in uninfected and infected rabbits ranged from 151.4 to 455.6 ng/mL and 177.7 to 578.3 ng/mL, respectively, over the dose levels tested in this study (P>0.05).

Relationship between plasma concentration and effect

The applicant conducted several analyses of POPPK and PK-PD using results from some of the nonclinical efficacy studies.

Rabbit data

SIGA-PCS-100

The applicant aimed to develop a model linking the rabbit PK and survival data obtained in SR13-007F to assess potential exposure-survival relationships and identify potentially effective clinical doses using data from 46 rabbits with 651 measurable plasma concentrations. A 1-compartment PK model with zero-order absorption was found appropriate to model the concentration-time profiles of tecovirimat.

The POPPK-model derived PK parameters of tecovirimat showed that apparent clearance (CL/F) was 22.0 L/h, a value greater than that in monkeys (~2 L/h). The apparent central volume of distribution (Vc/F) was 244 L, which is ~10-fold greater than monkeys (~20 L) despite similar body weights. Mean $t_{1/2}$ was ~7.69 h compared to ~6.93 h in monkeys. The between-subject variability ranged from 31.6 to 81.1%, while IOV varied from 28.8 to 36.9%, suggesting variability in the PK of tecovirimat across the population and within each rabbit across multiple dose administrations. There were no statistically significant covariates. However, female rabbits had Vc/F and CL/F approximately 1.4- and 1.3-fold higher than male rabbits while infected rabbits had Vc/F and CL/F 2.1- and 1.5-fold higher than non-infected rabbits.

An exposure-response analysis used survival data from SR13-007F and individual predicted post-hoc PK parameters derived from the POPPK model. In addition to steady state parameters, the time of tecovirimat administration relative to infection was accounted for by deriving a cumulative exposure (Cavg) metric which was computed up to Day 6 (i.e. $AUC_{0-168/168}$; regardless of number of doses, AUCs were divided by 168 h). An initial Kaplan-Meir analysis to estimate the probability of survival over time showed a distinct trend of increased survival with increased exposure for all PK metrics used. The exposure-response relationship was clearly separated and apparent for Cminss and Cavg to Day 6. Also, the survival rate was greater in rabbits that were treated within 4 days post-challenge.

A ROC analysis identified a cut-off that optimised sensitivity (the probability of being a responder among those really responding; true positive/total number of dead rabbits) and specificity (the probability of being a non-responder among true non-responders; true negative/total number of surviving rabbits). A cut-off value of 75.4 µg/L for Cavg to Day 6 was the best predictor for survival ($p < 0.001$) as all rabbits that were found dead after challenge had a Cavg to Day 6 < 75.4 µg/L. Similar results were obtained with Cminss, although this parameter was not as good a predictor as Cavg.

Using a Kaplan-Meier analysis, the median (95 percentiles) Cavg to Day 6 target was determined to be 157 (85.2 – 645) µg/L. The target based on the alternative exposure metric (Cminss = 142 µg/L) was consistent with that derived for Cavg to Day 6.

Table 31: Definition of exposure targets in challenged rabbits

Exposure	Cutoff (µg/L)	Target Median (µg/L)	Target 90 % CI (µg/L)
Best Exposure Metric - $C_{avg\ to\ Day\ 6}$	≥75.4	157	85.2 – 645
Alternative Exposure Metric - C_{minss}	≥91.2	142	91.2 – 687
Other Exposure Metric - C_{ss}	NS	NA	NA
Other Exposure Metric - C_{maxss}	NS	NA	NA

NS = Not Significant, NA = Not Applicable

Tecovirimat PK parameters after dosing healthy subjects with 400 mg or 600 mg once daily were derived from the POPPK model. For both dose groups, all subjects were predicted to have a Css above target, with the 95th percentile of predicted human exposures (85.2 µg/L) greater than 75.4 µg/L. For Cminss, 96.2% were predicted to be above target (91.2 µg/L) when dosed with 600 mg vs. 83.3% when dosed with 400 mg.

finalSIGA-PCS-104

This report presents a POPPK and PK-PD analysis of rabbit data obtained in SR14-008F, SR13-025F and 029251 as well as information from SR14-015F. A 1-compartment model with zero-order absorption provided the best fit for the rabbit data. Total volume of distribution was ~170 L in uninfected animals and ~40% higher (239 L) in infected rabbits. The estimated $t_{1/2}$ was 6.9 h in uninfected vs. 9.7 h in infected animals. Infection did not affect other PK parameters in the model.

Overall, 91.8% of rabbits treated with 20, 40, 80 or 120 mg/kg tecovirimat survived rabbitpox infection. A ROC analysis indicated that duration (K0) predicted survival well. Logistic regression analysis identified Cmin and Cavg as exposure-related predictors.

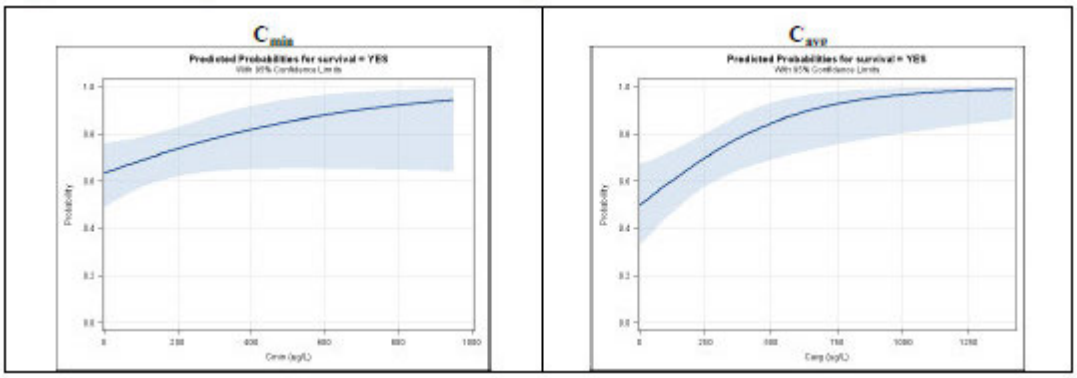


Figure 23: Exposure-survival relationship for tecovirimat in rabbit

Table 32: Logistic regression parameters of exposure-survival model for tecovirimat in rabbits

Selected Exposure Metric	Slope Estimate of the Effect	p-value (Pr > Chi-Square)	Fit Statistics R-Square	Hosmer-Lemeshow GoF p-value (Pr > Chi-Square)
C_{avg}	0.00342	0.0055	0.2185	<0.0001
C_{min}	0.00242	0.0749	0.0767	<0.0001

The exposure-survival relationship for tecovirimat was statistically significant only for Cavg although the slope of each exposure parameter was very shallow and similar overall. Furthermore, there was no statistically significant difference between Cavg and Cmin in terms of prediction potential on survival.

A recursive ROC analysis identified Cavg 185 ng/mL as the best predictor of survival in rabbits.

Table 33: Efficacious exposure leading to increased survival in rabbits – target definition

Exposure	Cutoff (ng/mL)	Target Median (ng/mL)	Target 90% CI (ng/mL)
With False Positives C_{avg} (n=56)	≥185	344	75.3 – 1254
Without False Positives C_{avg} (n=43)	≥185	466	187.5 – 1254

The model indicated that the target median exposure for increased survival (344 ng/mL; with 90% CI as above) would be achieved at the 30 mg/kg QD dose in rabbits. Administration of 400 mg and 600 mg tecovirimat were simulated in uninfected healthy human volunteers from a previous POPPK model. The median Cavg was 424 (95th percentiles 227-702) ng/mL for 400 mg and 588 (342 – 991) ng/mL for 600 mg, which compare with the target derived from rabbits as shown below.

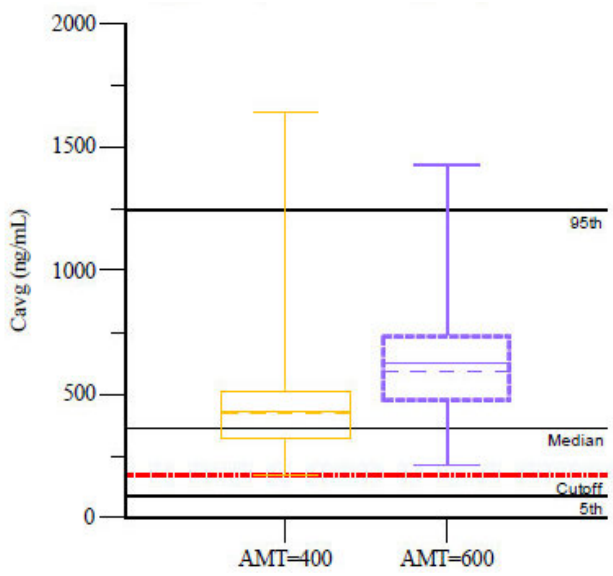


Figure 24: Tecovirimat exposure (C_{avg}) in healthy volunteers (AMT – 400 mg and AMT = 600 mg QD Dose) vs. rabbits target exposures

There were no predicted human exposures below the 95th percentile of the target (75.3 ng/mL) at either dose. All of the predicted human exposures had a steady state tecovirimat Cavg above the minimum target concentration (185 ng/mL). Therefore, a dosing regimen of 400 mg QD in humans was thought to be sufficient to achieve the equivalent efficacious levels in rabbits.

NHP data

SIGA-RAS-003 POPPK

This describes the development of a first POPPK model using NHP and human data as follows:

- FY10-087 (rich PK data; infected and uninfected monkeys)
- SIGA AP-06-021G (sparse PK data; infected monkeys)
- 1151-065 (rich PK data; uninfected monkeys)
- SR10-037F (sparse PK data, infected monkeys, external validation)
- SIGA 246-004 (PK data; human volunteers; see the human POPPK model in section 2.1.8)

A statistically significant improvement in the model fit was observed when a 2-compartment model with correlation between CL/F and Vc/F and a lag time in absorption (TLAG) was used to fit the plasma concentration data as compared to a 1-compartment model. The structural model included IOV and

infection effect on constant rate of absorption (Ka) and CL/F. Individual predicted concentrations of tecovirimat obtained in FY10-087 fitted with the structural PK model were very well distributed around the line of identity. The 2-compartment model with correlation between CL/F and Vc/F, IOV and infection effect on CL/F and Ka with mixed error and IIV on all PK parameters except TLAG, was retained as the structural model and fitted to PK data collected from 1151-065, AP-06-021G and FY10-087. The model was parameterised in terms of TLAG, Ka, CL/F, Q/F, Vc/F and Vp/F.

Individual predicted concentrations of ST-246 were very well fitted with the proposed base population PK model, with high and low concentration values well distributed around the line of identity.

Exploratory analyses were performed to visually assess the effect of key covariates (dose and infection status) on tecovirimat PK parameters in monkeys. Overall, the final population PK model included weight on Vc/F, CL/F, Q/F and Vp/F, infection status on CL/F and Ka, as well as dose level on Ka, CL/F and Vc/F. The observed vs. population and individual predicted concentrations of tecovirimat were well distributed around the line of identity (low to high values) but visual examination suggested some possible underestimation of peak concentrations. CWRES values were homogeneously distributed around 0, suggesting no bias in the predictions of high and low concentrations. The residual variability derived with the error model was low.

The POPPK model was used to predict individual concentration-time profiles for each monkey on Day 1 and 14. Similar AUC/Dose, Cmax/Dose and Cmin/Dose ratios were observed between infected and uninfected monkeys. This is explained by the minimal effect of infection status on apparent clearance.

Table 34: Systemic exposure to ST-246 in uninfected and infected monkeys on Day 1 and at steady-state (SS)

	Statistics	AUC/Dose (µg.h/L)/(mg/kg)		C_{max}/Dose (µg/L)/(mg/kg)		C_{min}/Dose (µg/L)/(mg/kg)	
		Day 1	SS	Day 1	SS	Day 1	SS
Uninfected Monkeys	n	48	48	48	48	48	48
	Mean	1034.1	1256.9	104.6	119.8	14.2	18.3
	SD	316.9	360.4	49.6	50.9	5.2	6.9
	Min	361.8	524.5	23.9	33.7	4.9	7.0
	Median	1062.9	1268.4	95.5	110.2	14.3	17.6
	Max	1652.9	2016.4	262.4	275.2	32.0	39.1
	CV%	30.7	28.7	47.4	42.5	36.5	37.9
	Geom. Mean	980.7	1201.0	94.0	109.8	13.3	17.0
	CV% Geom. Mean	35.5	32.6	50.6	44.9	38.3	40.0
Infected Monkeys	N	30	30	30	30	30	30
	Mean	945.8	1217.8	88.3	106.3	15.5	20.9
	SD	332.1	380.0	38.6	39.4	5.7	8.3
	Min	431.1	527.9	29.6	42.8	4.9	7.0
	Median	924.5	1276.8	83.5	103.6	15.8	20.5
	Max	1644.2	2014.4	198.5	216.9	30.0	36.8
	CV%	35.1	31.2	43.7	37.1	36.6	39.6
	Geom. Mean	890.0	1156.9	80.3	99.2	14.4	19.1
	CV% Geom. Mean	37.2	34.6	47.4	40.0	43.2	48.3

The final population PK model developed for monkeys was used to predict exposures in infected monkeys receiving tecovirimat doses from 3 to 18 mg/kg (i.e. equivalent to 3.6 to 216 mg/m^2). In each dose group and infection status, 77 monkeys were included in the simulation dataset.

The final POPPK model developed for healthy humans and the effect of infection in monkeys were used to predict tecovirimat exposures in infected humans using simulations based on a daily dose of 400 or 600 mg for 14 consecutive days. In each dose group, two subgroups of 264 subjects each were included according to the infection status (infected/uninfected), each having the same demographic characteristics as the SIGA-246-004 study population. Similar dose-normalised AUC and Cmin values were obtained in infected and uninfected humans, whereas dose-normalised Cmax values were 1.12-fold higher in infected humans as compared to uninfected ones.

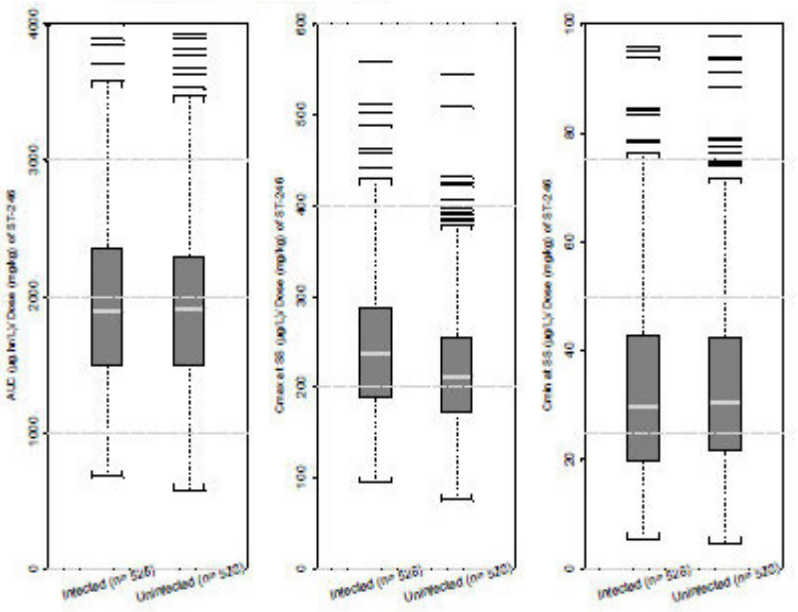


Figure 25: Dose-normalised simulated exposure of ST-246 under steady state conditions in uninfected and infected humans

Simulations were used to determine the dose of tecovirimat in monkey that is equivalent to a dose in humans of 400 - 600 mg. The exposure in monkeys was simulated using the dose range of 3 to 18 mg/kg. In each dose group, 77 subjects having same body WT range as the population used for the final NHP POPPK model (i.e. 2.26 to 11.6 kg) were included in the simulation dataset. The median AUC and Cmax in infected monkeys after the first dose and at steady state after doses of 8 to 10 mg/kg were equivalent to median AUC and Cmax values predicted in infected humans receiving a dose of 400 mg. At these dose levels, median Cmin for infected monkeys were slightly higher than predicted in infected humans but they remained within the acceptable range of the targeted Cmin values in infected humans. A dose of 12 to 14 mg/kg administered to infected monkeys gave similar exposures as the 600 mg dose administered to infected humans.

SIGA-RAS-003 PK-PD

Concentration-time data and PD data from the following six studies were used for the survival analysis:

- FY10-087 (rich PK and PD data)
- SIGA AP-06-021G (sparse PK and PD data)
- SIGA AP-09-026G (sparse PK and PD data)
- SIGA AP-06-21 (PD data; experiments 1 and 2)
- SIGA AP-06-021E6 (PD data)

Among the 96 monkeys with available survival data, 67 had PK data collected from studies FY10-087 (n=24), AP-06-021G (n=16) and AP-09-026G (n=27) in which the tecovirimat dose range was from 0.3 to 20 mg/kg once daily. The final NHP POPPK model was updated with the additional relevant concentration-time data from these studies. Among the 96 monkeys (82 males), 73 received tecovirimat doses ranging from 0.3 to 300 mg/kg. All monkeys who died during the study started their treatment on Day 4 post-infection or later. Among the monkeys treated with 0.3 and 1 mg/kg tecovirimat, the percentage of survival after 15 and 14 days post-infection, respectively, was 60%. This dropped to 20% after 18 and 16 days, respectively.

Tecovirimat 3 mg/kg (n=14) and 10 mg/kg (n=25) gave survival probabilities of those treated at an early stage of infection of 92.9% on Day 5 and 96.0% on Day 11, respectively. At higher dose levels (> 10 mg/kg), all monkeys survived until the end of the study (i.e. up to 42 days).

Table 35: Statistics of survival days by ST-246 dose

	QD Treatment						
	Placebo	0.3 mg/kg	1 mg/kg	3 mg/kg	10 mg/kg	> 10 mg/kg	ALL
Number of Dead Monkeys	23	4	5	1*	1*	0	34
Total Number of Monkeys	23	5	5	14	25	24	96
% Dead per TRT group	100.0%	80.0%	100.0%	7.1%	4.0%	0.0%	35.4%
Survival Days							
Mean	13.4	15.3	16.6	5.0	11.0	NA	13.8
SD	2.5	2.5	6.1	NA	NA	NA	3.8
Median	14.0	15.5	15.0	5.0	11.0	0	14.0
Minimum	8	12	11	5	11	NA	5
Maximum	20	18	27	5	11	NA	27
Length of Study (days)	21-42	42	42	28-42	28-42	21-42	21-42
Start of Treatment (days)	1-4	4	4	3-4	3-5	1-4	1-5

SD: Standard deviation; TRT: Treatment; NA: Not applicable, QD: once daily

* According to histology/pathology report,[5] the death of theses monkeys was probably not related to the MPXV infection

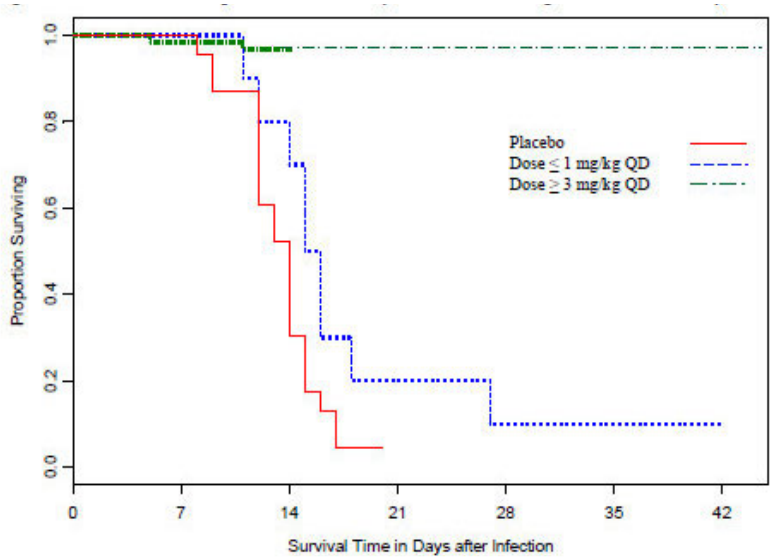
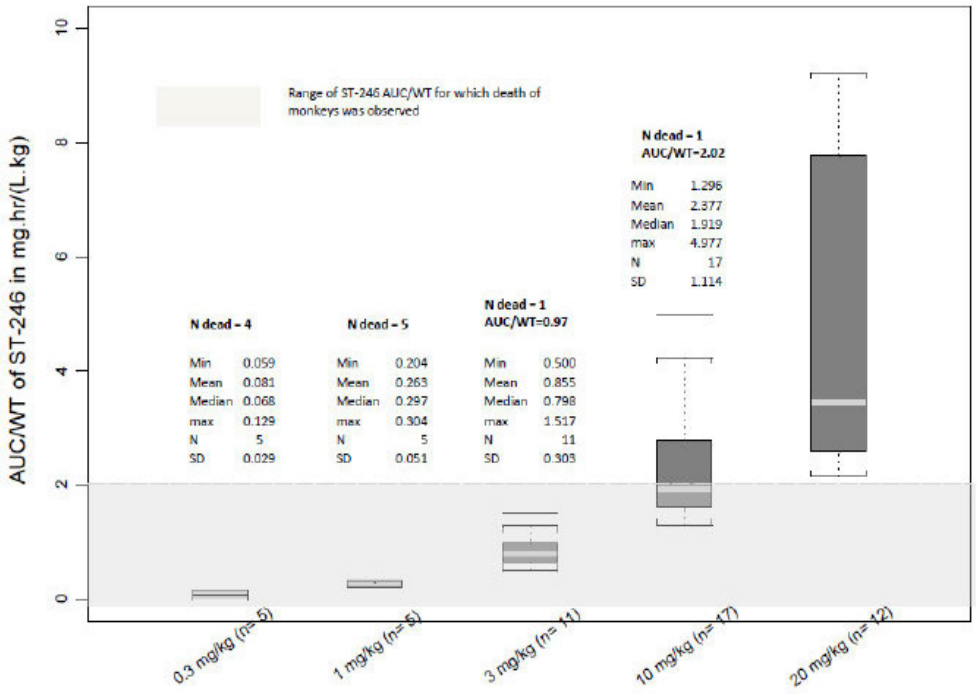


Figure 26: Survival Kaplan-Meier plot by treatment categories – all monkeys included

Taken together, the results indicated that tecovirimat exhibited dose dependent rescue effects on MPXV-infected monkeys and 100% survival probability was observed at 3 mg/kg QD. It was concluded that the effective dose for 50% rescue was between 1 and 3 mg/kg.

Based on the same NHP POPPK model, individual post-hoc parameters were estimated for infected monkeys that were included in the PK-PD analyses (n=50). The mean and median exposures at steady state (AUC/WT) for dose levels up to 20 mg/kg are shown below.



AUC/WT: Weight-normalized area under the curve at steady-state; Max: Maximum; Min: Minimum; n: Number of monkeys; QD: Once daily; SD: Standard deviation; WT: Body weight

Figure 27: Distribution of ST-246 exposure by once daily dose

As shown above, deaths occurred with exposures from 0.06 to 2 mg.hr/(L.kg) but none occurred at more than 2.02 mg.hr/(L.kg), which equates with ≥10 mg/kg QD. Overall, 11/31 monkeys (35%) with exposures <2.02 mg.hr/(L.kg) did not survive MPXV infection. At exposures <0.5 mg.hr/(L.kg), 9/11 (82%) died before the end of study while 2/38 (5.3%) with exposures ≥0.5 mg.hr/(L.kg) died.

Kaplan-Meier analysis was performed on survival probability that was categorised in three exposure levels - 0 (for placebo), >0-<0.5 and ≥ 0.5 mg.hr/(L.kg).

Without the exclusion of MK 21 and MK 27 (these two monkeys were in AP-09-26G and their deaths appeared probably not related to monkeypox), the survival probability for exposure <0.5 mg.hr/(L.kg) was 54.5% on Day 16 post-infection and 18.2% at the end of the study. The survival probability for exposure ≥0.5 mg.hr/(L.kg) was 94.9% after Day 11 post-infection.

With the exclusion of MK 21 and MK 27, the survival probability did not change for AUC/WT below 0.5 mg.hr/(L.kg) but the survival probability for ≥0.5 mg.hr/(L.kg) was 100%.

These results suggest that survival probability of infected monkey increased with increase in tecovirimat exposure and a maximal rescue was observed at exposure value greater than 0.5 mg.hr/(L.kg).

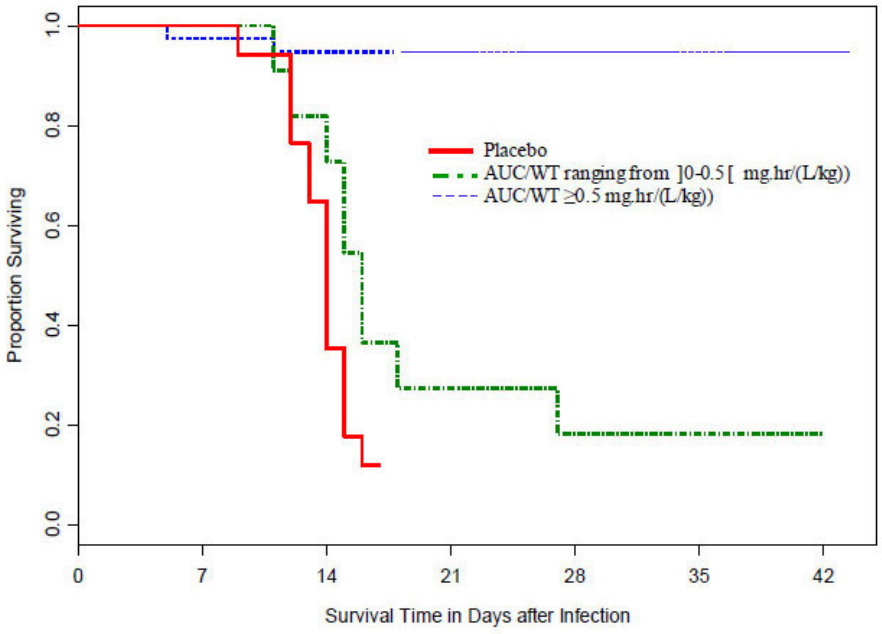


Figure 28: Survival Kaplan-Meier plot – survival probability by ST246 Exposure – all monkeys included

By excluding MK 21 and MK 27, all deaths were observed for Cmin and $Cmin_{SS}$ values ≤18.7 µg/L and 25.2 µg/L, respectively, and 100% survival was observed for ≥21.6 µg/L and 32.4 µg/L, respectively.

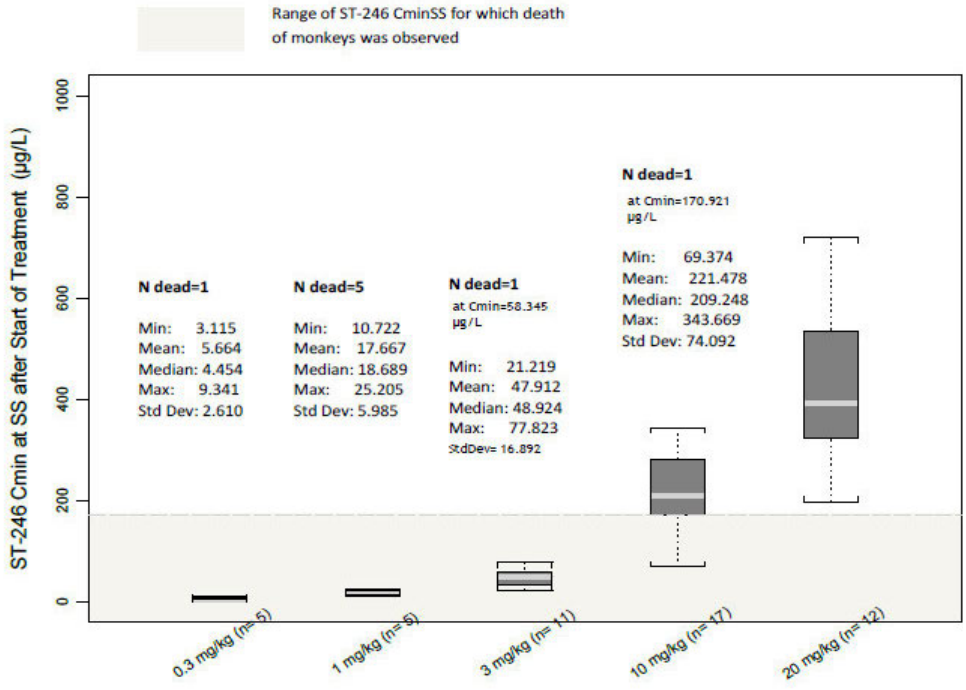


Figure 29: Distribution of ST-246 C_{min} at steady-state by treatment

Kaplan-Meier analysis was performed based on categorical Cmin and $Cmin_{SS}$ of 0, 0-<40, 40-<200 and > 200 µg/L. With MK 21 and MK 27 included, survival probability on Day 27 for Cmin and $Cmin_{SS}$ values ≤40 µg/L was 50.0% and 38.5%, respectively.

For Cmin and $Cmin_{ss}$ from 40-200 µg/L, the survival probability on Day 11 post-infection was markedly higher than 90% and a complete rescue (100% survival probability) was observed with Cmin >200

µg/L. By excluding monkeys MK 21 and MK 27, similar results were obtained for Cmin and $Cmin_{ss}$ ranging from 0 to 40 µg/L but a complete rescue (100% survival probability) was observed for Cmin >40 µg/L. The results indicated that survival probability increased when Cmin or $Cmin_{ss}$ increased and the maximal rescue was observed at Cmin and $Cmin_{ss}$ >40 µg/L.

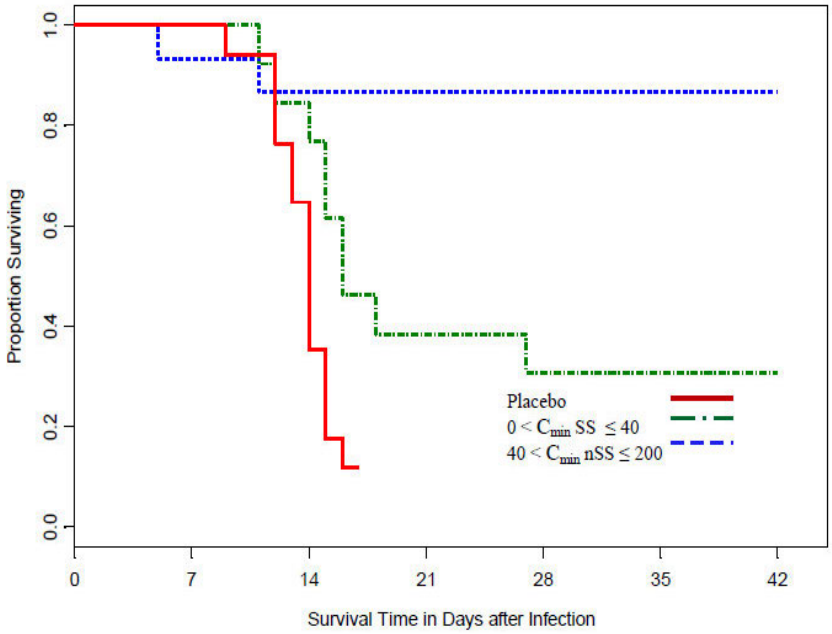
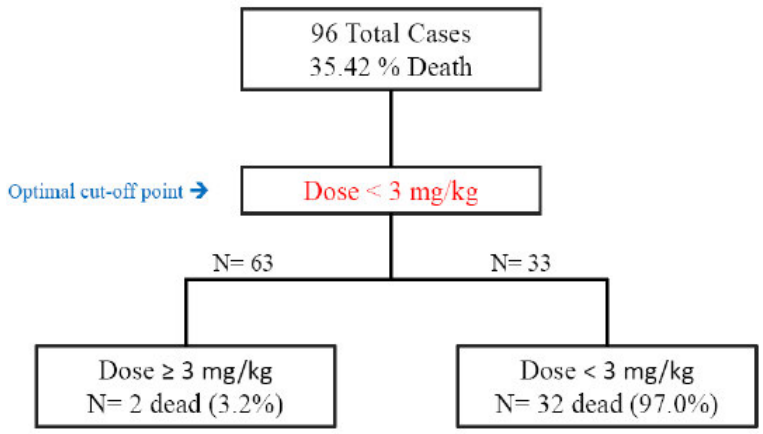


Figure 30: Survival Kaplan-Meier plot – survival probility by C_{min} at Steady-State - all monkeys included

ROC analysis was used to statistically determine these cut-off values, with an equal emphasis on false positive and false negative. Tecovirimat 3 mg/kg QD was statistically determined to be the cut-off value for survival of 96 monkeys with a sensitivity and specificity of 94.1% and 98.4%, respectively.

Tree plot of the ROC analysis- Treatment



Of 96 monkeys, 33 were treated with <3 mg/kg and 63 received ≥3 mg/kg. At <3 mg/kg only 3.0% of monkeys survived MPXV infection but at ≥3 mg/kg 96.8% survived (the other 3.2% is accounted for by death of MK 21 and MK 27, which were regarded as false negatives).

The exposure of 0.50 mg.hr/(L.kg) was found to be the optimal cut-off value for survival of 67 monkeys with a sensitivity and specificity of 92.9% and 97.4%, respectively. Among the 27 monkeys

with exposure <0.50 mg.hr/(L.kg), 26 died during the study. The 2/40 with exposure ≥0.50 mg.hr/(L.kg) that died were MK 21 and MK 27.

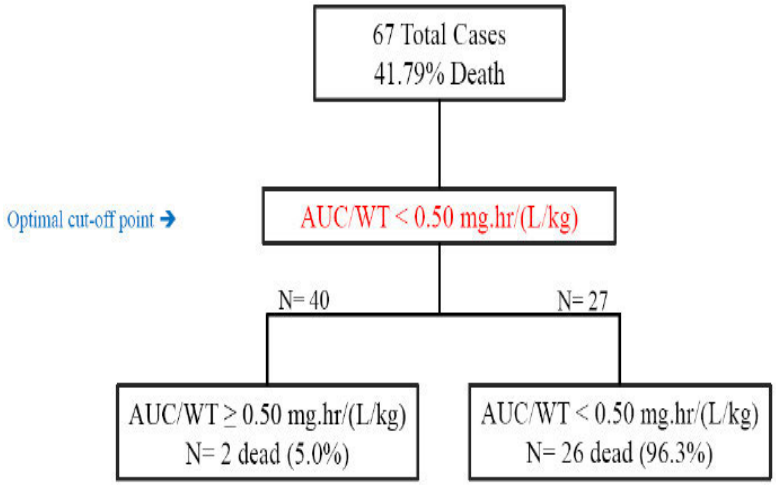


Figure 31: Tree Plot of the ROC analysis – ST-246 exposure

A Cmin after first dose of 21.63 µg/L was found to be the cut-off value for survival of the 67 monkeys with PK data with a sensitivity and specificity of 92.9% and 94.9%, respectively, whereas a $Cmin_{SS}$ of

21.22 µg/ was the cut-off with sensitivity and specificity of 89.3% and 97.4%, respectively. Among the monkeys with Cmin and $Cmin_{SS}$ ≥ these cut-off values for survival, the 2 that died were MK21 and MK27.

Finally, when all markers were simultaneously tested with the ROC analysis, 3 mg/kg was found to be the most significant (p=0.05 level) predictor of survival outcomes, with specificity and sensitivity of 92.9 and 97.4%, respectively.

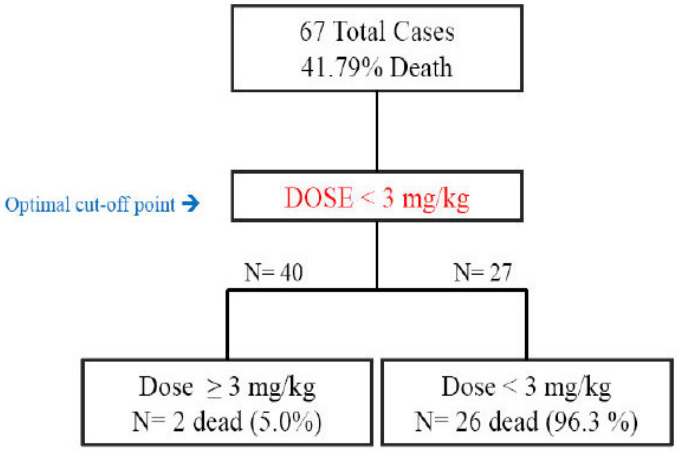


Figure 32: Tree plot of the ROC analysis – All markers

SIGA-RAS-005-01

This report is based on the same studies and monkeys as reported in SIGA-RAS-003 but it examined the relationship between mortality and each of quantitative viral loads and lesion counts (maximum values, AUCs and time-weighted means [TWM] from first day of treatment to last study day in common across the studies). Logistic regression and ROC analysis were used. Plots indicated strong

relationships between the viral load and lesion count metrics and each of dose and mortality. For example, some TWM plots vs. mortality are shown below.

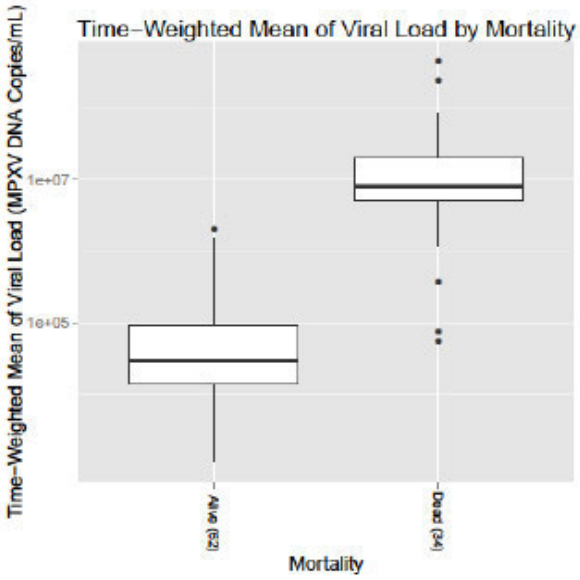


Figure 33: Comparative box plot of TWM of viral load by mortality

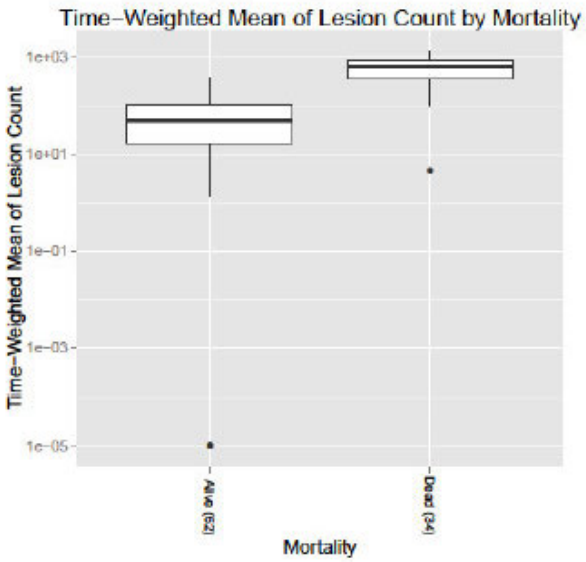


Figure 34: Comparative box plot of TWM of lesion count by mortality

A correlation matrix plot indicated very strong correlations between all metrics, in particular within the (viral load and lesion count) outcomes, but also between the outcomes. This had implications for regression modelling where typically strong correlations between predictors in a multivariable regression model should be avoided.

The viral load and lesion count measures were transformed on a (natural) log scale before univariable logistic regression was used to identify the biomarker and metric that was best associated with mortality. AUC as well as TWM were strongly associated with mortality but AUC was estimated with more precision and AUC of viral load had slightly better properties than TWM of viral load in terms of the deviance and the Akaike Information Criterion (AIC).

Table 36: Comparison of univariable logistic models for viral load

Comparison	DF	Deviance	AIC
Model 1 (AUC)	94	30.18	34.18
Model 2 (TWM)	94	35.05	39.05

DF = Degrees of freedom of the model; AIC = Akaike's Information Criterion (lower is better).

Table 37: Comparison of univariable logistic models for lesion count

Comparison	DF	Deviance	AIC
Model 3 (AUC)	65	74.18	78.18
Model 4 (TWM)	65	44.78	48.78

DF = Degrees of freedom of the model; AIC = Akaike's Information Criterion (lower is better).

The ROC assessments showed that the discriminative performance of AUC of viral load and TWM of lesion count was very high, i.e. 0.98 and 0.94, respectively, indicating a 98% and 94% accuracy of predicting mortality. Assuming equal weights of false positives and false negatives, the optimal cut-off point on the log scale of AUC of viral load was 16.49, and for lesion count 5.72.

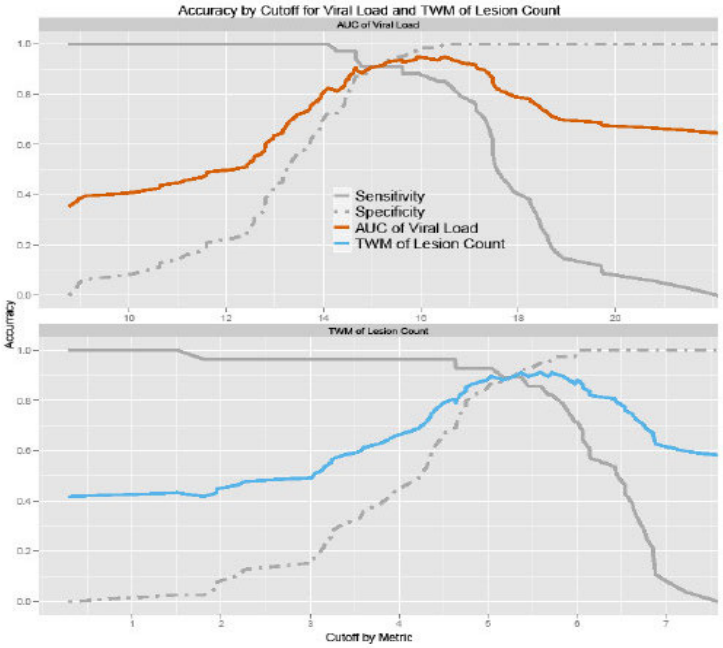


Figure 35: Illustration of cut-off point derivation for viral load and lesion count

An exploratory regression analysis with time-to-event as the outcome was undertaken to assess whether the choice of metric and outcome would be the same.

A proportional hazard model was used and, consistent with the logistic regression analysis, AUC of viral load was the preferred predictor. Both TWM of lesion count and AUC of viral load were significantly associated with survival (P<0.001). In addition, all graphical and numerical analyses were repeated on a subset of the full dataset that was restricted to monkeys for which treatment was started at day 4 or the day on which lesions became visible. This subset included only animals for which treatment was initiated on Day 4 or later. The results of this analysis were qualitatively identical, with minor numerical differences. The AUC of viral load demonstrated the best predictive and discriminative properties as a biomarker for mortality of cynomolgus monkeys in the treatment of pathogenic

orthopoxvirus. The TWM of lesion count was also predictive, but not quite as good as the AUC of viral load.

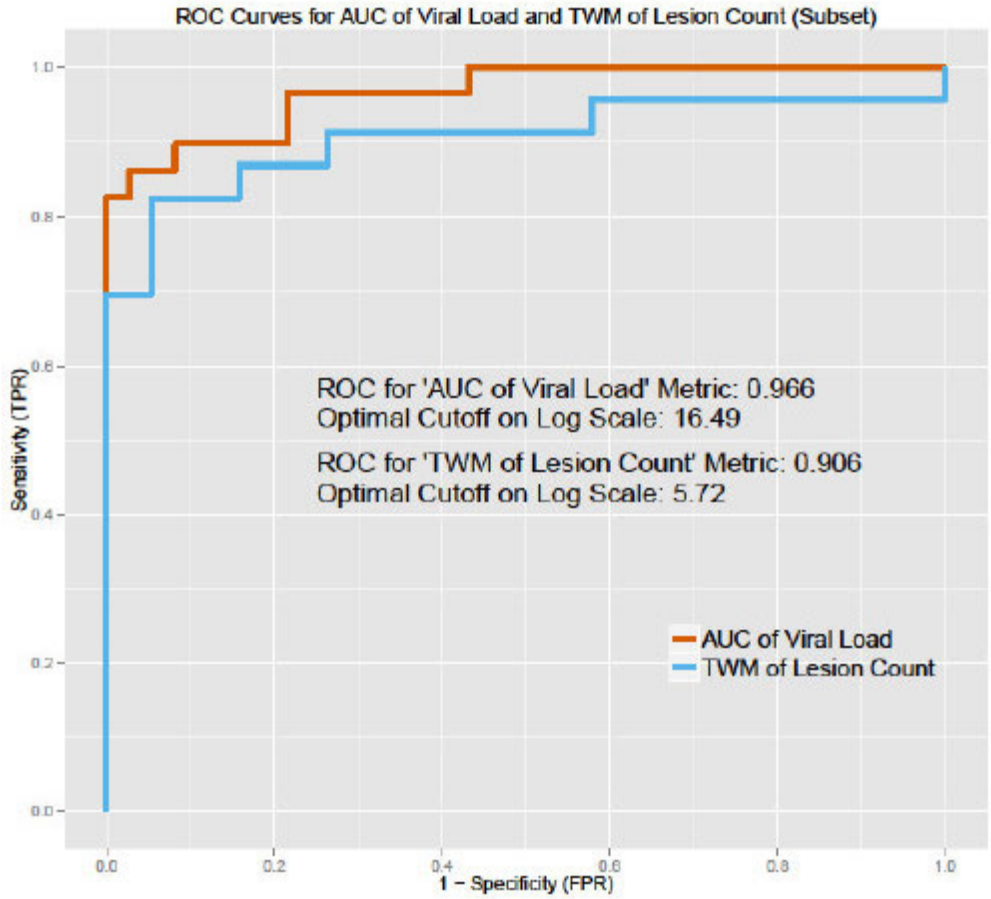


Figure 36: ROC Curves for AUC of viral load and TWM of lesion count in subset of animals for which ST-246 treatment was initiated on Day 4 or later

SIGA-RAS-005

This addendum report analysed survival in four nonclinical studies of monkeypox infections, two of which were included in the analyses reported in SIGA-RAS-003 plus two others as listed below.

- FY10-087 (rich PK and PD data)
- AP-09-026G (sparse PK and PD data)
- SR10-037F (sparse PK and PD data)
- SR10-038F (sparse PK and PD data)

The dose range in these studies was from 0.3-20 mg/kg/day.

Concentration-time profiles of tecovirimat were available for 97 monkeys from FY10-087 (n=24), AP-09-026G (n=27), SR10-037F (n=21) and SR10-038F (n=25). Rich concentration-time profiles on Day 1 of dosing and at steady-state were simulated using the individual post-hoc PK parameters derived from the POPPK model in infected monkeys (SIGA-RAS-003). Cmin on Day 1 and $Cmin_{SS}$ for each monkey were derived from predicted concentration-time profiles and the AUC/WT was calculated as dose-adjusted by the body weight divided by CL/F.

Overall, 94 monkeys were included in the PK-PD analysis. MK 21 and MK 27 (see above) and one monkey in SR10-038F with an uncertain dosing history were excluded from the survival analysis. The dose-survival relationship was assessed using the Kaplan-Meier approach. Overall, tecovirimat doses of 0.3 to 1 mg/kg exhibited a weak rescue effect (0-20%) whereas 3 mg/kg (n=10) and 10 mg/kg gave survival probabilities of treated monkeys that were 100% (i.e. up to 42 days).

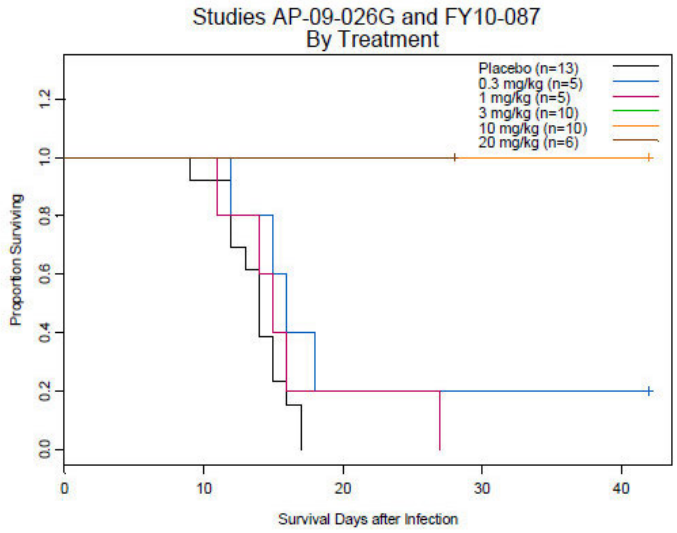


Figure 37: Dose-survival Kaplan-Meier plot by treatment group – studies AP-09-026G and FY10-087

In SR10-037F, the survival probability of monkeys with treatment initiation at Days 4 and 5 post-infection was not statistically significantly below 100%, i.e. in each of these groups 1/6 died or was euthanised as moribund within 8 to 12 days post-infection. The survival probability of monkeys with treatment starting at Day 6 post-infection decreased to 50% after 13 days post-infection.

In SR10-038F, the survival probability for the groups receiving 5, 7 or 10 daily doses of 10 mg/kg administered at Day 4 post-infection was not statistically significantly below 100%, i.e. amongst these three groups, only 1/17 was euthanised as moribund prior to the end of the study.

The probability of survival in the group receiving only 3 doses was 67% and 33% after Day 15 and Day 17 post-infection, respectively. One survived in the 3-dose group but was excluded due to an unexpectedly high tecovirimat concentration 76 h after the last dose.

The applicant concluded that 3 mg/kg and administered for 14 consecutive days would rescue 100% of MPXV-infected monkeys. Maximal efficacy could be obtained with a dose of 10 mg/kg initiated 4 or 5 days post-infection for at least 5 consecutive doses.

TQT study with 1,000 mg dose

SIGA-246-010 was a TQT study with a crossover design to determine if a single dose of 1,000 mg tecovirimat delayed cardiac repolarisation. The correlation between the QTcF change from baseline and plasma concentrations of tecovirimat and its major metabolites (M4, M5, and TFMBA) was explored. All dosing was at 30 min after a meal of 600 kcal and 25 g fat.

After the 1,000 mg dose, mean concentrations of tecovirimat and the major metabolites (M4, M5 and TFMBA) were measurable up to 23 h (i.e. the last sampling time). The mean Cmax and of tecovirimat were 2500 ng/mL and 23719 h•ng/mL, respectively.

The moxifloxacin group generally met the assay sensitivity criteria with 3 of the 5 predefined time points (3, 4 and 5 h post dose) having a lower confidence bound ≥5 msec. None of the tecovirimat

group time points demonstrated an upper bound that approached or exceeded 10 msec, demonstrating no signal of any effect of tecovirimat on cardiac repolarisation.

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

General PK properties

The absolute bioavailability of tecovirimat in humans has not been determined but is likely low to moderate based on the estimates from nonclinical studies in several species (at best, ~50% was reported in fed monkeys) and from the amount of intact (likely non-absorbed) drug in human faeces.

Tecovirimat is slowly absorbed. Exposures are less than dose proportional for single doses above 1000 mg administered in the fasted state. In the fed state, increases in plasma exposures are less than dose proportional below 1000 mg. In SIGA-246-002, using Form V, as the dose increased from 250 to 400 mg/day (1.6-fold), the mean Day 21 AUC_{tau} also increased 1.6-fold but when the dose was further increased to 800 mg (3.2-fold), the AUC_{tau} increased 2.25-fold. Similar results were observed for Cmax values. In SIGA-246-004, using Form I, the ratios of dose-normalised Cmax and AUC_{tau} values with 400 mg and 600 mg daily doses ranged from 80% to 85%, and the 90% confidence intervals did not include 1.0.

Furthermore, in study SIGA-246-018 using the contents of open capsules, exposures with 100 mg and 200 mg doses exceeded 1/6 and 1/3, respectively, of those after 600 mg doses. The less than dose-proportional increments in exposure across the range 100-600 mg may reflect the limited solubility of tecovirimat rather than a saturable absorption process, noting that tecovirimat is not a substrate for major gut transporters.

Whilst SIGA-246-005 demonstrated that the Form I was less bioavailable than Form V when each was administered in capsules of the same composition, this does not affect the conclusions drawn on PK, PK-PD or dose selection since these are based on studies that used Form I.

In the pivotal study SIGA-246-008, when dosing 48 subjects at 600 mg BID with a moderate fat and kcal meal, Tmax occurred at ~4 h on Day 14. Steady state concentrations were achieved within 6 days. On Day 14, mean Cmax was ~1.4-fold that on Day 1 while AUC_{0-24} increased ~1.2-fold and AUC_{0-last} increased 2.3-fold, indicating some accumulation in plasma.

The volume of distribution of tecovirimat is large, compatible with wide distribution into tissues as was observed in nonclinical studies. Protein binding of tecovirimat is ~80% at 10 µM in human plasma. The differences in % unbound between species was accounted for in the human dose selection process (see section 3.2 and report 724 for the unbound ratios applicable to human dosing with 600 mg BID and NHP dosing with 10 mg/kg/day). The estimated unbound fraction in monkeys (12.5%) is lower than that for humans (20.3%), which indicates that if total tecovirimat plasma concentrations in humans dosed at 600 mg BID with food considerably exceed those achieved in monkeys dosed with 10 mg/kg/day, the difference in unbound fraction is expected to be even greater. See further below under *Human dose selection*.

The study with radiolabelled tecovirimat (SIGA-246-009) did not detect conversion of tecovirimat to TFMBA due to lack of a radiolabelled carbon atom in this metabolite. Based on SIGA-246-009 and the other studies in which metabolites were measured, tecovirimat undergoes extensive biotransformation to at least 10 metabolites (when including TFMBA) and metabolic clearance is the major route of elimination of the proportion of tecovirimat that is absorbed. The time course of tecovirimat vs. major

metabolites indicates that much of the initial metabolism of parent drug occurs within 6 h of administration.

Although 73% of the radiolabel was recovered in urine vs. 23% in faeces, almost none of this material was intact tecovirimat, supporting the conclusion that whatever fraction of the dose is absorbed is extensively metabolised. The observation that faecal excretion of total radioactivity (23%) was lower than faecal excretion of tecovirimat (35.6%) at all collection intervals indicates that much of the oral dose of unlabelled tecovirimat was not absorbed.

The applicant considers that the major primary step in tecovirimat biotransformation is via amide hydrolysis. Furthermore, several UGT isoenzymes (UGT1A1, 1A3 and 1A4) are involved in glucuronidation of tecovirimat and metabolites.

Major metabolites

When dosing at 600 mg BID with food to steady state in SIGA-246-008, TFMBA exposures on Day 1 and Day 14 exceeded those of parent drug and the other two major metabolites combined. The metabolites accumulated in plasma with AUC0-24 ratios of 1.7 for M4, 14.1 for M5 and 2.4 for TFMBA. On Days 1 and 14, M4 and TFMBA, but not M5, had AUC values >10% of those for parent drug. The applicant has described the plasma PK of the three major metabolites when dosing humans with 600 mg BID. Of these 3 major metabolites in humans, TFMBA has the highest plasma protein binding (98.6% bound in human plasma) whereas the plasma protein binding of M4 is in a range of 4.6 to 20.7% and that for M5 ranges from 6.6 to 33.0% in mouse, monkey and human plasma.

The three major metabolites have no antiviral effect so do not contribute to efficacy. Regarding safety, TFMBA exposures at steady state in humans are higher than in species used in the nonclinical studies whereas the opposite applies for M4 and M5.

Table 38: Exposure comparisons of mean AUC_{0-24} between animals and humans at Day 14

Tecovirimat dose, mg/kg/day:	17.1	1,000	300
Species:	Humans	Mice	NHP
AUC_{0-24}, ng•h/mL			
Tecovirimat	30,632	827,000	25,350
M4	23,487	40,900	5,320
M5	13,067	31,450	25,250
TFMBA	159,583	14,700	29,300

Effect of food and type of food

The relative bioavailability of tecovirimat is approximately 40% higher when the compound is administered to subjects in the fed state (moderate fat and kcal meal) compared with the fasted state. This finding would fit with improved solubility in fat vs. aqueous media. This was confirmed in the Lead-in phase of SIGA-246-008, which led to administration of 600 mg BID with food in the expanded portion of the study. The analysis of the Lead-in phase PK data (reported in SIGA-PCS-104) showed that tecovirimat 600 mg BID taken with meals provided a greater exposure margin relative to the effective 10 mg/kg dose in NHPs. The human median Cmin, AUC and Cmax on Day 1 and Day 14 all exceeded values in infected NHPs (e.g. on day 14 respective ratios for total tecovirimat were 4.2, 1.9 and 1.5). Thus, the 600 mg BID dose administered with meals was selected for the Expanded portion of the study since it provided plasma exposures that exceeded by several fold those achieved in NHPs at the efficacious dose of 10 mg/kg. Subsequently, the dose-finding analyses were all based on dosing with food to achieve the required exposures.

Study SIGA-246-018 demonstrated that tecovirimat PK was not affected by opening the capsules and mixing them with milk, supporting this optional mode of administration to those unwilling or unable to swallow whole capsules until such time as a suitable paediatric formulation has been identified.

Intrinsic factors

Renal impairment

In mild and moderate impairment, tecovirimat AUCs tended to be higher vs. the control group, while CL/F and Vz/F decreased. There were also modest increases in AUCs of M4, M5 and TFMBA. In contrast, lower tecovirimat exposures were observed in subjects with severe renal impairment and in those with ESRD requiring haemodialysis, with no apparent effect of HD except for M4, which is substantially removed. The applicant considered that a dose increase would be inappropriate because it would result in significant accumulation of TFMBA, potentially impacting safety, and because the tecovirimat plasma levels would still be comparable to those achieved in NHPs at 10 mg/kg/day.

The applicant further assessed the impact of severe renal impairment on the unbound fraction of tecovirimat. Using published estimates of albumin binding capacity in severe renal impairment, the applicant calculated that the unbound tecovirimat Cmax, Cmin and AUC would be comparable or slightly higher compared to subjects with normal renal function. The findings gave no concern for safety or efficacy of tecovirimat when dosed at 600 mg BID in subjects with severe renal impairment.

Unlike parent drug and metabolites M4 and M5, TFMBA is highly protein bound (>98%). The total TFMBA Cmax values did not show a consistent trend to increase as renal function decreased. Free TFMBA levels in plasma will be higher in those with severe renal impairment. However, the possible safety issues are unknown since the renal impairment study involved only a single 600 mg dose and the TFMBA exposures in mice and monkeys are lower than in humans dosed with 600 mg BID. Therefore, while no dose adjustment can be recommended, caution should be advised when using tecovirimat in subjects with severe renal impairment, including those with ESRD and on haemodialysis.

Hepatic impairment

There were no major or consistent effects of hepatic impairment on exposure to total tecovirimat or on the major metabolites although M4 exposure increased by up to 2-fold in severe impairment. The impact of hepatic impairment on the unbound fraction of tecovirimat was assessed by calculating unbound drug levels based on published albumin binding capacity (see above for renal impairment). The mean tecovirimat unbound Cmax in the Child-Pugh C subjects was well above the unbound level calculated from the upper safety target derived from dogs as applied during the dose selection process. With an expected 1.4-fold increase in total tecovirimat Cmax during 600 mg BID dosing, the mean unbound Cmax could be expected to reach ~1050 ng/mL in subjects with severe hepatic impairment. However, based on more recent data generated in an IV NHP study (246-TX-019), in which no CNS toxicity was observed at higher tecovirimat unbound Cmax values compared to the dog study (mean unbound 1922 ng/mL), no dose adjustment seemed to be warranted. The observed and calculated means are compared below.

In the hepatic impairment study, the maximum Cmax observed for total tecovirimat was ~1500 ng/mL. Multiplying this value 1.4-fold gives a possible maximum Cmax after 600 mg BID dosing of ~2100 ng/mL. This would give a calculated maximum unbound Cmax of ~1260 ng/mL. This is still below the safety target derived from the more recent NHP study.

Table 39: Unbound exposures

Species	Study[a]	Dose	%Protein Binding	Max C_{max} (ng/mL)		Mean C_{max} (ng/mL)	
				Total	Unbound	Total	Unbound
Human	SIGA-246-008	600 mg BID	80	4460	892	2209	442
Dog	246-TX-015	100 mg/kg	90.6	5575	524	5575	524
NHP	ITRI 2083 003-001 SN6 3-month Study	300 mg/kg	87.5	6720	840	5303	663
NHP	246-TX-019	30 mg/kg 6h infusion	87.5	15375	1922	13,883	1735
Mouse	ITRI 2083 003-001 SN3 3-month study	1000 mg/kg	87.7	64900	7983	64900	7983
Paediatric BWt 13 kg	Simulated data	50 mg BID	75[b]	5250	1313[c]	3477	869[c]
Paediatric BWt 25 kg	Simulated data	100 mg BID	75[b]	4449	1112[c]	3200	800[c]

[a]Oral administration unless indicated
[b]Plasma protein ratio of adult:kid = 59/63 (Sethi et al, 2016; Section 5.4)
[c]Simulated C_{max} based on total plasma protein binding

Unlike parent drug and metabolites M4 and M5, TFMBA is highly protein bound (see above). The TFMBA Cmax values did not markedly increase as hepatic function decreased. However, for the same reasons as explained above for severe renal impairment, caution should be advised when using tecovirimat in subjects with severe hepatic impairment.

Body weight

This was a significant covariate for clearance of tecovirimat across 54-145 kg, the range observed in the PK subset of SIGA-246-008. See also below regarding body weight as a covariate. The applicant is conducting a further study to assess the impact of high body weight (>120 kg) on tecovirimat PK and has committed to provide the results when available.

Gender

Overall, it is agreed that no dose adjustment according to gender is required.

Age

There were six subjects aged >65 years included in the PK population of SIGA-246-008. The results for these few older subjects appeared to be driven by body weight rather than age. There are no data from subjects older than 72 years but no dose adjustment appears necessary based on age.

It is acceptable that no PK data have been or will be generated in children, given that no possible benefit could be expected. Basing the paediatric dose recommendations on modelling and simulation is appropriate. Whilst not relevant for the present application where the indication is restricted to children weighing at least 13 kg, factors related to ontogeny or organ maturity would need to be considered for dosing simulations in paediatric patients <2 years of age. See further below on the recommended doses for subjects of 13-<40 kg body weight.

Drug-drug interactions

The Mwt of tecovirimat is ~394 g/mol (1M = 394 g/L). Mean Cmax at the recommended dose is ~2200 ng/mL = 0.0022 g/L = 5.6 x 10^{-6} M = 5.6 µM = 1.12 µM unbound Cmax. Thus, 50 x unbound human Cmax (1.12 µM) would be ~56 µM. The in-vitro studies relevant to drug-drug interactions were conducted generally with at least 19 µM tecovirimat and frequently with 100-300 µM. Therefore, concentrations of parent drug used in the in-vitro studies seem generally acceptable.

The inhibition potential of M4, M5 and TFMBA for 7 cytochrome P450 isoenzymes was assessed at ~ 2 times, 4 times and 17 times the calculated free plasma concentrations at steady state, respectively. The time dependent inhibition (TDI) potential of M4, M5 and TFMBA on the same 7 CYP isoforms was evaluated at ~ 20 times, 40 times and 170 times the free plasma concentrations at steady state in fed subjects, respectively. The potential for induction of CYP1A2, CYP2B6 and CYP3A4 mRNA expression by M4, M5 and TFMBA was evaluated using human hepatocytes after induction treatment with three concentrations of each tecovirimat metabolite (M4: 10.4, 104 and 412 µM; M5: 7.93, 79.3 and 266 µM; TFMBA: 0.92, 9.2 and 131.5 µM).

M4 showed strong induction of CYP2B6 at all concentrations and significant induction of CYP3A4 above 10.4 µM (roughly twice its clinically relevant concentration). M5 was shown to be a strong inducer of CYP2B6 at all concentrations and weak inducer of CYP3A4 at 79.3 µM and above (more than 30 times its clinically relevant concentration). TFMBA was an unlikely inducer of CYP1A2, CYP2B6, or CYP3A4.

Tecovirimat may be a victim of DDIs mediated via UGT1A1or UGT1A4 inhibition.

In summary, tecovirimat is a weak inhibitor of CYP2C19 and CYP2C8 and a weak inducer of CYP3A4. Tecovirimat, M4 and M5 have some potential to inhibit BCRP and to induce CYP3A4, 2B6, 2C8, 2C9 and 2C19. Based on these data, the exposures of drugs that are substrates for BCRP, CYP2C8 and CYP2C19 may increase while the exposures of drugs that are substrates for CYP3A4 may decrease.

SIGA-246-015 demonstrated that the net effect when dosing with 600 mg BID to steady state was inhibition of CYP2C8 and CYP2C19 (increases in repaglinide and omeprazole) and induction of CYP3A4 (decrease in midazolam). The effect on buproprion (CYP2B6) was a modest reduction in exposure.

Population PK analyses

In support of the human dose selection process, the earliest model of human PK data (reported in SIGA-RAS-003) was based on SIGA-246-004, which used 400 mg or 600 mg QD. The GOF plots showed that the model described the data adequately. Simulated exposures in infected humans, based on the differences observed in total tecovirimat PK between uninfected and infected monkeys, suggested no important effect of infection on human exposures.

Simulations were conducted to determine the tecovirimat dose in monkey that is equivalent to human doses of 400 - 600 mg as documented in SIGA-246-004. The exposure in infected monkeys was simulated using a dose range of 3 to 18 mg/kg using the final POPPK model developed in monkeys. It was concluded that exposures in infected monkeys given 8 to 10 mg/kg were equivalent to those achieved in humans given 400 mg/day while exposures when dosing with 12 to 14 mg/kg in infected monkeys were equivalent to those achieved in humans given 600 mg/day.

Due to the FDA requirement that the human dose should achieve plasma exposures substantially in excess of those associated with efficacy in nonclinical studies, the applicant conducted SIGA-248-008 with 600 mg BID and compared the exposures in fed and fasted states in the Lead-in phase with the NHP exposures (see above re SIGA-PCS-106). In another analysis using data from SIGA-246-008, the applicant compared observed human exposures with those in NHPs and rabbits. It was concluded that the NHP target resulted in a more conservative (i.e. higher) human dose. See further below on derivation of the pharmacodynamic targets from nonclinical models and the final analyses in support of the 600 mg BID dose.

Pharmacodynamics

Mechanism of action

Tecovirimat is not directly virucidal in that protein production and virus assembly are not affected up to the point of virion envelopment and release. Tecovirimat was shown to target the F13L gene product in

VACV, which is the homologue to the C17L gene in VARV and the C19L gene in MPXV. The gene product is the VP37 peripheral membrane protein required for the production of extracellular forms of virus, which is highly conserved among the orthopoxviruses. It seems that tecovirimat prevents envelopment of the virus and active egress from the cell, thus blocking the ability of the viral infection to spread in the host.

It is proposed that this blocking of viral spread allows for development of an adaptive immune response to clear the virus. Such a mechanism of action has potentially important implications for immunocompromised persons, perhaps especially those who may not develop an adequate cell-mediated response to achieve viral clearance.

Virological studies and selection of resistance to tecovirimat

Studies demonstrated that tecovirimat is active against and specific for the orthopoxviruses, including CPXV, MPXV, VACV and VARV. Tecovirimat reduced extracellular VACV titres by ~10-fold at 24 h post-infection and inhibited viral cytopathic effects by all orthopoxviruses tested. The tecovirimat EC_{50} values for the 4 target viruses are of the order 0.01 to 0.05 µM. Mean unbound Cmax at the recommended dose is ~1.12 µM, which is at least 20-fold the highest EC_{50} value. Using a similar comparison, in SIGA-246-008 the mean Cmin on Day 1 and $Cmin_{ss}$ values were ~400 ng/mL and ~680 ng/mL, respectively. These values equate to ~1 µM and 1.5 µM, with corresponding unbound values of 0.2 µM and 0.3 µM, which are at least 4x the highest EC_{50} values.

In VACV, the amino acid changes that correlate with reduced susceptibility to tecovirimat mapped to a 64-amino acid region (aa 238 to 302) in the VP37 protein. The VACV variants vvN267D and vvL302P, which showed reduced susceptibility to tecovirimat, were shown to be as pathogenic as wild-type virus in mice. Moreover, the applicant has reported resistance monitoring from in-vivo studies in rabbits (RPXV) and NHPs (MPXV), which identified 9 treatment-emergent amino acid substitutions in virus isolated from animals that failed drug therapy or showed inadequate clearance of virus after treatment. Five of these substitutions have been demonstrated to contribute to reduced tecovirimat susceptibility *in vitro* and the 4 remaining substitutions have not been characterised.

Tecovirimat treatment has been shown not to prevent development of neutralizing antibody titres.

Pivotal nonclinical efficacy studies

The nonclinical efficacy studies that have been designated as pivotal by the applicant used IV MPXV challenge in cynomolgus monkeys and ID RPXV challenge in NZW rabbits. There is no model that has been established as highly predictive for protection against human disease with orthopoxviruses.

The figure and table below summarise the findings across these studies.

The forest plot highlights 3 and 20 mg/kg as the minimum effective once daily oral doses required to confer protection against mortality in NHP and rabbit models, respectively.

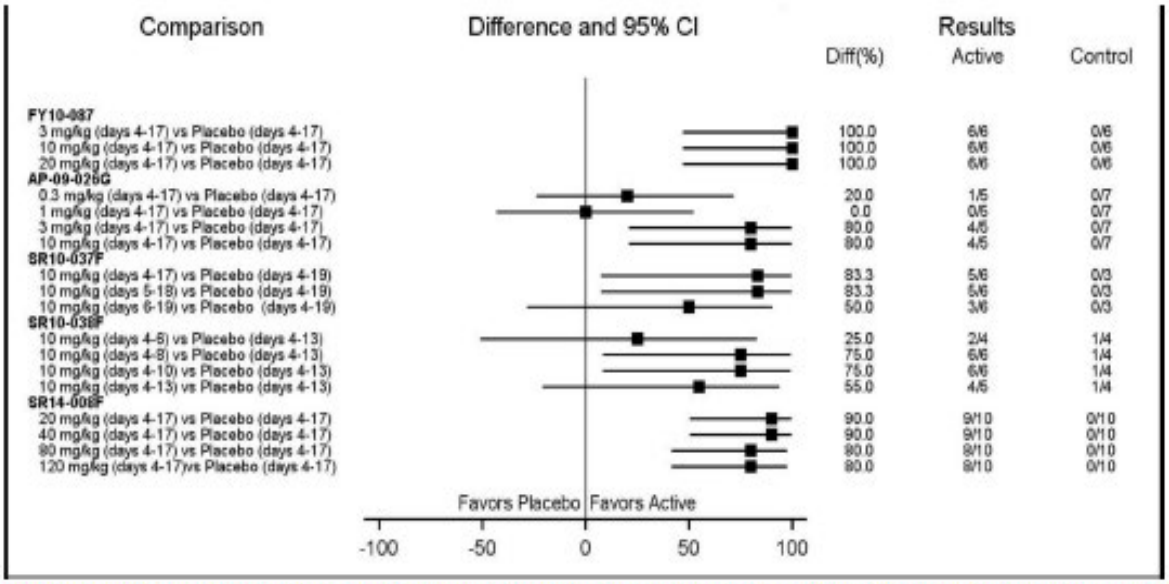
Across the NHP studies, ≥3 mg/kg for 14 days starting on Day 4 after MPXV infection conferred significant protection against mortality. In addition, treatment at 10 mg/kg was effective if started on Day 5. Daily dosing for a minimum of 5 days was necessary to provide a survival advantage relative to placebo controls.

Across the rabbit studies, ≥20 mg/kg oral tecovirimat for 14 days starting on Day 4 after RPXV infection conferred significant protection against mortality.

Doses above these minimum effective doses did not confer a greater survival advantage in either animal model.

Species	Study No.	Tecovirimat Dose	Regimen (Days)	Survival Rate (n [%])	P-value[a]
Cynomolgus monkey	FY10-087	Placebo	4–17	0 (0)	--
		3 mg/kg	4–17	6 (100)	0.0012[b]
		10 mg/kg	4–17	6 (100)	0.0012[b]
		20 mg/kg	4–17	6 (100)	0.0012[b]
	AP-09-026G	Placebo	4–17	0 (0)	--
		0.3 mg/kg	4–17	1 (20)	0.2551
		1 mg/kg	4–17	0 (0)	1.0000
		3 mg/kg	4–17	4 (80)	0.0048[b]
		10 mg/kg	4–17	4 (80)	0.0048[b]
	SR10-037F	Placebo	4–19	0 (0)	--
		10 mg/kg	4–17	5 (83)	0.0160[b]
		10 mg/kg	5–18	5 (83)	0.0160[b]
		10 mg/kg	6–19	3 (50)	0.1241
	SR10-038F	Placebo	4–13	1 (25)	--
		10 mg/kg	4–6	2 (50)	0.3643
		10 mg/kg	4–8	6 (100)	0.0141[b]
		10 mg/kg	4–10	6 (100)	0.0141[b]
		10 mg/kg	4–13	4 (80)	0.0972
New Zealand White Rabbit	SR13-025F	40 mg/kg	4–17	7 (87.5)	--
		80 mg/kg	4–17	7 (87.5)	--
		120 mg/kg	4–17	8 (100)	--
	SR14-008F	Placebo	4–17	0 (0)	--
		20 mg/kg	4–17	9 (90)	0.0010[b]
		40 mg/kg	4–17	9 (90)	0.0010[b]
		80 mg/kg	4–17	8 (80)	0.0011[b]
		120 mg/kg	4–17	8 (80)	0.0011[b]

[a]P-value is from a 1-sided Boschloo test (with Berger-Boos modification of gamma = 0.001) compared with placebo.
[b]Denotes statistical significance at the 0.025 level.



NOTE: Five efficacy studies that included a placebo comparator are listed, with active treatment groups shown. The charted data show the percent difference in survival (Diff%) between the active treatment groups and the placebo comparator group for each study (black box symbols). The "whiskers" indicate 95% confidence intervals. The vertical line indicates no effect. The number of animals surviving versus the number treated (#surviving/#treated) in each active treatment group (Active) and placebo controls (Control) are listed on the right.

In NHPs, tecovirimat 10 mg/kg on Days 4-17 after MPXV infection conferred the greatest protection in terms of lesion formation and resolution and conferred protection against viraemia. Although 3 and 10 mg/kg doses conferred equivalent survival benefit, the 10 mg/kg dose decreased viral load to a greater extent and provided additional protection against morbidity. In addition, 10 mg/kg was associated with

earlier viral clearance when start was delayed to Day 5 and daily dosing with 10 mg/kg for a minimum of 5 days was necessary to confer protection against viral load relative to placebo controls. Conclusions regarding the impact of tecovirimat treatment on lesions following RPXV challenge in rabbits cannot be made. Tecovirimat at ≥20 mg/kg on Days 4-17 after RPXV infection conferred protection against viraemia. Assessment of efficacy in subgroups of NHPs and rabbits stratified by demographic variables revealed no significant differences between sexes or according to baseline body weight above or below the median of 3.45 kg.

The duration of treatment in nonclinical studies is that proposed for humans. It has been based on expectation of inhibition of systemic virus dissemination by tecovirimat until development of sufficient neutralizing antibody to clear the virus. NHPs and rabbits were shown to mount such an immune response within this time frame. Five of the pivotal studies assessed persistence of efficacy over 11-39 days after treatment discontinuation. Across these studies, 3 animals died after conclusion of a full 14-day tecovirimat treatment regimen. Lesion counts and viral load also generally continued to improve post-treatment in surviving tecovirimat-treated animals.

Exposure-response relationship

The selection of the pharmacodynamic target to underpin human dose selection was based on the results of the six pivotal nonclinical efficacy studies. In the rabbit model, a target cut-off for C_{avg} of 185 ng/mL, corresponding to a 30 mg/kg dose, was determined to be the best predictor of survival. In the NHP model, maximal efficacy (i.e. based on survival plus reductions in lesion counts and viral loads) could be obtained with 10 mg/kg/day initiated on day 4 or 5 post-infection and given for at least 5 days. Median exposures after dosing at 10 mg/kg were AUC/WT of 2.67 mg•h/(L•kg) and $Cmin_{SS}$ of 204.52 µg/L.

When a conservative tecovirimat dose of 40 mg/kg in rabbits (versus 30 mg/kg) was used for a comparison of exposure relative to NHP dosed at 10 mg/kg, plasma concentrations were still lower in rabbits among both uninfected and infected animals. Therefore, exposure-response analyses based on the NHP model were considered more robust for the determination of effective doses in humans. This can be agreed. The final recommended dose of 600 mg BID provides predicted plasma exposures (including Cmin) for total and unbound tecovirimat that substantially exceed exposures in NHPs dosed at 10 mg/kg/day. Initially, the applicant's analyses suggested that 400 mg once daily would be a sufficient human dose to meet the rabbit Cavg target while 600 mg once daily in humans would provide plasma exposures observed with 12-14 mg/kg administered to infected NHPs. This NHP dose is well above the estimated effective dose for 50% rescue and also above 10 mg/kg, which gave complete survival.

TQT study

After a single 1,000 mg dose, total tecovirimat Cmax was about the same as that observed on Day 14 of BID dosing. No ECG changes of concern were observed in this study or in other clinical studies in which ECGs were obtained

2.6.4. Conclusions on clinical pharmacology

There are no remaining questions pertaining to the clinical pharmacology which would preclude the issue of a Marketing Authorisation.

2.6.5. Clinical efficacy

There have been no clinical efficacy studies due to the nature of the viruses to be treated and their lack of or rare circulation in humans. The applicant derived the final recommended dose regimen for tecovirimat (600 mg BID for up to 14 days) from the nonclinical efficacy studies and the human PK data.

Applicant's report 724

This report provides a summary of the evidence and analyses leading to the final recommended regimen of 600 mg BID. The elements taken into account in this report include:

- The POPPK models and PK-PD analyses that used data from rabbits (**SIGA-PCS-100** and **final SIGA-PCS-104**) and NHPs (**SIGA-RAS-003 PK-PD and POPPK reports**; **SIGA-RAS-005 and 005-01**).
- **SIGA-RAS-003**, which describes the POPPK analysis of the human PK data obtained in SIGA-246-004, in which there was once daily administration of 400 mg or 600 mg for 14 days.
- **SIGA-PCS-106**, which compared tecovirimat PK in humans at 600 mg BID dose and in NHPs at 10 mg/kg to support dosing in the expanded phase of SIGA-246-008.
- **SIGA-PCS-104**, which provided a triangulation of tecovirimat PK in rabbits, non-human primates and humans in order to guide the selection of the most relevant animal species for smallpox infection.

To summarise, including information presented in the previous section:

In rabbits

A 1-compartment model with zero-order absorption provided the best fit for the rabbit data. Total volume of distribution was approximately 170 L in uninfected animals and ~ 40% higher (239 L) in infected rabbits with respective t½ of 6.9 h and 9.7 h. Infection did not appear to affect other PK parameters in the model. The ROC defined the Cavg cut-off for increased survival at 185 ng/mL.

In NHPs

Concentration-time profiles of tecovirimat were adequately fitted with a 2-compartment model with lag-time of absorption, an effect of weight on CL/F and Q/F with a power function of 0.75 and an effect of weight on Vc/F and Vp/F with a power function of 1. The median steady state (i.e. Day 14) AUC/Dose, Cmin/Dose and Cmax/Dose ratios of tecovirimat for infected monkeys were similar to those predicted in uninfected monkeys. A Kaplan-Meier analysis of treatment indicated that doses of < 3 mg/kg QD (0.3 and 1 mg/kg QD) showed no statistical survival benefit compared to placebo. Once daily dosing at ≥3 mg/kg resulted in survival of ~ 95% of the monkeys. Using the non-parametric Kaplan-Meier approach there was a trend toward a higher probability of surviving when AUC/WT exceeded 2.02 mg.hr/L.kg and when Cmin values were above 200 µg/L.

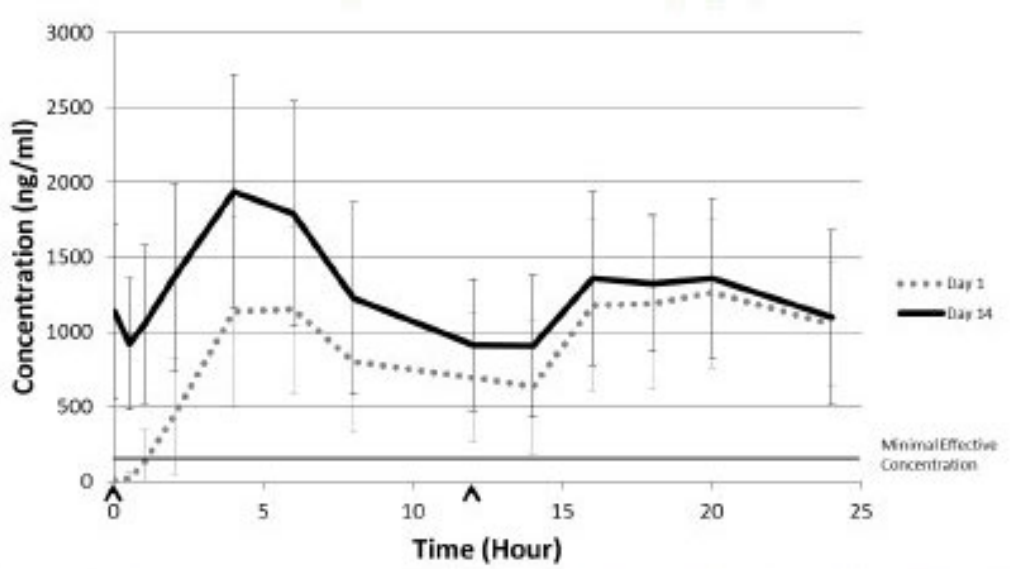
Additional data obtained from SR10-037F and SR10-038F were used to assess the optimal starting treatment day and number of doses. The survival probability of monkeys with a daily dose of 10 mg/kg starting at Days 4 and 5 post-infection was slightly but not statistically significantly below 100%. However, the survival probability decreased to 50% after 13 days post-infection when treatment was initiated 6 days post-infection. The probability of survival with only 3 daily doses of tecovirimat was 67% and 33% after Day 15 and Day 17 post-infection, respectively, but survival in the group receiving

up to 5, 7 or 10 daily doses of 10 mg/kg starting on Day 4 post–infection was slightly but not significantly below 100% (16/17 monkeys survived).

PK-PD considerations for human dose selection

It was assumed that the E/R relationship in humans will be similar to that in animals. The approach to human dose selection was based on comparing exposure parameters (e.g. AUC_{0-t}, Cmax, Cmin, Cavg) between humans and animals. Since it was concluded that the NHP model was more conservative than the rabbit, the aim was to find a human dose that gave exposures higher than achieved with 10 mg/kg in NHPs. Further to find a dose to give exposure below the NOEL established in toxicological studies.

Using the data from SIGA-246-008 with tecovirimat 600 mg BID given in the fed state, the human exposures were several-fold higher than effective exposures in NHPs at Day 1 and steady state.



Legend: Shown are mean drug exposure values ± SD at various time points (0, 0.5, 1, 2, 4, 6, 8, 12, 14, 16, 18, 20, 24h) over a 24 hour period from healthy volunteers (N = 48) who received 600 mg TPOXX® twice a day at 12 hour intervals. The dotted line represents data from the first day of drug administration (Day 1). The solid line represents data from the last day of drug administration (Day 14). The average effective minimal concentration (C_{min} of 169 ng/mL) is depicted as a straight line across the graph. The C_{min} was identified as the most critical PK parameter for prediction of efficacy based on NHP PK/PD analysis. The arrowheads indicate the time points (0 and 12h) at which the TPOXX was orally administered.

Figure 38: Tecovirimat pharmacokinetic profiles after the first dose (Day 1) and at steady state after the last dose (Day 14)

Table 40: Mean of non-compartmental exposures in NHPs and humans

Comparisons	Treatment Day	C_{max} (ng/mL)	C_{min} (ng/mL)	C_{avg} (ng/mL)	AUC_{0-t} (ng.h/mL)
Human 600 mg BID	1 (first dose)	1591	560	924	25876
NHP 10 mg/kg		749	158	318	7629
Human to NHP ratio (Unbound Ratio)		**2.1 (3.4)**	**3.5 (5.8)**	**2.9 (4.7)**	**3.4 (5.5)**
Human 600 mg BID	14 (steady state)	2209	690	1270	30632
NHP 10 mg/kg		1403	143	569	13650
Human to NHP ratio (Unbound Ratio)		**1.6 (2.6)**	**4.8 (7.8)**	**2.2 (3.6)**	**2.2 (3.6)**

The safety margin analysis (see table below) shows that the highest tecovirimat Cmax values are at least 29-fold in mouse and 2.4-fold in monkeys vs. human Cmax after 600 mg BID dosing. Similarly, the highest AUC values are at least 28-fold in mouse and 2.5-fold in monkeys vs. humans after 600 mg BID. The Cmax ceiling is 5,575 ng/mL based on the CNS signals such as salivation, licking and twitching observed in a dog study. This toxic level in dogs compares with a maximum Cmax of 4,460 ng/mL in humans after 600 mg twice daily.

Table 41: Tecovirimat safety margins based on animal repeat dose studies and the recommended clinical dose

Species	Treatment Period (days)	NOAEL/ NOEL Dose (mg/kg/day)	Safety Margin in Terms of Dose[a]	C_{max} (ng/mL)	Safety Margin in Terms of C_{max}[b]	AUC_{0-24h} (ng·hr/mL)	Safety Margin in Terms of AUC[b]
Mice	90[c]	1,000[d]	58	53029	24.0	700,618	22.9
	28[e]	2,000[d]	117	64900	29.4	858,599	28.0
NHP	90[f]	300[g]	18	3274	1.5	77,689	2.5
	28[h]	300[g]	18	5389	2.4	43,036.5	1.4
Human[i]	Recommended clinical dose: 17.1 mg/kg/day (calculated assuming that 1,200 mg was given daily and the human body weight is 70 kg)			2,209		30,632	

[a]Animal dose divided by recommended clinical dose in humans
[b]C_{max} and AUC in animals divided by C_{max} and AUC, respectively in humans (obtained from Study SIGA-246-008, Section 5.3.5.1)
[c]Study IITRI 2083-003-001 SN3, Section 4.2.3.2
[d]NOAEL = Highest dose at which there are no adverse events at the end of the study (before the recovery period)
[e]Study 246-TX-006, Section 4.2.3.2
[f]Study IITRI 2083-003-001 SN6, Section 4.2.3.2
[g]NOEL = No Observed Effect Level
[h]Study 246-TX-007, Section 4.2.3.2
[i]Study SIGA-246-008, Section 5.3.5.1

Additional comparisons were made using calculated unbound plasma levels from various species. The table below shows mean human and NHP total and unbound PK values. Total and unbound human exposures based on data from SIGA-246-008 comfortably exceed the NHP exposures following 10 mg/kg dosing, which was associated with efficacy, on days 1 and 14.

Table 42: Mean human and NHP drug exposures and human/NHP ratios (total and unbound)

	Treatment	%Protein Binding	C_{max} (ng/mL)	C_{min} (ng/mL)	AUC_{0-t} (ng.h/mL)	C_{avg} (ng/mL)
Human	1		1591	560	25876	924
NHP			809	193	8110	338
Human to NHP Ratio (Total)			2.0	2.9	3.2	2.7
Human Unbound		80	318	112	5175	185
NHP Unbound		87.5	101	24	1014	42
Human to NHP Ratio (Unbound)			3.1	4.6	5.1	4.4
Human	14		2209	690	30632	1271
NHP			1444	169	14352	598
Human to NHP Ratio (Total)			1.5	4.1	2.1	2.1
Human Unbound		80	442	138	6126	254
NHP Unbound		87.5	181	21	1794	75
Human to NHP Ratio (Unbound)			2.4	6.5	3.4	3.4

The assessment of 600 mg BID from the safety standpoint, also based on calculated unbound levels, was also addressed. The comparison took into account recent data from an IV NHP study. There were tremors noted in 3 of 4 animals dosed with 30 mg/kg tecovirimat using a 4-hour infusion. These observations were detected at the end of infusion (EOI) on Day 1 and resolved at approximately 2 hours following EOI with no recurrence over the next 24 hours. Tremors were not detected in animals dosed with 30 mg/kg infused over 6 hours or in any animals dosed with 20 mg/kg.
When 30 mg/kg tecovirimat was infused over 6 hours the Cmax and AUCinf were ~50% and 20% lower, respectively, compared to 30 mg/kg infused over 4 hours. However, the calculated PK parameters were not significantly different for the 2 infusion durations and the 2 doses.

Table 43: Unbound exposures

Species	Study[a]	Dose	%Protein Binding	Max C_{max} (ng/mL)		Mean C_{max} (ng/mL)	
				Total	Unbound	Total	Unbound
Human	SIGA-246-008	600 mg BID	80	4460	892	2209	442
Dog	246-TX-015	100 mg/kg	90.6	5575	524	5575	524
NHP	ITRI 2083 003-001 SN6 3-month Study	300 mg/kg	87.5	6720	840	5303	663
NHP	246-TX-019	30 mg/kg 6h infusion	87.5	15375	1922	13,883	1735
Mouse	ITRI 2083 003-001 SN3 3-month study	1000 mg/kg	87.7	64900	7983	64900	7983
Paediatric BWt 13 kg	Simulated data	50 mg BID	75[b]	5250	1313[c]	3477	869[c]
Paediatric BWt 25 kg	Simulated data	100 mg BID	75[b]	4449	1112[c]	3200	800[c]

[a]Oral administration unless indicated
[b]Plasma protein ratio of adult:kid = 59/63 (Sethi et al, 2016; Section 5.4)
[c]Simulated C_{max} based on total plasma protein binding

In conclusion

- Human dosing and target exposures were based on PK-PD analyses of NHP studies since this was

found to be the more conservative model.

- A statistically significant reduction in mortality was observed at 3 mg/kg in the IV MPXV/NHP model. However, the 10 mg/kg dose not only reduced mortality, but also led to a reduction in morbidity as represented by clinical scores, lesion count and viral load. Therefore, selection of the human dose aimed to achieve higher human plasma exposures vs. those in NHPs treated with 10 mg/kg.
- The 600 mg BID dose taken in the fed state gives human exposures (total and unbound tecovirimat) that exceed efficacious exposures in NHPs. Furthermore, the maximum unbound tecovirimat Cmax derived from 246-TX-019 at which no CNS toxicity was observed (1922 ng/mL) is considerably higher than the calculated maximum unbound Cmax in healthy adults dosed to steady state with 600 mg BID (from SIGA-246-008 [892 ng/mL]). It is also considerably higher than the maximum unbound Cmax predicted to occur in children using the recommended dose adjustment by body weight and that predicted to occur in subjects with severe renal or hepatic impairment.
- The proposed dose of tecovirimat, 600 mg twice daily, will provide Cmin exposures in excess (7.8-fold higher) of those demonstrated to be efficacious in the NHP model.

2.6.6. Discussion on clinical efficacy

Since it is accepted that the applicant cannot provide human efficacy data, the critical discussion rests on the nonclinical efficacy data and the derivation of the final dose regimens for adults and for children from 13 kg. The nonclinical efficacy data and the derivation of the pharmacodynamic targets for identifying potentially efficacious human doses are presented and discussed in section 2.6.2.2.

As discussed in section 2.6.2.2., the human dose is based on exceeding exposures achieved with 10 mg/kg/day in NHPs, which was considered a conservative target for the dose selection process. Further calculations indicated that the clinical dose of 600 mg BID provides unbound tecovirimat concentrations that are considerably in excess of those achieved in NHPs when dosed with 10 mg/kg/day.

The comparisons of total and unbound concentrations were also viewed from the safety perspective. The recently reported data from the IV NHP study allowed for further evaluation of the safety of plasma levels (total and unbound) that exceeded those documented in a prior dog study. Using calculated unbound exposures, the human Cmax values appear to be well below the highest Cmax in NHPs at which there were no signs of CNS toxicity. Based on the revised calculations, the recommended adult dose can be accepted.

The treatment duration of 14 days is proposed since this increased survival in NHPs dosed at ≥ 3 mg/kg and is theoretically supported by the proposed mechanism of action of tecovirimat. It is not possible to state a definitive interval post-onset of clinical disease within which treatment should be started. Based on indications from nonclinical studies, the SmPC advises that treatment should start as early as possible after the diagnosis is made.

No paediatric studies have been conducted and none is planned as per the PIP. The applicant considered that SIGA-246-018 showed a linear correlation between drug exposures and doses of tecovirimat from 100-600 mg. From POPPK modelling, the applicant derived dose recommendations for use from 3 kg but the application concerns a minimum body weight of 13 kg. These are supported by the additional analyses of predicted unbound Cmax when using the recommended paediatric weight-based dose adjustments. Doses for the <13 kg categories would involve fractions of capsule contents,

which is not a feasible approach. Therefore, dosing recommendations for 3-12 kg will follow once a suitable paediatric dose form has been developed.

Additional efficacy data needed in the context of a MA under exceptional circumstances

In order to further characterise the efficacy of tecovirimat in the treatment of smallpox, the MAH should conduct and submit the results of the open-label field study SIGA-246-021, upon the occurrence of a smallpox outbreak in the US.

The MAH should provide summary case report information for those cases of monkeypox, cowpox or complications due to replication of vaccinia that may occur in the European Union for which tecovirimat is used***.***

2.6.7. Conclusions on the clinical efficacy

The data support the proposed human dosing regimen of tecovirimat 600 mg twice daily for 14 days, which is to be taken with/just after food.

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a Marketing Authorisation under exceptional circumstances:

Upon the occurrence of a smallpox outbreak the MAH should conduct and submit the efficacy results from:

- open-label field study SIGA-246-021

The MAH should provide summary case report information for those cases of monkeypox, cowpox or complications due to replication of vaccinia that may occur in the European Union for which tecovirimat is used***.***

2.6.8. Clinical safety

2.6.8.1. Patient exposure

There have been 788 adults exposed to tecovirimat across 11 Phase I studies. The data most relevant to this application come from studies SIGA-246-008 and SIGA-246-015, in which adults received 600 mg BID tecovirimat using the final capsule formulation for 14 days. In SIGA-246-008, 359 subjects took at least one dose of tecovirimat of which 95% took drug for at least one week. The median duration of treatment was 14 days. In SIGA-246-015, all of the 78 subjects received 600 mg BID on Days 8-22.

2.6.8.2. Adverse events

In SIGA-246-008, 164 subjects (36.5%) experienced at least one AE and 19.2% had at least one AE considered treatment-related.

	Placebo (N = 90)		Tecovirimat 600 mg (N = 359)		Total (N = 449)	
	n (%)	E	n (%)	E	n (%)	E
TEAEs	30 (33.3)	68	134 (37.3)	318	164 (36.5)	386
Serious TEAEs	0	0	1 (0.3)	1	1 (0.2)	1
Treatment-related TEAEs	15 (16.7)	32	71 (19.8)	176	86 (19.2)	208
TEAEs leading to drug withdrawal	2 (2.2)		6 (1.7)		8 (1.8)	
TEAEs leading to death	0	0	1 (0.3)	1	1 (0.2)	1

The AEs most commonly reported mapped to the SOCs of nervous system disorders (18.9%) and gastrointestinal disorders (13.6%), with higher rates in the tecovirimat group. The most commonly reported AEs by PT were headache (17.0% tecovirimat and 14.4% placebo) and nausea (5.6% for both groups).

Table 44: Treatment-emergent adverse events experienced by at least 2% of subjects in either treatment group by preferred term and descending frequency overall (safety population)

	Placebo (N = 90)		Tecovirimat 600 mg (N = 359)		Total (N = 449)	
Preferred Term	n (%)	E	n (%)	E	n (%)	E
Subjects with at least 1 TEAE	30 (33.3)	68	134 (37.3)	318	164 (36.5)	386
Headache	13 (14.4)	19	61 (17.0)	104	74 (16.5)	123
Nausea	5 (5.6)	5	20 (5.6)	29	25 (5.6)	34
Diarrhoea	3 (3.3)	4	11 (3.1)	13	14 (3.1)	17
Dizziness	3 (3.3)	3	9 (2.5)	9	12 (2.7)	12
Fatigue	4 (4.4)	4	5 (1.4)	5	9 (2.0)	9
Vomiting	0	0	9 (2.5)	10	9 (2.0)	10
Constipation	2 (2.2)	2	5 (1.4)	5	7 (1.6)	7
Somnolence	2 (2.2)	2	2 (0.6)	2	4 (0.9)	4
Back pain	2 (2.2)	2	1 (0.3)	1	3 (0.7)	3
Oropharyngeal pain	2 (2.2)	2	1 (0.3)	1	3 (0.7)	3

Five (1.1%) subjects (4 tecovirimat) experienced a Grade 3 or higher TEAE. Two in the tecovirimat group had a severe headache (definitely related), one had severe osteoarthritis (possibly related) and one had a fatal pulmonary embolism (unrelated). All of the events resolved within 1 to 4 days from time of onset.

Overall, 19.2% of subjects experienced at least one related TEAE: 19.8% of subjects in the tecovirimat 600 mg group and 16.7% in the placebo group. The most commonly reported in the tecovirimat were headache (12.3%) and nausea (4.5%). In the placebo group, the most commonly reported related TEAEs were headache (7.8%), nausea (4.4%), fatigue (3.3%), diarrhoea (2.2%) and constipation (2.2%).

Table 45: Treatment-related "treatment-emergent adverse events" experienced by at least 2% of subjects in either treatment group by system organ class and preferred term (safety population)

System Organ Class Preferred Term	Placebo (N = 90)		Tecovirimat 600 mg (N = 359)		Total (N = 449)	
	n (%)	E	n (%)	E	n (%)	E
Subjects with at least 1 related TEAE	15 (16.7)	32	71 (19.8)	176	86 (19.2)	208
Nervous system disorders	8 (8.9)	13	50 (13.9)	92	58 (12.9)	105
Headache	7 (7.8)	11	44 (12.3)	80	51 (11.4)	91
Gastrointestinal disorders	5 (5.6)	9	35 (9.7)	58	40 (8.9)	67
Nausea	4 (4.4)	4	16 (4.5)	22	20 (4.5)	26
Diarrhoea	2 (2.2)	2	7 (1.9)	9	9 (2.0)	11
Constipation	2 (2.2)	2	2 (0.6)	2	4 (0.9)	4
General disorders and administration site conditions	3 (3.3)	3	9 (2.5)	9	12 (2.7)	12
Fatigue	3 (3.3)	3	3 (0.8)	3	6 (1.3)	6
Skin and subcutaneous tissue disorders	2 (2.2)	3	5 (1.4)	6	7 (1.6)	9
Psychiatric disorders	2 (2.2)	2	3 (0.8)	4	5 (1.1)	6
Ear and labyrinth disorders	2 (2.2)	2	0	0	2 (0.4)	2

In the Lead-in and PK cohorts, subjects had ECGs performed at baseline, after the second dose on day 2, after the first dose on day 6 and after the last dose on day 15. The same applied to all other subjects except for omission of a day 2 tracing. The exact timing of tracings in relation to dose is not stated. There were no AEs related to ECG findings. Overall, the mean QTcF interval at Baseline was 406.714 msec (means were 404.8 msec in the placebo group and 407.1 msec in the tecovirimat group. Day 6 mean values were 404.4 and 407.0 msec, respectively, with Day 15 values of 404.6 msec and 405.5 msec.

For HR, RR and PR interval, there were no important differences in changes from baseline between the placebo and tecovirimat groups. For QRS duration the mean change from baseline on Day 6 was -0.258 msec for the placebo group and -0.006 msec for the tecovirimat mg group. The differences on Day 15 were 0.256 msec for the placebo group and -0.300 msec for the tecovirimat group.

In the Lead-in cohort and PK cohorts only, EEGs were obtained at the Screening visit and after the morning doses on Days 2, 6 and 14. All EEGs after dosing were at 4 h ± 30 min. At Screening, all subjects had EEG readings that were graded E0 (95.1%; normal) or E1 (4.9%; <3 focal epileptiform abnormalities or non-epileptiform abnormalities). On Days 2 and 6, one subject had an AE reported due to post-dose Grade E3 readings (sharp/slow complex, runs of epileptiform discharges [>1/s], more than 10 epileptiform discharges). The subject discontinued the study. At the Day 14 Post-dose Visit, all subjects had EEG readings that were graded E0 (88.9%) or E1 (9.9%).

In SIGA-246-015, the safety data of most interest pertain to days 8-21, when tecovirimat 600 mg BID was given alone (columns labelled T below). During treatment with tecovirimat alone, percentages with at least one AE were 20.8% (5/24) in Arm 1, 10/30 (33.3%) in Arm 2 and 7/24 (29.2%) in Arm 3.

Table 46: Overall summary of adverse events (Safety Population)

	Arm 1				Arm 2				Arm 3				
	FOM (N=24) n (%)	T (N=24) n (%)	FOM+T (N=24) n (%)	Total (N=24) n (%)	R (N=30) n (%)	T (N=30) n (%)	R+T (N=30) n (%)	Total (N=30) n (%)	B (N=24) n (%)	T (N=24) n (%)	B+T (N=24) n (%)	Total (N=24) n (%)	Overall (N=78) n (%)
Any AEs	2 (8.3)	5 (20.8)	2 (8.3)	5 (20.8)	4 (13.3)	10 (33.3)	14 (46.7)	18 (60.0)	2 (8.3)	7 (29.2)	3 (12.5)	11 (45.8)	34 (43.6)
Any AE by relationship to study drug													
Not related	2 (8.3)	0	0	0	4 (13.3)	0	9 (30.0)	5 (16.7)	1 (4.2)	0	0	1 (4.2)	6 (7.7)
Unlikely related	0	4 (16.7)	1 (4.2)	3 (12.5)	0	1 (3.3)	3 (10.0)	4 (13.3)	1 (4.2)	3 (12.5)	3 (12.5)	6 (25.0)	13 (16.7)
Possibly related	0	0	0	0	0	1 (3.3)	1 (3.3)	1 (3.3)	0	2 (8.3)	0	2 (8.3)	3 (3.8)
Probably related	0	1 (4.2)	1 (4.2)	2 (8.3)	0	7 (23.3)	1 (3.3)	7 (23.3)	0	2 (8.3)	0	2 (8.3)	11 (14.1)
Definitely related	0	0	0	0	0	1 (3.3)	0	1 (3.3)	0	0	0	0	1 (1.3)
Any AE by intensity													
Grade 1 - Mild	2 (8.3)	5 (20.8)	2 (8.3)	5 (20.8)	4 (13.3)	8 (26.7)	10 (33.3)	12 (40.0)	2 (8.3)	7 (29.2)	3 (12.5)	11 (45.8)	28 (35.9)
Grade 2 - Moderate	0	0	0	0	0	2 (6.7)	4 (13.3)	6 (20.0)	0	0	0	0	6 (7.7)
Grade 3 - Severe	0	0	0	0	0	0	0	0	0	0	0	0	0
Grade 4 - Life threatening	0	0	0	0	0	0	0	0	0	0	0	0	0
Grade 5 - Death	0	0	0	0	0	0	0	0	0	0	0	0	0
Any serious AE	0	0	0	0	0	0	0	0	0	0	0	0	0
Any AE leading to discontinuation	0	0	0	0	0	0	0	0	0	0	0	0	0

Abbreviations: AE, adverse event; B, bupropion; FOM, flurbiprofen, omeprazole, and midazolam; R, repaglinide; T, tecovirimat;
Note: In each study arm, subjects received a single oral dose of probe substrates (Arm 1: flurbiprofen 50 mg, omeprazole 20 mg, midazolam 2 mg [FOM]; Arm 2: repaglinide 2 mg [R]; Arm 3: bupropion 150 mg [B]) on Day 1, followed by a washout period (Day 2 through Day 7). Subjects received tecovirimat 600 mg [T] twice daily for 15 days (Day 8 through Day 22). A single oral dose of probe substrates was co administered with the morning dose of tecovirimat on Day 22.
Percentages were based on the number of subjects in the safety population who received the specified treatment and overall.
At each level of subject summarization, a subject was counted once if the subject reported one or more events.
Each AE was counted only once as occurring during the treatment period during which the AE began, even if the AE continued into the next treatment period.

In Arm 1, during tecovirimat alone, one subject (4.2%) reported AEs of abdominal pain, diarrhoea and gastroesophageal reflux that were each considered probably related and anxiety that was considered possibly related to drug. All AEs in Arm 1 were considered mild in intensity.

In Arm 2, during tecovirimat alone, the AEs of infrequent bowel movements and insomnia (2 subjects each [6.7%]) and abdominal pain, vomiting, abdominal discomfort, flatulence, aphthous ulcer and dizziness (1 subject each [3.3%]) were considered possibly related to study drug. The AEs of headache

(4 [13.3%]), nausea (3 [10.0%]), decreased appetite (2 [6.7%]) and abdominal pain, vomiting and palpitations (1 each [3.3%]) were considered probably related to tecovirimat. The AE of diarrhoea in one subject [3.3%] was considered definitely related to tecovirimat. One subject in Arm 2 had palpitations starting on Day 9, sometimes associated with shallow respirations but telemetry was commenced and there were no significant ECG findings.

In Arm 3, during tecovirimat alone, the AEs of infrequent bowel movements (2 [8.3%]) and abdominal pain, abdominal distension, headache and feeling jittery (1 each [4.2%]) were considered possibly related to study drug. The AE of decreased appetite (2 [8.3%] was considered probably related to tecovirimat. All AEs in Arm 3 were considered mild in intensity.

2.6.8.3. Serious adverse event/deaths

There has been one death in the clinical programme, which occurred in SIGA-246-008. A subject in the tecovirimat group experienced a fatal SAE of pulmonary embolism on Day 21 after completing the 14-day dosing period with no other TEAEs. This occurred in a 46-year-old female who had a history of deep vein thrombosis in her right leg from Aug 2011 to Feb 2012 but there was no current anticoagulant use and she had not been a smoker. Ongoing concomitant medications at the time of the event included Depo-Provera 150 mg every 3 months. The subject completed the Day 15 visit on 19-May-2016. On 25-May-2016, the subject experienced a pulmonary embolus and died on the way to hospital. An autopsy revealed extensive pulmonary embolism unrelated to study drug.

The only SAE in SIGA-246-008 was the fatal pulmonary embolism described above. There were no SAEs in SIGA-246-015 or in the other multiple dose studies SIGA-246-002 and SIGA-246-004.

2.6.8.4. Laboratory findings

In SIGA-246-008, the haematology and chemistry mean values were mostly within the reference ranges for all analytes and generally similar between treatment groups. Some subjects had abnormal routine chemistry results that were greater than Grade 1. An abnormal low phosphate (Grade 2) occurred in seven subjects in the tecovirimat group at Day 6 and seven at Day 15 while one had a Grade 3 abnormality at Day 6 (0.61 mmol/L; lower end of normal range 0.81 mmol/L).

Three tecovirimat subjects had an abnormal serum creatinine at Day 6 (Grade 2). Grade 2 abnormalities in creatinine clearance occurred in 52 to 56 subjects in the tecovirimat group and 10 to 19 subjects in the placebo group throughout study while Grade 3 abnormalities occurred in 4 to 10 subjects in the tecovirimat group and 1 to 2 subjects in the placebo group.

Abnormally high glucose occurred pre-dose in 4 tecovirimat and 1 placebo subjects. During dosing, this occurred in 2 subjects in the tecovirimat group at Day 1/2, 7 in the tecovirimat group and 2 in the placebo group at Day 6 and 6 vs. 1 in respective groups at Day 15 (Grade 2). Abnormally low glucose occurred in 4 subjects in the tecovirimat group at Day 6 and 2 in the tecovirimat group at Day 15 (Grade 2).

Other laboratory test results of DAIDS Grade 3 (severe) were:

- One subject in the tecovirimat group had a lymphocyte value of 0.4×10^9/L on Day 15 compared to serial prior values of $1.5\text{-}1.6 \times 10^9$/L.
- Creatinine clearance in 2 placebo and 16 tecovirimat subjects.

One subject in the tecovirimat group had haematocrit and haemoglobin decreased starting on Day 7 that were reported as AEs and were considered to be possibly related to study drug.

In SIGA-246-015, mean haematology and serum chemistry results were within the normal ranges at the time points assessed and the mean values observed after dosing were generally similar to those observed at baseline. No apparent treatment- or dose-related trends were observed.

One subject in Arm 1 had clinically significant haematology and serum chemistry abnormalities. Following onset of an influenza-like illness on Day 20 that was not confirmed by finding virus, on

Day 22 the subject's leukocyte and platelet counts were low but not considered clinically significant. By Day 24 the influenza-like symptoms had subsided, but the leukocyte and platelet counts had further decreased and were reported as AEs of leukopenia and thrombocytopenia. Additionally, the LFT results on Day 24 were abnormally high and reported as an AE. The investigator considered the AEs of

leukopenia, thrombocytopenia and abnormal LFT results as likely due to a combination of study drug effects and viral syndrome. The subject remained asymptomatic and the abnormalities resolved at days 29 (haematological) and 43 (LFTs).

2.6.8.5. Safety in special populations

There are single dose administrations only in subjects with renal or hepatic impairment. Across studies, 33 subjects were aged 65-74 years, 4 were aged 75-84 years and none was older than 84 years. With such small numbers, it can only be observed that age itself likely explains the few incidences of higher AE rates with increasing age.

2.6.8.6. Immunological events

There have been ADRs reported that include skin reactions and urticaria.

2.6.8.7. Safety related to drug-drug interactions and other interactions

There are no data except for single dose administrations at tecovirimat steady state in the drug-drug interaction study.

2.6.8.8. Discontinuation due to adverse events

- There were no discontinuations due to AEs in SIGA-246-015.
- In SIGA-246-002 one subject discontinued from the 800 mg QD dose group due to a severe headache.
- In SIGA-246-004 two subjects withdrew from 400 mg QD dosing due to AEs of upper respiratory infection and haematoma at venepuncture site.

In SIGA-246-008, there were 8 subjects (1.8%) who discontinued study drug because of AEs, of which 6 (1.7%) were in the tecovirimat group. TEAEs leading to study drug discontinuation reported by more than 1 subject were nausea (2 tecovirimat) and pyrexia (2 tecovirimat). Most AEs that led to study drug discontinuation were considered drug-related and most were mild or moderate in intensity.

Tecovirimat 600 mg						
101-164 (M/W/21)	*Investigations/ Electroencephalogram abnormal/ Abnormal EEG result – Grade 3*	2	14	Mild/ Possibly related	Other: dosing was stopped permanently	Recovered/ Resolved
	Gastrointestinal disorders/ Nausea/ Nausea	9	10	Mild/ Possibly related	None	Recovered/ Resolved
	General disorders and administration site conditions/ Fatigue/ Fatigue	11	12	Mild/ Possibly related	None	Recovered/ Resolved
103-151 (F/W/60)	*Gastrointestinal disorders/ Abdominal discomfort/ Slight upset stomach*	3	5	Mild/ Possibly related	None	Recovered/ Resolved
	Gastrointestinal disorders/ Dry mouth/ Dry mouth	3	5	Mild/ Possibly related	None	Recovered/ Resolved
	Psychiatric disorders/ Dysphoria/ Dysphoric	3	5	Mild/ Possibly related	None	Recovered/ Resolved
	Nervous system disorders/ Disturbance in attention/ Decreased concentration	3	6	Mild/ Possibly related	None	Recovered/ Resolved
104-110 (M/W/47)	*General disorders and administration site conditions/ Pyrexia/ Fever*	2	4	Mild/ Definitely related	Con med	Recovered/ Resolved
	Gastrointestinal disorders/ Diarrhoea/ Diarrhea	2	6	Moderate/ Definitely related	None	Recovered/ Resolved
	Gastrointestinal disorders/ Nausea/ Nausea	2	6	Mild/ Definitely related	None	Recovered/ Resolved
	Nervous system disorders/ Headache/ Headache	2	6	Severe/ Definitely related	Con med	Recovered/ Resolved
106-138 (F/W/58)	*Skin and subcutaneous tissue disorders/ Palpable purpura/ Palpable purpura*	2	16	Mild/ Definitely related	Other: dosing was stopped permanently	Recovered/ Resolved

106-151 (M/W/56)	*Gastrointestinal disorders/ Nausea/ Nausea*	8	13	Mild/ Definitely related	Other: dosing interrupted	Recovered/ Resolved
	General disorders and administration site conditions/ Chills/ Chills	12	13	Mild/ Unlikely related	None	Recovered/ Resolved
	General disorders and administration site conditions/ Pyrexia/ Fever	12	13	Mild/ Unlikely related	None	Recovered/ Resolved
109-114 (F/W/37)	*Skin and subcutaneous tissue disorders/ Erythema/ Facial redness*	2	5	Mild/ Not related	None	Recovered/ Resolved
	Skin and subcutaneous tissue disorders/ Pruritus/ Pruritus	2	5	Mild/ Not related	None	Recovered/ Resolved
	Skin and subcutaneous tissue disorders/ Swelling face/ Facial swelling	2	5	Mild/ Not related	None	Recovered/ Resolved

2.6.8.9. Post marketing experience

There are no post-marketing safety surveillance data.

There is experience from 6 cases of emergency use in the US (from 2007 – 2016) and 4 cases of Named Patient use in Europe (the first in Finland in 2009 and three (3) further cases during 2019 in Germany and Sweden). The limited safety information available is very difficult to interpret due to concomitant treatments and underlying conditions. These cases were as follows:

Emergency use in the US

- A 28-month-old male (10 kg) received tecovirimat orally for 14 days at a dose of 50 mg (2 days), 75 mg (2 days) and 100 mg (10 days) once daily.
- A 20-year-old male received treatment for 73 days with daily oral tecovirimat (400-1200 mg; total of nearly 75 g) and for 68 days with topical tecovirimat (39.7-1110 ng/mL).
- A 37-year-old female received tecovirimat orally for 14 days at a dose of 400 mg once daily.
- A 25-year-old female received tecovirimat orally for 14 days at a dose of 400 mg once daily.
- A 19-year-old male received tecovirimat for two months at a dose of 600 mg twice daily.
- A 26-year-old female received tecovirimat orally for 14 days at a dose of 600 mg twice daily.

Named Patient use in Europe:

- A 32-year-old female in Finland received tecovirimat orally for 14 days at a dose of 400 mg once daily for cowpox infection.
- A 32-year-old male in Germany received tecovirimat orally for nine (9) days twice daily (dose not specified) for cowpox infection.
- A 57-year-old female in Sweden received tecovirimat orally for four (4) months at a dose of 600 mg twice daily for cowpox infection. The dose was then increased to 800 mg twice daily. A month later, the dose was again increased to 1000 mg twice daily.
- A 34-year-old female in Germany received tecovirimat orally for seven (7) days at a dose of 400 mg twice daily for orthopoxvirus infection.

2.6.9. Discussion on clinical safety

The focus of the assessment of safety is SIGA-246-008, in which subjects received the final dose regimen of 600 mg BID for 14 days and the majority received this dose under the recommended fed conditions. Section 4.8 of the applicant's SmPC was initially based on AEs from SIGA-246-008. This was later revised to include data from another 78 subjects from SIGA-246-015 and to focus on ADRs.

It is noted that vomiting does occur on occasion (~2.5%). Given the importance of adequate dosing to prevent disease that carries a high fatality rate, section 4.2 now includes advice on re-dosing in case of vomiting.

ECGs obtained while dosing with 600 mg BID support the conclusions drawn from the TQT study.

The two deaths were unrelated to tecovirimat and there were no non-fatal SAEs.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

Additional safety data needed in the context of a MA under exceptional circumstances:

In order to further characterise the safety of tecovirimat in the treatment of smallpox, the MAH should conduct and submit the results of the open-label field study SIGA-246-021, upon the occurrence of a smallpox outbreak in the US.

The MAH should provide summary case report information for those cases of monkeypox, cowpox or complications due to replication of vaccinia that may occur in the European Union for which tecovirimat is used***.***

2.6.10. Conclusions on the clinical safety

Overall, the safety profile of 600 mg BID taken with food in uninfected subjects seems to be acceptable.

The CHMP considers the following measures necessary to address the missing safety data in the context of a Marketing Authorisation under exceptional circumstances:

Upon the occurrence of a smallpox outbreak in the US, the MAH should conduct and submit the safety results from:

- open-label field study SIGA-246-021

The MAH is expected to provide summary case report information for those cases of monkeypox, cowpox or complications due to replication of vaccinia that may occur in the European Union for which tecovirimat is used***.***

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 47: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Use in pregnancy and lactation

Summary of safety concerns	
	Use in immunocompromised subjects

2.7.2. Pharmacovigilance plan

The following Table outlines proposed additional pharmacovigilance activities in RMP version 1.0

Table 48: Summary of pharmacovigilance and risk minimisation measures

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
SIGA-246-021 (A Phase 4, Observational Field Study to Evaluate the Safety and Clinical Benefit in TPOXX® (Tecovirimat)-Treated Patients Following Exposure to Variola Virus and Clinical Diagnosis of Smallpox Disease) Planned	Observational field study to evaluate safety and clinical benefit in tecovirimat-treated patients following exposure to variola virus and clinical diagnosis of smallpox disease.	Missing information: Use in pregnancy and lactation Use in immunocompromised subjects	Start date Final report	Study will start with enrolling patient when the first case of smallpox is noted To be provided in annual re-assessment and no later than 12 months after the last administration of tecovirimat for the treatment of smallpox or last data collection in case of retrospective data collection.
Category 3 - Required additional pharmacovigilance activities				
None				

2.7.3. Risk minimisation measures

Table 49: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Use in pregnancy and lactation	Routine risk minimisation measures: *SmPC section 4.6* *PL section 2* *Pack size* *Legal status* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Targeted follow-up form* *Summary case report information of any cases involving pregnancy and lactation or immunocompromised patients in the following indications: monkeypox, cowpox and the treatment of complications due to replication of vaccinia virus following vaccination against smallpox* Additional pharmacovigilance activities: *Observational smallpox field study (*SIGA-246-021)
Use in immunocompromised subjects	Routine risk minimisation measures: *SmPC section 4.4* *PL section 2* *Pack size* *Legal status* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Targeted follow-up form* *Summary case report information of any cases involving pregnancy and lactation or immunocompromised patients in the following indications: monkeypox, cowpox and the treatment of complications due to replication of vaccinia virus following vaccination against smallpox* Additional pharmacovigilance activities: *Observational smallpox field study (*SIGA-246-021)

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 13.07.2018. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Labelling exemptions

None

2.9.3. Quick Response (QR) code

None requested.

2.9.4. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Tecovirimat SIGA (tecovirimat) is included in the additional monitoring list as:

- *It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU*
- *It is approved under exceptional circumstances [REG Art 14(8), DIR Art (22)]*

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

Tecovirimat is proposed for the treatment of orthopoxvirus disease (cowpox, monkeypox, smallpox and vaccinia complications) in adults and in paediatric patients weighing at least 13 kg.

The applicant requested consideration of the application under exceptional circumstances based on fact that the indication is encountered so rarely that it cannot reasonably be expected to provide comprehensive evidence in the present state of scientific knowledge, and it would be contrary to generally accepted principles of medical ethics to collect such information.

3.1.1. Disease or condition

Orthopoxviruses are large linear double-stranded deoxyribonucleic acid (DNA) viruses that replicate in the cytoplasm of cells and have a high degree of antigenic similarity. The orthopoxviruses that can cause disease in humans are:

- Variola virus (VARV), which causes smallpox and has been eliminated from global circulation;
- Monkeypox virus (MPXV);
- Cowpox virus (CPXV); and
- Vaccinia virus (VACV).

Smallpox is a serious, contagious, and often fatal infectious disease with an incubation period of 7-17 days. Prior to the worldwide eradication campaign, there were two clinical forms of smallpox, variola major and variola minor.

- Variola major represented the more severe and more common form of smallpox, with an extensive rash and high fever. There were four observed clinical variants of variola major smallpox: 1) ordinary (the most frequent type, >90% of cases); 2) modified (mild and occurring in previously vaccinated persons); 3) flat; and 4) haemorrhagic (both rare and very severe). Historically, variola major had an overall fatality rate of about 30%; however, flat and haemorrhagic smallpox is usually fatal.
- Variola minor was a less common presentation of smallpox, causing a much less severe disease, with death rates historically of 1% or less.

Monkeypox is endemic in central Africa and causes epizootic disease in humans. This virus is easily transmitted.

In 2003 a monkeypox outbreak occurred in the US caused by pet dealers, pet owners and veterinary care workers handling infected rodents imported from Africa, resulting in 37 human infections. Europe has also faced problems of monkeypox outbreaks in primate-holding facilities as well as transmission to the UK from people traveling from Nigeria. Worldwide, the incidence of MPXV infection has increased due to increased exposure to virus-infected animals through ecosystem degradation, changing population densities and fewer people having received smallpox vaccination.

Cowpox is endemic in many regions of the world and is maintained in the environment through infection of mammals, birds, domestic animals, cattle, and rodent hosts. Contact with these reservoirs by susceptible animals or people can lead to the onset of disease characterised by lesions mainly on

fingers, hands or face. Sequence analysis of virus isolates from human cases revealed a close association with VACV strains used during the smallpox eradication vaccination campaign.

VACV-based vaccines would be widely deployed in case of a worldwide emergency response to a smallpox outbreak. In case of such an event, drug treatment would be especially important for individuals who are too late in the incubation period to benefit from vaccination or in case of vaccine shortages. If in response to a smallpox outbreak the existing live VACV vaccines (such as ACAM2000) with replication capacity were to be used, the availability of an antiviral drug for the treatment of vaccinia complications would also be of potential importance.

3.1.2. Available therapies and unmet medical need

There is no antiviral agent approved in the EU for the prevention or treatment of orthopoxvirus diseases. Cidofovir has activity against orthopoxviruses but it is not licensed for this use and it has recognised safety issues.

Nevertheless, cidofovir mentioned as an option in some guidelines for management in case of a deliberate release of smallpox virus. Some EU countries have their own replication-competent VACV-based vaccines in storage. The only smallpox vaccine licensed via the centralised procedure in the EU is the MVA-based product Imvanex, which was approved under exceptional circumstances by the CHMP due to global eradication of smallpox.

While human zoonotic orthopoxvirus infections are rare, they are increasingly encountered outside their usual geographic range. This said, cases are still too sporadic, and in many instances, occur in regions where it is too difficult and/or too dangerous to conduct controlled clinical trials.

3.1.3. Main clinical studies

There were no clinical efficacy studies conducted because these are not feasible. The predicted efficacy of tecovirimat when dosed at 600 mg BID for 14 days is based on efficacy studies in animal models of orthopoxvirus disease. A comparison of tecovirimat exposures achieved in healthy human subjects to those observed in animal models of orthopoxvirus infection was conducted to support the dose regimens for treatment of children, adolescents and adults.

The clinical course of human smallpox infection resembles that of ectromelia (ECTV) infection of mice or rabbitpox (RPXV) infection of rabbits, where acute systemic infection results from inoculation with a small amount of virus at the periphery. In addition, intravenous MPXV infection of non-human primates closely mimics human smallpox from the point of the eruptive phase of disease, including fever and viraemia and the development of dermal lesions that progress in a manner identical to human smallpox.

While no single animal model is likely to be fully predictive of human disease outcome, either the use of multiple animal models using host adapted viruses or viruses that cause smallpox-like disease in a surrogate host are informative in assessing antiviral activity and predicting efficacy in humans.

To support a conclusion on efficacy and the clinical dose, the applicant identified some of the nonclinical efficacy studies, which used the final I form of tecovirimat as intended for the market, as being pivotal. These studies are summarised in the table.

Study No.	Type of Study	N	Objective(s)
Nonhuman Primate (cynomolgus monkey)			
FY10-087	PK in NHPs infected with MPXV; tecovirimat doses of 3, 10, and 20 mg/kg	24	PK and efficacy in NHPs who received 14 daily doses of tecovirimat or placebo from 4-17 days post-infection with MPXV
AP-09-026G	Repeat-dose efficacy study to determine the minimum effective therapeutic dose in NHPs infected with MPXV; tecovirimat doses of 0.3, 1, 3, and 10 mg/kg	27	Minimum effective dose of tecovirimat Form I for the treatment of MPXV in the lesional NHP model of smallpox, with tecovirimat or placebo treatment beginning on the day of onset of pox lesions in each animal and continuing for 14 days
SR10-037F	Efficacy of delayed tecovirimat treatment following lethal MPXV challenge in NHPs; tecovirimat dose of 10 mg/kg	21	Maximum delay post–MPXV challenge at which 14 daily doses of tecovirimat is effective at preventing mortality in NHPs
SR10-038F	Efficacy of 3, 5, 7, and 10 daily doses of tecovirimat 10 mg/kg in NHPs infected with MPXV	25	Minimum dose duration post–MPXV challenge at which tecovirimat is effective at preventing mortality in NHPs
Rabbit (New Zealand White rabbit)			
SR13-025F	PK in rabbits infected with RPXV; tecovirimat doses of 40, 80, and 120 mg/kg	24	PK and efficacy in rabbits who received 14 daily doses of tecovirimat from 4-17 days post-infection with RPXV
SR14-008F	Dose-response relationship in rabbits infected with RPXV; tecovirimat doses of 20, 40, 80, and 120 mg/kg	50	Minimum efficacious dose that provides maximal survival benefit in rabbits infected with RPXV receiving 14 daily doses of tecovirimat or placebo

KEY: MPXV = monkeypox virus; N = sample size; NHP = nonhuman primate; PK = pharmacokinetics; RPXV = rabbitpox virus

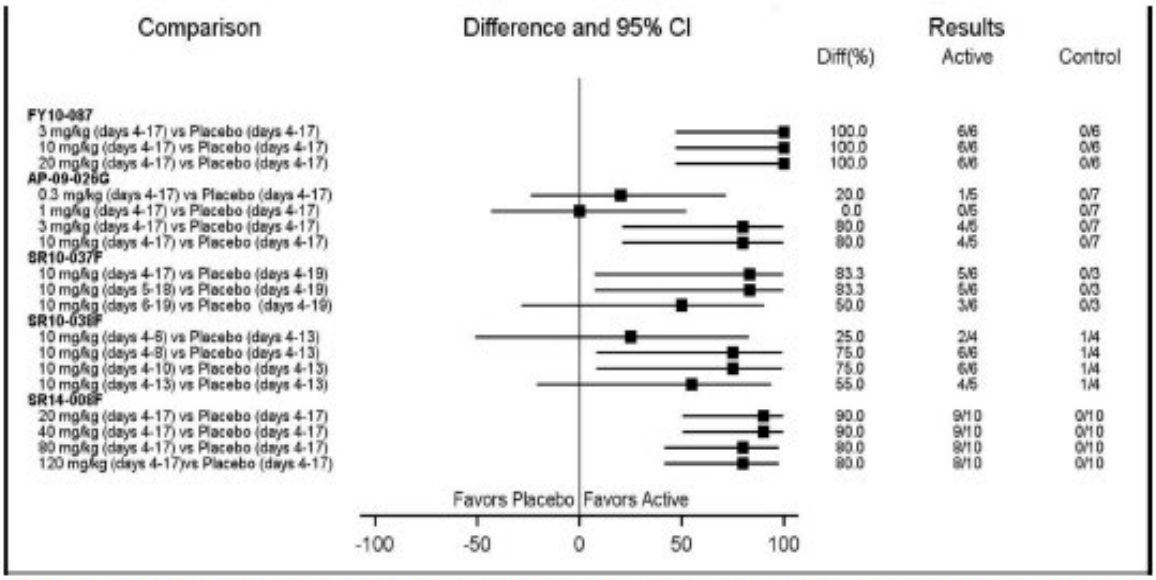
The applicant conducted a pivotal human PK study with the I form of tecovirimat given at the final recommended posology (SIGA-246-008). The PK data from this study were used to confirm the adequacy of the dose based on the most stringent pharmacodynamic target (PDT) obtained from NHPs. SIGA-246-008 was a double-blind study that compared tecovirimat 600 mg BID for 14 days vs. placebo in adults. The Lead-in cohort of 40 subjects compared tecovirimat PK when dosing was in the fed (within 30 min of a meal of ~ 600 kcal and 25 g fat) and fasted (no food or drink 2 h before or 2 h after dosing) states. Another 382 subjects were to be enrolled into the Expanded portion, of which 40 in the tecovirimat group were to be assessed for PK. Dosing of this cohort was in the fed state. Blood sampling was conducted to determine plasma concentrations of tecovirimat and the three major but inactive metabolites - M4, M5 and 4-trifluoromethyl-benzoic acid [TFMBA].

3.2. Favourable effects

The pivotal nonclinical efficacy studies used IV MPXV challenge in cynomolgus monkeys and ID RPXV challenge in NZW rabbits. Across the NHP studies, ≥3 mg/kg for 14 days starting on Day 4 after MPXV infection conferred significant protection against mortality. Treatment at 10 mg/kg was effective if started on Day 5 and at least 5 days of dosing was necessary to provide a survival advantage relative to placebo controls. Across the rabbit studies, ≥20 mg/kg oral tecovirimat for 14 days starting on Day 4 after RPXV infection conferred significant protection against mortality. Doses above these minimum effective doses did not confer a greater survival advantage in either animal model.

Species	Study No.	Tecovirimat Dose	Regimen (Days)	Survival Rate (n [%])	P-value[a]
Cynomolgus monkey	FY10-087	Placebo	4–17	0 (0)	--
		3 mg/kg	4–17	6 (100)	0.0012[b]
		10 mg/kg	4–17	6 (100)	0.0012[b]
		20 mg/kg	4–17	6 (100)	0.0012[b]
	AP-09-026G	Placebo	4–17	0 (0)	--
		0.3 mg/kg	4–17	1 (20)	0.2551
		1 mg/kg	4–17	0 (0)	1.0000
		3 mg/kg	4–17	4 (80)	0.0048[b]
		10 mg/kg	4–17	4 (80)	0.0048[b]
	SR10-037F	Placebo	4–19	0 (0)	--
		10 mg/kg	4–17	5 (83)	0.0160[b]
		10 mg/kg	5–18	5 (83)	0.0160[b]
		10 mg/kg	6–19	3 (50)	0.1241
	SR10-038F	Placebo	4–13	1 (25)	--
		10 mg/kg	4–6	2 (50)	0.3643
		10 mg/kg	4–8	6 (100)	0.0141[b]
		10 mg/kg	4–10	6 (100)	0.0141[b]
		10 mg/kg	4–13	4 (80)	0.0972
New Zealand White Rabbit	SR13-025F	40 mg/kg	4–17	7 (87.5)	--
		80 mg/kg	4–17	7 (87.5)	--
		120 mg/kg	4–17	8 (100)	--
	SR14-008F	Placebo	4–17	0 (0)	--
		20 mg/kg	4–17	9 (90)	0.0010[b]
		40 mg/kg	4–17	9 (90)	0.0010[b]
		80 mg/kg	4–17	8 (80)	0.0011[b]
		120 mg/kg	4–17	8 (80)	0.0011[b]

[a]P-value is from a 1-sided Boschloo test (with Berger-Boos modification of gamma = 0.001) compared with placebo.
[b]Denotes statistical significance at the 0.025 level.



NOTE: Five efficacy studies that included a placebo comparator are listed, with active treatment groups shown. The charted data show the percent difference in survival (Diff%) between the active treatment groups and the placebo comparator group for each study (black box symbols). The "whiskers" indicate 95% confidence intervals. The vertical line indicates no effect. The number of animals surviving versus the number treated (#surviving/#treated) in each active treatment group (Active) and placebo controls (Control) are listed on the right.

In NHPs, tecovirimat 10 mg/kg on Days 4-17 after MPXV infection conferred the greatest protection in terms of lesion formation and resolution.

Although 3 and 10 mg/kg doses conferred equivalent survival benefit, the 10 mg/kg dose decreased viral load to a greater extent and provided additional protection against morbidity. In addition, 10 mg/kg was associated with earlier viral clearance when start of treatment was delayed to Day 5. Daily dosing with 10 mg/kg for a minimum of 5 days was necessary to confer protection against viral load relative to placebo controls. Assessment of efficacy in subgroups of NHPs stratified by demographic variables revealed no significant differences between sexes or according to baseline body weight above or below the median of 3.45 kg.

The selection of the pharmacodynamic target to underpin human dose selection was based on the results of the six pivotal nonclinical efficacy studies. In the rabbit model, a target cut-off for C_{avg} of 185 ng/mL, corresponding to a 30 mg/kg dose, was determined to be the best predictor of survival. In the NHP model, maximal efficacy (i.e. based on survival plus reductions in lesion counts and viral loads) could be obtained with 10 mg/kg/day initiated on day 4 or 5 post-infection and given for at least 5 days. Median exposures after dosing at 10 mg/kg were AUC/WT of 2.67 mg•h/(L•kg) and $Cmin_{SS}$ of 204.52 µg/L.

When a conservative tecovirimat dose of 40 mg/kg in rabbits (versus 30 mg/kg) was used for a comparison of exposure relative to NHP dosed at 10 mg/kg, plasma concentrations were still lower in rabbits among both uninfected and infected animals. Therefore, exposure-response analyses based on the NHP model were considered more robust for the determination of effective doses in humans. Initially, the applicant's analyses suggested that 600 mg once daily in humans would provide plasma exposures observed with 12-14 mg/kg administered to infected NHPs. This NHP dose is well above the estimated effective dose for 50% rescue and also above 10 mg/kg, which gave complete survival. The final recommended adult dose of 600 mg BID provides predicted plasma exposures (including Cmin) for total and unbound tecovirimat that substantially exceed exposures in NHPs dosed at 10 mg/kg/day.

The duration of treatment in nonclinical studies is that proposed for humans. It has been based on expectation of inhibition of systemic virus dissemination by tecovirimat until development of sufficient neutralizing antibody to clear the virus. NHPs and rabbits were shown to mount such an immune response within this timeframe.

Five of the pivotal studies assessed persistence of efficacy over 11-39 days after treatment discontinuation. Across these studies, 3 animals died after conclusion of a full 14-day tecovirimat treatment regimen. Lesion counts and viral load also generally continued to improve post-treatment in surviving tecovirimat-treated animals.

No paediatric studies have been conducted and none is planned as per the PIP. From POPPK modelling, the applicant derived dose recommendations for use from 3 kg but doses for the <13 kg categories would involve fractions of capsule contents, which is not a feasible approach. Therefore, dosing recommendations for 3-12 kg will follow once a suitable paediatric dose form has been developed.

3.3. Uncertainties and limitations about favourable effects

Relevant to selecting a final dose to provide unbound tecovirimat concentrations that are considerably in excess of those achieved in NHPs when dosed with 10 mg/kg/day, the average percent binding of tecovirimat in mouse, rat, rabbit, dog, monkey and human plasma was 87.7, 95.8, 88.7, 90.6, 87.5 and 79.7%, respectively. Thus, at the same total tecovirimat plasma concentration in NHPs and humans, the proportion that is unbound would be slightly higher in humans. To compare unbound concentrations, the applicant calculated PK values using in-vitro protein binding estimates. Whilst these are calculated estimates only, the results as summarised below support a conclusion that unbound tecovirimat will be higher in humans dosed with 600 mg BID compared to NHPs given the effective dose of 10 mg/kg.

Table 50: Mean human and NHP drug exposures and human/NHP ratios (total and unbound)

	Treatment	%Protein Binding	C_{max} (ng/mL)	C_{min} (ng/mL)	AUC_{0-t} (ng.h/mL)	C_{avg} (ng/mL)
Human	1		1591	560	25876	924
NHP			809	193	8110	338
Human to NHP Ratio (Total)			2.0	2.9	3.2	2.7
Human Unbound		80	318	112	5175	185
NHP Unbound		87.5	101	24	1014	42
Human to NHP Ratio (Unbound)			3.1	4.6	5.1	4.4
Human	14		2209	690	30632	1271
NHP			1444	169	14352	598
Human to NHP Ratio (Total)			1.5	4.1	2.1	2.1
Human Unbound		80	442	138	6126	254
NHP Unbound		87.5	181	21	1794	75
Human to NHP Ratio (Unbound)			2.4	6.5	3.4	3.4

Furthermore, taking into account the additional data from a recent IV tecovirimat NHP study (246-TX-019), in which tremors were not observed at unbound plasma levels up to at least 1922 ng/mL, the human dose is expected to have an acceptable safety profile.

Table 51: Unbound exposures

Species	Study[a]	Dose	%Protein Binding	Max C_{max} (ng/mL)		Mean C_{max} (ng/mL)	
				Total	Unbound	Total	Unbound
Human	SIGA-246-008	600 mg BID	80	4460	892	2209	442
Dog	246-TX-015	100 mg/kg	90.6	5575	524	5575	524
NHP	IITRI 2083 003-001 SN6 3-month Study	300 mg/kg	87.5	6720	840	5303	663
NHP	246-TX-019	30 mg/kg 6h infusion	87.5	15375	1922	13,883	1735
Mouse	IITRI 2083 003-001 SN3 3-month study	1000 mg/kg	87.7	64900	7983	64900	7983
Paediatric BWt 13 kg	Simulated data	50 mg BID	75[b]	5250	1313[c]	3477	869[c]
Paediatric BWt 25 kg	Simulated data	100 mg BID	75[b]	4449	1112[c]	3200	800[c]

[a]Oral administration unless indicated
[b]Plasma protein ratio of adult:kid = 59/63 (Sethi et al, 2016; Section 5.4)
[c]Simulated C_{max} based on total plasma protein binding

The treatment duration of 14 days was associated with increased survival in NHPs dosed at ≥ 3 mg/kg and is theoretically supported by the proposed mechanism of action of tecovirimat. Whilst it is not possible to state a definitive interval post-exposure in which treatment should be started, the SmPC advises that treatment should start as early as possible after the diagnosis is made.

In conclusion, there will always be some uncertainties regarding the efficacy of tecovirimat when used to treat the specified poxviruses at the recommended dose since it may never be possible to obtain confirmative clinical efficacy data.

The MAH should provide summary case report information for those cases of monkeypox, cowpox or complications due to replication of vaccinia that may occur in the European Union for which tecovirimat is used. The applicant should provide summary case report information for those cases of monkeypox,

cowpox or complications due to replication of vaccinia that may occur in the European Union for which tecovirimat is used. All cases of treated patients in the indications (monkeypox, cowpox or the treatment of complications due to replication of vaccinia virus following vaccination against smallpox) and in particular pregnant/lactating women and immunosuppressed patients need to be provided and discussed in context healthy individuals whom have taken Tecovirimat SIGA and other patients who were either pregnant and lactating or immunocompromised

In addition, in order to further characterise the efficacy and safety of tecovirimat in the treatment of smallpox, the MAH should conduct and submit the results of the open-label field study SIGA-246-021, upon the occurrence of a smallpox outbreak as per protocol.

3.4. Unfavourable effects

The focus of the assessment of safety is SIGA-246-008, in which 359 subjects received the final dose regimen of 600 mg BID for 14 days and the majority received this dose under the recommended fed conditions. Another 78 subjects received 600 mg BID alone for 14 days in SIGA-246-015 and some safety data are available from other Phase 1 studies in which the total daily dose was close to or exceeded 1200 mg.

In SIGA-246-008, 164 subjects (36.5%) experienced at least one AE and 19.2% had at least one AE considered treatment-related. The AEs most commonly reported mapped to the SOCs of nervous system disorders (18.9%) and gastrointestinal disorders (13.6%), with higher rates in the tecovirimat vs. placebo group. The most commonly reported AEs by PT were headache (17.0% tecovirimat and 14.4% placebo) and nausea (5.6% for both groups). Vomiting was reported for ~2.5%. Given the importance of adequate dosing to prevent disease that carries a high fatality rate, advice has been added to the SmPC regarding re-dosing in case of vomiting.

Five (1.1%) subjects (4 tecovirimat) experienced a Grade 3 or higher TEAE. Two in the tecovirimat group had a severe headache (definitely related), one had severe osteoarthritis (possibly related) and one had a fatal pulmonary embolism (unrelated). All of the events resolved within 1 to 4 days from time of onset. Overall, 19.2% of subjects experienced at least one related TEAE: 19.8% of subjects in the tecovirimat 600 mg group and 16.7% in the placebo group. The most commonly reported in the tecovirimat group were headache (12.3%) and nausea (4.5%). In the placebo group, the most commonly reported related TEAEs were headache (7.8%), nausea (4.4%), fatigue (3.3%), diarrhoea (2.2%) and constipation (2.2%).

There have been two deaths in the clinical programme, one of which occurred in SIGA-246-008. A subject in the tecovirimat group experienced a fatal SAE of pulmonary embolism on Day 21 after completing the 14-day dosing period with no other TEAEs. This was considered unrelated to study drug. This was also the only SAE in SIGA-246-008, SIGA-246-015 and the multiple dose studies SIGA-246-002 and -004. The other death was in a subject who received tecovirimat 600 mg in SIGA-246-013 who died from the SAEs of cholecystitis, sepsis, acute myocardial infarction and cardiac arrest, not considered to be drug-related.

In SIGA-246-008, the haematology and chemistry mean values were mostly within the reference ranges for all analytes and generally similar between treatment groups. ECGs obtained while dosing with 600 mg BID support the conclusions drawn from the TQT study.

In SIGA-246-008, there were 8 subjects (1.8%) who discontinued study drug because of AEs, of which 6 (1.7%) were in the tecovirimat group. TEAEs leading to study drug discontinuation reported by more than 1 subject were nausea (2 tecovirimat) and pyrexia (2 tecovirimat). Most AEs that led to study drug discontinuation were considered drug-related and most were mild or moderate in intensity.

There are no post-marketing safety surveillance data.

3.5. Uncertainties and limitations about unfavourable effects

The most important limitation of the safety database is that all of the data come from uninfected subjects. Based on the nonclinical studies, tecovirimat PK is not expected to be clinically significantly different between uninfected and infected subjects who can take it orally with food. That being the case, the safety profile should also not be substantially different between populations. The number exposed to the final dose regimen is rather modest but acceptable in light of the intended usage and proposal for approval under exceptional circumstances.

Section 4.8 of the applicant's SmPC was updated to include data from SIGA-246-008 and -015. It was also updated to reflected ADRs rather than AEs.

3.6. Effects Table

Table 52: Effects table for tecovirimat in the treatment of orthopoxvirus disease.

Effects Table for tecovirimatEffect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects – not applicable; clinical efficacy is predicted from nonclinical data						
Unfavourable Effects – tecovirimat 600 mg BID taken with food						
	Type of AE/ADR	n/N (%)	Tecovirimat	Placebo	Limited denominator and all healthy subjects	SIGA-246-008
TEAEs	All	%	134/359 (37.3%)	30/90 (33.3%)		
	GI disorders		54/359 (15%)	7/90 (7.8%)		
ADRs			71/359 (19.8%)	15/90 (16.7%)		
SAEs			1/359 (0.3%)	0		
AEs leading to withdrawal			6/359 (1.7%)	2/90 (2.2%)		
Deaths			1/359 (0.3%)	0		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Tecovirimat is intended for treatment of smallpox, which is currently eradicated from global circulation. If there should ever be an accidental or deliberate release of virus, the fatality rates can be expected to be very high. Furthermore, with very little remaining natural or vaccine-induced immunity in the global population, considerable numbers of cases and deaths can be expected before reintroduction of

vaccination controls the epidemic. In such a setting, the potential benefit of any antiviral agent with predicted ability to treat smallpox could be profound.

For the other poxviruses included in the proposed indication statement, these can all be serious and potentially fatal infections although they occur very rarely in humans. There are no vaccines against monkeypox. Vaccinia virus vaccines intended to prevent smallpox would be expected to prevent cowpox but there has been no use of these vaccines since the early 1980s. The use of tecovirimat to manage these infections when they do occur can be supported from the available data.

The complications of vaccination with vaccinia vaccines can be life-threatening. Theoretically, tecovirimat may be able to treat at least some of these complications. It is not foreseen that vaccinia vaccines would be used again unless individual countries wish to continue to vaccinate a vanguard of front-line health care workers and/or there is an accidental or deliberate release event. Nonetheless, with no licensed alternative, and due to the inherent toxicity of cidofovir, there is no *a priori* objection to inclusion of this type of possible use in the indication statement.

While tecovirimat has some unwanted gastrointestinal effects, the safety profile as documented in a limited number of healthy subjects does not raise any major concerns.

3.7.2. Balance of benefits and risks

Based on nonclinical efficacy, human PK and PK-PD to support the clinical posology, the predicted benefit of tecovirimat can be assumed to outweigh the risks of treatment with 600 mg BID.

3.7.3. Additional considerations on the benefit-risk balance

Marketing authorisation under exceptional circumstances

As comprehensive data on the product are not available, a marketing authorisation under exceptional circumstances was requested by the applicant in the initial submission.

The CHMP considers that the applicant has sufficiently demonstrated that it is not possible to provide comprehensive data on the efficacy and safety under normal conditions of use, because the applied for indication is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence in the present state of scientific knowledge, and it would be contrary to generally accepted principles of medical ethics to collect such information:

- Orthopoxvirus diseases are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence of clinical safety and efficacy data in patients and,
- It would be contrary to generally accepted principles of medical ethics to collect such information.
    - Smallpox has been eradicated in humans, and as such, the disease can no longer be studied or treated in humans.
    - The occurrence of cowpox is a rare event worldwide, with fewer than 200 human cases reported since 1969.
    - Vaccinia complications of smallpox infection are very rare. Vaccinia virus vaccines are now used very rarely to vaccinate "vanguard cohorts" in case of a deliberate release.
    - Monkeypox is a rare disease that occurs mostly in central and western Africa. There has only been one outbreak ever reported elsewhere in the world, and this occurred in the United States in early June 2003, when several persons became ill after contact with pet

prairie dogs with suspected monkeypox. However, the recent outbreak in Nigeria led to two UK citizens acquiring monkeypox in the country and one healthcare worker contracted monkeypox from one of the travellers.

All cases of treated patients in the indications (monkeypox, cowpox or the treatment of complications due to replication of vaccinia virus following vaccination against smallpox) and in particular the applicant should provide summary case report information for those cases of monkeypox, cowpox or complications due to replication of vaccinia that may occur in the European Union for which tecovirimat is used. All cases of treated patients in the indications (monkeypox, cowpox or the treatment of complications due to replication of vaccinia virus following vaccination against smallpox) and in particular pregnant/lactating women and immunosuppressed patients need to be provided and discussed in context healthy individuals whom have taken Tecovirimat SIGA and other patients who were either pregnant and lactating or immunocompromised, pregnant/lactating women and immunosuppressed patients will be provided and discussed in context of healthy individuals whom have taken Tecovirimat SIGA and other patients who were either pregnant and lactating or immunocompromised.

In addition, in order to further characterise the efficacy of tecovirimat in the treatment of smallpox, the MAH should conduct and submit the results of the open-label field study SIGA-246-021, upon the occurrence of a smallpox outbreak as per protocol.

Therefore, recommending a marketing authorisation under exceptional circumstances is considered appropriate.

3.8. Conclusions

The overall benefit/risk balance of Tecovirimat SIGA is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Tecovirimat SIGA is favourable in the following indications:

Tecovirimat SIGA is indicated for the treatment of the following viral infections in adults and children with body weight at least 13 kg:

- *Smallpox*
- *Monkeypox*
- *Cowpox*

Tecovirimat SIGA is also indicated to treat complications due to replication of vaccinia virus following vaccination against smallpox in adults and children with body weight at least 13 kg (See sections 4.4 and 5.1).
Tecovirimat SIGA should be used in accordance with official recommendations.

The CHMP therefore recommends the granting of the marketing authorisation under exceptional circumstances subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Specific Obligation to complete post-authorisation measures for the marketing authorisation under exceptional circumstances

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	**Due date**
Non-interventional post-authorisation studies: SOB 1. SIGA-246-021: A Phase 4, Observational Field Study to Evaluate the Safety and Clinical Benefit in TPOXX® (Tecovirimat)-Treated Patients Following Exposure to Variola Virus and Clinical Diagnosis of Smallpox Disease) In order to further characterise the efficacy and safety of tecovirimat in the treatment of smallpox, the MAH should conduct and submit the results of the open-label field study SIGA-246-021, upon the occurrence of a smallpox outbreak (as per protocol).	To be provided in annual re-assessment and no later than 12 months after the last administration of tecovirimat for the treatment of smallpox or last data collection in case of retrospective data collection

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that tecovirimat is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.