26 March 2026
EMADOC-1700519818-2986900-Corr.[1]
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procedure under Article 20 of Regulation (EC) No 726/2004

Tecovirimat SIGA

INN: tecovirimat

Procedure number: EMA/REF/0000287477

Note:

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

[1] 21 April 2026

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1. Information on the procedure

In the context of the third annual re-assessment of the marketing authorisation under exceptional circumstances for Tecovirimat SIGA (EMA/S/0000248804), a preliminary review of the available data from the completed PALM007[2] and the STOMP[3] trials of tecovirimat for the treatment of mpox suggested that the studies did not meet their primary or secondary endpoints. While full datasets were not yet available, this new information raised concerns regarding a possible lack of efficacy of Tecovirimat SIGA in the mpox indication. Furthermore, similar concerns regarding the other authorised indications could not be ruled out.

On 21 July 2025, high level results of the UNITY trial evaluating tecovirimat with a similar study design to STOMP were published[4] and appeared to be consistent with those from STOMP and PALM007. Other mpox clinical trials with tecovirimat were ongoing or recently completed, but results were not yet available from these studies.

The findings from these emerging data needed to be reviewed, taking into account all available data, to determine whether there was an impact on the benefit-risk balance of Tecovirimat SIGA in the authorised indications.

On 23 July 2025 the EC therefore triggered a procedure under Article 20 of Regulation (EC) No 726/2004 and requested the CHMP to assess the impact of the above concerns on the benefit-risk balance of Tecovirimat SIGA and to issue a recommendation on whether the relevant marketing authorisation should be maintained, varied, suspended or revoked.

2. Scientific discussion

2.1. Introduction

Tecovirimat inhibits the activity of the orthopoxvirus VP37 protein, which is encoded by a highly conserved gene 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 and long-range dissemination of virus.

On 6 January 2022, Tecovirimat SIGA was granted a marketing authorisation under exceptional circumstances pursuant to Article 14(8) of Regulation (EC) No. 726/2004 for the treatment of smallpox, mpox (previously referred to as monkeypox, while the virus that causes mpox continue to be referred to as monkeypox virus (MPXV)), cowpox, and complications due to replication of vaccinia virus following vaccination against smallpox, in adults and children with body weight at least 13 kg.

The benefits of Tecovirimat SIGA in humans were predicted from studies in animal models of orthopoxvirus disease (four in cynomolgus monkeys and two in New-Zealand White rabbits). These data indicated that it should be used as soon as possible after diagnosis, in accordance with official recommendations. Human pharmacokinetic (PK) and pharmacodynamic (PD) supported the clinical posology. At the time of the initial assessment, no clinical studies were conducted due to the nature of the viruses to be treated and their limited circulation in humans.

In that regard, specific obligations to complete two post-authorisation measures were imposed. One of these measures consists in the provision of yearly updates on any new information concerning the

[2] https://www.nih.gov/news-events/news-releases/antiviral-tecovirimat-safe-did-not-improve-clade-i-mpox-resolution-democratic-republic-congo
[3] https://www.nih.gov/news-events/news-releases/nih-study-finds-tecovirimat-was-safe-did-not-improve-mpox-resolution-or-pain
[4] https://mpx-response.eu/large-international-trial-unity-reports-no-clinical-benefit-from-tecovirimat-for-mpox-resolution/

safety and efficacy of tecovirimat in its authorised indications (SOB002). These updates were provided in the context of the annual reassessments. No new information is currently available in relation to the other specific obligation to submit results of an open-label controlled phase 4 trial upon the occurrence of a smallpox outbreak (SOB001).

In the third annual re-assessment (EMA/S/0000248804) new efficacy data emerged. High-level results of the completed PALM007 and the STOMP randomized, placebo-controlled, double-blind trials of tecovirimat for the treatment of mpox, both sponsored by the National Institutes of Health's (NIH) and National Institute of Allergy and Infectious Diseases (NIAID), were published in August 2024 and December 2024 respectively. The results of PALM007 were further published in the New England Journal of Medicine (NEJM) in April 2025 (PALM group, 2025)[5]. A preliminary review of the available data suggested that the studies did not meet their primary endpoint, as tecovirimat did not significantly reduce the number of days to lesion resolution in patients with mpox compared to placebo. It also appeared that in both trials there was no treatment benefit with respect to the secondary endpoints (e.g. depending on the trial: pain reduction, time to lesion healing and mortality).

In these studies, tecovirimat was well-tolerated with no drug-related serious adverse events.

Additional analyses were planned to better assess outcomes observed in the studies. These analyses included whether there were any significant differences in clinical outcomes by days of symptoms prior to enrolment, severity of clinical disease, patient characteristics (people with compromised immune systems, children, and people who are pregnant are especially vulnerable to severe mpox regardless of the virus clade), or the genetic variant of MPXV being treated.

While full datasets were not yet available, this new information raised concerns regarding a possible lack of efficacy of Tecovirimat SIGA in the mpox indication. Furthermore, considering that the majority of studies underlying the granting of the marketing authorisation in the authorised indications for Tecovirimat SIGA were conducted in cynomolgus monkeys, similar concerns regarding the other three authorised indications could not be ruled out.

On 21 July 2025, high level results of the UNITY trial evaluating tecovirimat with a similar study design to STOMP were published and appeared to be consistent with those from STOMP and PALM007. It was noted that other non-MAH sponsored mpox clinical trials with tecovirimat were ongoing or recently completed (e.g. PLATINUM Canada and UK, EPOXI(EU)). Results from these studies were not yet available.

In view of the above, a procedure under Article 20 of Regulation (EC) No 726/2004 was initiated to review the findings from these emerging data and, taking into account all available data, their impact on the benefit-risk balance of Tecovirimat SIGA in its authorised indications.

The total worldwide exposure to tecovirimat is approximately 11,000 patients. In the European Union, it is marketed through the European Commission Health Emergency Preparedness and Response Authority in Austria, Belgium, Cyprus, France, Luxembourg and Spain. It is also available under compassionate use or named patient use in Finland, Sweden and Germany for cowpox only. It has also been sold or supplied through compassionate use in Greece, Ireland, Italy, Malta, Netherlands, Norway and Portugal.

Two distinct strains of MPXV have existed in different geographic regions, clade I and clade II which is less virulent. More recently, each clade was found to have subclades (clades Ia and Ib, and clades IIa and IIb). Analyses revealed that the vast majority of the 2022 global outbreak viruses was clade IIb.

[5] PALM007 Writing Group. Tecovirimat for Clade I MPXV Infection in the Democratic Republic of Congo. N Engl J Med. 2025 Apr 17;392(15):1484-1496.

The MAH had data sharing agreements in place with the sponsors from six randomized controlled trials (PALM007, STOMP, PLATINUM-UK, PLATINUM-CAN, UNITY, and EPOXI, see Table 1), as well as the Central African Republic (CAR) expanded access protocols (EAP) and the World Health Organization (WHO)-led "monitored emergency use of unregistered and investigational interventions" (MEURI) observational registry study. However, no agreements were established with the U.S. Centers for Disease Control and Prevention (CDC) EAP or the MOSAIC observational study. No raw data were available to the MAH from these studies, as well as from the CAR EAP, though manuscripts have been published. Data from PLATINUM Canada, EPOXI(EU) was not yet available to the MAH, however considering the low recruitment (EPOXI (n=13) and PLATINUM Canada (n=37)), these are not expected to bring significant new information. No information or data was available from MEURI either.

For the remaining four randomised controlled trials (RCTs), the final complete dataset and a publication were available for PALM007 and ad hoc soft locked raw data and subsequently a publication for STOMP (Zucker, 2026)[6]. More limited data were available from UNITY (topline summary results) and PLATINUM-UK (unpublished manuscript and published basic results[7]). While the protocols of all trials were available, CSRs were not (nor expected to be) available for any trial.

The final data sets from UNITY are anticipated in July 2026 and will bring some information on patients with HIV and suppressed CD4 counts. The mpox Clade IIb trials (STOMP, UNITY and PLATINUM) are participating in the Individual Participant Data Meta-Analysis (IPDMA) being conducted by the EPOXI trial investigators. As UNITY trial results are not expected until July 2026, any meta-analysis will be after this date. While this conjoined analysis may enable more statistical confidence in the analyses, it is unlikely to significantly change the overall interpretation of the RCT outcomes.

In the present review, the CHMP considered all available data, including from randomised controlled trials (PALM007, STOMP, UNITY, PLATINUM UK), access programmes (CAR and CDC) and an observational study (MOSAIC), PK data, preclinical efficacy data (in vitro and in vivo, including new interim results of a Clade II intravenous (IV) MPXV challenge in non-human primates (NHPs)) and the literature. The CHMP also considered the views expressed by the Scientific Advisory Group (SAG) on Vaccines and Therapies for Infectious Diseases at a meeting held during the procedure. This procedure was also discussed by the Emergency Task Force (ETF) in the context of its public health threats activities. A summary of the most relevant information is included below.

Table 1. Summary data from the randomised controlled trials of tecovirimat in the treatment of mpox

Study	Clade	Time to active lesion resolution		
		Tecovirimat	Placebo	Hazard ratio/ risk ratio
		Median (IQR)		
EPOXI	II	-	-	-
PALM007	I	N = 289 7 days (7-8 days)	N = 295 8 days (7-9 days)	HR 1.13 (95% CI 0.97 - 1.31) p = 0.14
PLATINUM-CAN	II	-	-	-
PLATINUM-UK	II	N = 18 6 days (4–7 days)	N = 17 6 days (4–7 days)	RR 0.93 (95% CI 0.42 - 2.02) p = 0.85
STOMP	II	N = 225	N = 111	HR 0.98 (95% CI 0.74

[6] Zucker J, Fischer WA 2nd, Zheng L, McCarthy C, Saha PT, Javan AC, et al; STOMP/A5418 Investigators. Tecovirimat for the Treatment of Mpox. N Engl J Med. 2026 Feb 26;394(9):884-895.
[7] https://www.isrctn.com/editorial/retrieveFile/ef8b52b3-bc95-414f-8aaa-d1b46122455e/42440

Study	Clade	Time to active lesion resolution		
		Tecovirimat	Placebo	Hazard ratio/ risk ratio
		Median (IQR)		
		By day 29, 155 achieved clinical resolution of skin lesions (69%)	By day 29, 78 achieved clinical resolution of skin lesions (70%)	- 1.31) p = 0.89
UNITY	II	N = 223 13 days (8-9 days)	N = 223 13 days (8-9 days)	-

2.2. Data on efficacy

2.2.1. Clinical aspects

2.2.1.1. PALM007

Study characteristics

PALM007 was a randomised, placebo-controlled, double-blind study evaluating the safety and efficacy tecovirimat in adults and children with laboratory-confirmed mpox (MPXV Clade I) and at least one active lesion, at two study sites in the Democratic Republic of Congo (DRC). Patients were randomly assigned to receive oral tecovirimat or placebo (1:1 via block randomisation, stratified by study site and days from onset of prodromal symptoms ≤7 days or >7 days), each administered in the hospital with standard-of-care (SOC) treatment for 14 days. Patients were followed for 28 days with an optional visit at Day 59 for long-term assessment. The study included 597 patients across a wide age range, but primarily in paediatric patients. At baseline, 65% of patients had severe or grave disease, defined as more than 100 lesions.

The primary endpoint was time to lesion resolution; defined as the number of days from randomisation until all skin lesions were scabbed, desquamated, or healed.

Results

Tecovirimat did not significantly reduce the number of days to lesion resolution in patients with mpox caused by Clade I MPXV. The stratified competing-risks hazard ratio (HR) for days to lesion resolution was 1.13 (95% confidence interval [CI], 0.97 - 1.31) p = 0.14, with an estimated one-day improvement in the median days to resolution with tecovirimat as compared with placebo (7 days vs. 8 days). Results were similar when patients were stratified according to the timing of symptom onset; the competing-risks hazard ratio was 1.16 (95% CI, 0.98 to 1.37) for patients with symptom onset within 7 days before randomisation and 1.00 (95% CI, 0.71 to 1.40) for patients with onset more than 7 days before randomisation.

Several baseline characteristics were associated with slower lesion resolution, including higher lesion count; positive polymerase chain reaction (PCR) results for MPXV in oropharyngeal or skin-lesion samples; lower PCR cycle-threshold values for blood, oropharyngeal, and skin-lesion samples; the presence of fever or mouth sores; and abnormally high aspartate aminotransferase levels and white-cell counts. Age, sex, days since symptom onset, malnutrition status, and positivity for malaria at baseline were not associated with slower resolution. Adjustments for each characteristic did not alter conclusions about treatment efficacy.

A prespecified subgroup analysis of treatment response by site showed evidence of faster lesion resolution among Kole patients receiving tecovirimat than among those receiving placebo HR 1.59 (95% CI 1.15 to 2.21), but not in Tunda. Models that adjusted for baseline imbalances in lesion counts

and PCR cycle-threshold values for blood, oropharyngeal, and skin-lesion samples were explored. With these adjustments, no interaction of treatment effect with site was observed.

Further analysis of the data was conducted looking at the time to symptom resolution depending on the time from symptom onset to initiation of treatment. A trend was observed favouring tecovirimat over placebo, in particular in those who received treatment within 4 days of symptom onset HR 1.30 (95% CI 0.97–1.73). This trend remained evident in patients starting treatment within 5-7 days of symptom onset HR 1.12 (95% CI 0.89-1.42) but was reduced in those starting tecovirimat treatment 7 or more days after symptom onset HR 1.03 (95% CI 0.72–1.48).

Likewise, a trend was observed favouring a 1-day faster resolution of lesions in patients treated with tecovirimat compared to patients treated with placebo in a subgroup analysis in patients with >100 lesions (severe or grave disease) HR 1.20 (95% CI 0.98-1.48).

In an attempt to identify which patients demonstrated a benefit based on timing from symptom onset to treatment, the MAH divided the patients into 4 subgroups. In a longitudinal analysis of lesion count in a prespecified target region (a single arm and leg (including the palm and sole of the foot)) and presenting the mean +/- standard error of the mean (SEM) by treatment arm for all patients for each study day, on treatment days 6-11, and to a greater extent on days 7-10 (nominal $p<0.001$), lesion counts were lower in tecovirimat treated patients than in patients who received placebo. For the patients in the 1st quartile (≤ 4 days from symptom onset to treatment) lesion counts were lower in tecovirimat treated patients than in patients who received placebo on treatment days 6-11, and to a greater extent on days 7-10 ($p<0.001$). The data for quartile 2 (=5 days) also demonstrated nominally statistically significant lower lesion counts for tecovirimat treated patients on treatment days 6-7, though p-values were not as low as quartile 1 due, in part, to smaller sample sizes. No significant differences were observed in quartile 3 (6-7 days) or quartile 4 (> 7 days). The MAH repeated the lesion analysis breaking the entire patient population into 2 groups, those treated ≤ 5 days and those treated >5 days from symptom onset. For the patients treated ≤ 5 days (approximately half of the PALM007 population), lesion counts were lower in tecovirimat treated patients than in patients who received placebo on treatment days 5-11, and especially on days 6-10 ($p<0.001$).

The same longitudinal lesion count data was also analysed using subgroups based on the WHO severity for baseline lesion count. Lesion counts were lower in tecovirimat treated patients than in patients who received placebo on treatment days 6-11, and to a greater extent on days 7-10 (nominal $p<0.001$). The effect was more marked in patients with baseline lesion count ≥100, for which counts were lower in tecovirimat treated patients than in patients who received placebo on treatment days 5-12, especially for patients treated on days 5-10 (nominal $p<0.001$).

Discussion

The primary analysis of the PALM007 trial found that tecovirimat did not significantly reduce the time to lesion resolution in patients with Clade I mpox.

Time from symptom onset to initiation of treatment was based on patient self-reporting of when mpox-related symptoms began. The PALM007 protocol did not require further specification regarding which symptoms were first noted or when lesions initially appeared, i.e. standardised criteria for defining the first symptom or lesion appearance were absent. This introduces recall bias and variability in defining "early treatment," potentially misclassifying patients and weakening subgroup analyses. Of note, unlike other studies conducted in mpox outbreaks, e.g. STOMP, patients were hospitalised during the treatment period for PALM007, facilitating every other day supervised sample collection. This most likely contributed to more reliable data collection in support of the study's objectives.

In the DRC, where malaria is endemic and its symptoms may overlap with the prodromal phase of mpox, it is likely that the first clearly distinguishable symptom reported by patients would be the appearance of lesions.

Given that the viraemic peak in Clade I mpox is believed to occur slightly before lesion onset and given our current understating of tecovirimat's mode of action in mpox, administration of tecovirimat after the point of lesion onset was unlikely to offer significant clinical benefit.

Secondary endpoints included time to PCR negativity in blood, oropharyngeal, and lesion swabs, as well as viral load slope analyses. These virologic measures were more closely aligned with tecovirimat's mechanism of action. Of note however, virologic measures are not validated pharmacodynamic markers of efficacy and their clinical relevance is questioned.

The planned timing of tecovirimat administration in relation to the poorly specified (and recorded) symptom onset is, therefore, the principal weakness of the PALM007 study design. However, this limitation is not unexpected, given that the study was modelled on an observational investigation of the natural clinical history of mpox.

Overall, while the endpoints were appropriate for a severe, hospital-based cohort, they were not optimal to capture early antiviral effects. The trial's design, requiring visible lesions for enrolment, meant most patients may have been past peak viraemia, thus, limiting the ability to demonstrate efficacy.

Exploratory analyses suggest potential antiviral activity, particularly in oropharyngeal viral load reduction and in specific subgroups such as younger patients, those with severe diseases, and those without malnutrition. However, the study's design, requiring visible lesions for enrolment, meant most patients were randomized after peak viraemia, limiting the ability to detect early antiviral effects consistent with tecovirimat's mechanism of action.

The MAH conducted additional post-hoc analyses, including longitudinal lesion count modelling and further subgroup evaluations (description of lesion progression longitudinally was a pre-specified exploratory objective, however these analyses by subgroups are not included in the protocol or statistical analysis plan (SAP)). These analyses showed lower lesion counts in patients treated with tecovirimat, particularly in patients treated earlier (≤4–5 days from symptom onset) and in those with more severe baseline lesion burden (≥100 lesions). When broken down into subgroups, patients treated ≤4 days and 5 days from symptom onset demonstrated statistically significant lower lesion counts on treatment days 6-11, and days 6-7 for the tecovirimat arm compared to the placebo arm respectively. For patients treated 6-7 days and >7 days from symptom onset, there was no difference between treatment arms at any time. When analysed by severity of lesion count, patients with mild (<25) or moderate (25-99) baseline lesion counts demonstrated statistically significant lower lesion

counts on treatment days 2-4 and 7-10 for the tecovirimat arm compared to the placebo arm respectively. The tecovirimat treatment effect was even more pronounced in patients with severe (100-250) and grave (>250) baseline lesion counts who demonstrated statistically significant lower lesion counts on treatment days 5-12 for the tecovirimat arm compared to the placebo arm respectively.

However, these findings arise from post-hoc, non-prespecified analyses and were not supported by statistically significant effects in the primary endpoint of the trial. Further, the PALM007 study lesions were measured over a target area rather than full body lesion counts. While overall, this is not expected to significantly impact interpretation of the trial results, it does lead to a further uncertainty about the inferred full body results. As such, while the additional analyses are suggestive of a possible treatment effect in certain subgroups, their clinical relevance has not been established; they remain exploratory in nature and cannot support conclusions regarding efficacy in the mpox indication.

2.2.1.2. STOMP

Study characteristics

STOMP was a Phase 3, randomised, placebo-controlled, double-blind study, with a separate open label arm for high-risk patients, to assess the safety and efficacy of tecovirimat oral capsules administered for 14 days for the treatment of mpox in adult and paediatric patients. Patients with at least one active (not yet scabbed) skin lesion, mouth lesion, or proctitis with or without visible ulcers, and laboratory-confirmed or presumptive MPXV clade II infection were included in the study. Randomisation was stratified by duration of symptoms (≤ 5 or > 5 days) and remote vs in-person enrolment and was balanced by site. 413 patients were randomised to receive either tecovirimat or placebo and 266 were assigned to receive open label tecovirimat. The majority of patients were cisgender male (≥ 97%). 263 patients (76%) opted for in-person visits while 81 patients (24%) were followed remotely. At baseline, the median symptom duration was 8 days in both treatment arms.

The primary endpoint of the study was time to clinical resolution defined as all skin lesions being scabbed, desquamated, or healed, and all visible mucosal lesions being healed. Patients self-monitored lesions daily from enrolment (day 1) through day 29, with self-reports of resolution confirmed during an in-person or remote visit.

Results

By day 29, 177 of 255 patients (79%) in the tecovirimat arm and 90 of 111 (81%) in the placebo arm achieved clinical resolution of skin lesions. The estimated cumulative incidence of clinical resolution was 83% (95% CI, 77% - 87%) for tecovirimat and 84% (95% CI, 76% - 90%) for placebo (subdistribution hazard ratio [sHR], 0.98 [95% CI, 0.74 - 1.31] p = 0.89). In line with these results, the trial closed early for futility following the data and safety monitoring board (DSMB) recommendation following the second interim analysis.

Tecovirimat did not lead to faster resolution of mpox skin lesions and did not improve pain control in those with mpox and did not lead to statistically significant reductions in MPXV detection. Although no antiviral effect was observed in skin lesions, a trend towards faster MPXV DNA clearance in index lesions at day 8 was observed in the tecovirimat treatment group compared (48%) with the placebo group (37%), but this was not statistically significant (difference 12%; 95% CI, -2% - 26%; p = 0.12).

Discussion

The STOMP trial found that tecovirimat did not significantly reduce the time to lesion resolution in patients with clade II mpox.

For both remote and in-person enrolments, lesions were self-assessed daily. Photos could be taken by patients of their lesions, however this was not a requirement. This represents a limitation of the trial, as lesion assessment is subjective, and patients may not have been confident at lesion assessment. Lesions may have been difficult to self-monitor, depending on the location of the lesions (back lesions, anal region lesions, groin lesions could be difficult to assess and track).

There is no data available on treatment compliance, and whether or not patients actually took their medication.

Most of the patients were advanced in their illness at the time of starting trial treatment. The study protocol did not require further specification regarding which symptoms were first noted and may have been prodromal symptoms or when lesions initially appeared. Standardised criteria for defining the first symptom or lesion appearance were absent. The lack of information regarding initial symptom presentation introduces recall bias and variability in defining "early treatment," potentially misclassifying patients and weakening subgroup analyses.

In STOMP, 25% of both tecovirimat and placebo treated patients were treated ≤5 days from symptom onset. No difference was noted in the time to lesion resolution between tecovirimat and placebo in either stratum, in fact earlier treatment initiation following onset of symptoms results slightly favoured the placebo arm. A sensitivity analysis looking at treatment ≤ 3 days from symptom onset was of limited value as patient numbers were low. It should also be noted that it seems that not all of these analyses (including the ≤/> 3 days) were prespecified.

Overall, all efficacy results from the STOMP study are consistently negative with no significant differences observed between tecovirimat and placebo in treating sexually transmitted clade II mpox. A trend towards reduced lesion swab viral load at day 8 was observed in tecovirimat patients.

2.2.1.3. UNITY

Study characteristics

UNITY was a randomised, placebo-controlled, double-blind study, with a separate open label arm for high-risk or severe disease subjects, to assess the safety and efficacy of tecovirimat oral capsules administered for 14 days for the treatment of mpox in adult and adolescent patients. Patients with at least one visible active skin or mucosal lesion and laboratory-confirmed PCR or highly suspected mpox (MPXV, clade II) illness of any duration (hospitalised or outpatients) were included in the study. Randomisation was stratified by number of days from the onset of symptoms (≤ 7 days versus > 7 days). 480 were randomised to receive either tecovirimat (n=238) or placebo (n=242) and 105 were assigned to receive open label tecovirimat. the majority of patients were male (≥ 99%) and 48.7% had human immunodeficiency virus (HIV). The median time between symptom onset and randomisation was 9 days in both the tecovirimat and placebo groups.

The primary endpoint of the study was time to complete lesion resolution, defined as a new fresh layer of skin re-epithelialisation (i.e. resurfacing of a wound with a new epithelium layer) for all visible lesions (skin, mucosal).

Active lesion resolution, which in theory could reflect an earlier timepoint in the disease course, was a secondary endpoint in this study. It was used as a primary endpoint in the PALM007, STOMP, and PLATINUM-UK studies.

The protocol and initial highline results from the randomised part of the trial were available. Virologic outcomes and data from the open label arm are not yet available.

Results

The overall risk ratio for time to lesion resolution for tecovirimat compared to placebo was 1.02 (95% CI 0.92-1.12) p=0.73, with a median time to resolution of 17.5 days in the tecovirimat group and 17.6 in the placebo group. None of the factors examined (treatment, time from onset to randomization, baseline severity, and site) were significantly associated with the primary outcome of complete lesion resolution. Hazard ratios for all factors were close to unity, and confidence intervals included 1, indicating no evidence of a meaningful effect on event timing.

There was no difference in the time to active lesion resolution between the tecovirimat and placebo groups (median 13.4 days for both groups).

A higher proportion of patients in the placebo group developed new mpox-related complications at any time during the follow up (18 patients, 8.1%) compared with the tecovirimat group, (10 patients, 4.5%). There was a higher proportion of patients in the placebo group who developed complications leading to unblinding or switch to open-label treatment – tecovirimat group 2 patients (0.9%), placebo group 7 patients (3.1%).

Discussion

UNITY failed to show statistical significance comparing tecovirimat to placebo treated patients with respect to the primary endpoint of time to complete lesion resolution.

Lesions were assessed weekly at trial visits for outpatient subjects, and at 3-day intervals for those subjects that were inpatients. While it is a strength that the assessment of lesions was performed by a trained physician, it is not clear from the protocol how an accurate record of the time (days) to complete lesion resolution was possible if a daily assessment of lesions was not performed. For example, if at the 7-day visit there was there was not complete resolution, but at the 14-day visit there was complete resolution, the day of resolution may have occurred between the 2 visits and would be uncertain. This aspect may become clearer if more data becomes available.

Subjects with any duration of symptoms could enrol provided they had one active lesion. This may have contributed in some part to the recruitment of subjects who were longer into their disease course. Only 2.5% of subjects were randomised at < 3 days from symptom onset, and 17.8 % were randomised at 3-5 days since symptom onset, with 79.8% recruited at > 5 days from symptom onset.

This provisional assessment of the available data indicates that under the conditions tested in the UNITY trial, tecovirimat did not reduce the time to complete lesion resolution, or the time to active lesion resolution versus placebo. There is also no convincing trend to a benefit of tecovirimat versus placebo in the subgroups analysed, including time from symptoms onset, however, the numbers treated at < 3 days and 3-5 days are particularly small.

2.2.1.4. PLATINUM-UK

Study characteristics

PLATINUM-UK was a Phase 3, randomized, double-blind, placebo-controlled study, to assess the safety and efficacy of tecovirimat oral capsules administered for 14 days for the treatment of mpox in non-hospitalised adult and paediatric patients. Patients with at least one active skin lesion, and laboratory-confirmed MPXV, clade II infection were included in the study. The median number of days since first lesion was 7 days. A remote design, combining online forms for self-assessment of lesion resolution and telephone calls from study staff was used. Only 35 out of a planned recruitment of 500 subjects were recruited, the reason for the trial closing seems to have been stalled recruitment.

The primary endpoint of the study was time to active lesion resolution, defined as the first day on which all skin lesions were scabbed or desquamated (and mucosal lesions healed), up to 28 days after randomisation.

Results

There was no evidence of a statistically significant difference in active lesion resolution between patients in the tecovirimat group and those in the placebo group (event rate ratio [RR] 0.93 [95% CI 0.42 - 2.02] p = 0.85). There was also no evidence of a difference between both groups regarding the secondary outcome of complete lesion resolution.

Discussion

Due to the early termination of the trial, and the low number of subjects enrolled, any results from the trial are nominal as they are not statistically powered. The planned subgroup analyses were still carried out despite the low recruitment, but it is questionable how much value these add when the subgroups are so small.

While the detailed breakdown of time since first lesion for all subjects is not currently available, it appears that only 21 subjects were treated at ≤ 7 days from first lesion; of those subjects it is not clear how many were treated at < 5 days and < 3 days since lesion onset. However, it is likely that the number of subjects treated at < 5 days and < 3 days since lesion onset was very small, and as such these data on their own will not help inform the discussion on the optimal time to start treatment with tecovirimat, if any.

2.2.1.5. Expanded use programmes and observational studies

In the CDC/U.S. EAP, 7100 patients have been prescribed tecovirimat for Clade II mpox (Yu, 2024)[8]. The data on the efficacy and safety of tecovirimat from this programme is of limited value for assessing the benefit risk of tecovirimat in the treatment of mpox, as it is in a real-world setting with no control group. There was a high recovery without sequelae with an overall rate > 76%, but it is noted that the recovery without sequelae rate was significantly lower for the severely immunocompromised group. It is also noted that while this programme remains open at the time of this report, the conditions for use of tecovirimat within this programme have become more restricted; tecovirimat treatment is now only recommended for protracted and life-threatening disease, for pregnant and breastfeeding women, severely immunocompromised, children, and patients with active, severe skin conditions.

The MOSAIC study was a European based observational cohort study in patients with confirmed mpox. Of the 575 patients analysed, only 57 (approx. 10%) were treated with an antiviral (tecovirimat or cidofovir); most of these received tecovirimat, n=49. At day 14, 35% of the untreated patients and 33% of the treated patients had all lesions resolved and no serious complications (Pesonel, 2025)[9].

Only 14 patients were recruited in the CAR programme (Mbrenga, 2022)[10], while no information is currently available on MEURI.

[8] Yu PA, Elmor R, Muhammad K, Yu YC, Rao AK. Tecovirimat Use under Expanded Access to Treat Mpox in the United States, 2022-2023. NEJM Evid. 2024 Oct;3(10):EVIDoa2400189.
[9] Pesonel E, Laouénan C, Guiraud L, Bourner J, Hoffmann I, Molino D, et al. Clinical Characterization and Outcomes of Human Clade IIb Mpox Virus Disease: A European Multicenter Mpox Observational Cohort Study (MOSAIC). Clin Infect Dis. 2025 Jun 4;80(5):1060-1073.
[10] Mbrenga F, Nakouné E, Malaka C, Bourner J, Dunning J, Vernet G, et al. Tecovirimat for Monkeypox in Central African Republic under Expanded Access. N Engl J Med. 2022 Dec 15;387(24):2294-2295.

2.2.2. Clinical Pharmacology

The MAH's popPK model (Study 883) incorporated plasma concentration data from 5 clinical studies; SIGA-246-004, SIGA-246-008, SIGA-246-018 and SIGA-246-022, all of which were conducted in healthy volunteers (HV) and the sparse plasma concentration data from PALM007 which was conducted in mpox diseased patients. There were no discernible differences due to the effects of malaria status, nutritional status, or lesion severity on PALM007 exposure data. The visual predictive check (VPC) and the goodness of fit plots conducted, indicated that the model demonstrates good predictive performance for the data used to develop the model and can also adequately predict tecovirimat PK in the target population in addition to healthy volunteers. The MAH was not able to conduct any meaningful exposure-response analysis based on the limited data available from the PALM007 and STOMP studies.

2.2.3. Non-clinical aspects

2.2.3.1. Data from the initial marketing authorisation

A summary of the nonclinical development of tecovirimat was provided. In vitro and in vivo studies demonstrated potent inhibition of orthopoxviruses by targeting the conserved VP37 protein, essential for formation of extracellular enveloped virions (EV). Tecovirimat prevents viral dissemination and has shown consistent nanomolar activity across a range of orthopox viruses including Clade I and Clade II MPXV viruses. A total of 6 pivotal in vivo primary efficacy studies were conducted in NHPs infected with a lethal dose of Clade I MPXV and rabbits infected with a lethal dose of rabbitpox virus (RPXV). The lethal NHP models, originally developed to mimic smallpox in humans (although also relevant for mpox, as Clade I MPXV was used) and powered for mortality, demonstrated efficacy of tecovirimat even once lesions had developed. Pivotal lethal nonclinical efficacy studies in NHPs (MPXV) and rabbits (RPXV) demonstrated significant survival benefit, reduced lesion burden and lowered viremia. Tecovirimat prevented death and mitigates disease when administered before peak systemic infection, day 4–5 post-challenge in NHPs, with ≥5 days of dosing required to sustain benefit, which formed the basis for the authorisation under exceptional circumstances. In study SR10-037F median lesion counts demonstrated a clear time-to-treatment effect: day 6 initiation yielded lesion burdens similar to placebo, whereas day 4–5 initiation produced marked reductions and earlier resolution, with morbidity lowest when treatment began on day 4.

PK/PD modelling established a protective plasma concentration threshold (Cmin 169 ng/mL), which informed the authorised human dose of 600 mg twice daily.

2.2.3.2. Study 25-06 with Clade II mpox intravenous challenge in NHP

The MAH has developed a newer nonlethal NHP model (Aid, 2023; Jacob-Dolan, 2024)[11, 12]. The model is characterised by low mortality (<1%) and lesional disease. Lesional disease severity (i.e. maximum lesion counts and lesion progression through typical stages) correlates well with the levels of viremia seen in human mpox disease. Following a pilot study, Study 25-06 entitled 'investigation of effective treatment window for tecovirimat in an intravenous challenge model of clade II MPXV in cynomolgus macaques' was initiated.

[11] Aid M, Sciacca M, McMahan K, Hope D, Liu J, Jacob-Dolan C, et al. Mpox infection protects against re-challenge in rhesus macaques. Cell. 2023 Oct 12;186(21):4652-4661.e13.
[12] Jacob-Dolan C, Ty D, Hope D, McMahan K, Liu J, Powers OC, et al. Comparison of the immunogenicity and protective efficacy of ACAM2000, MVA, and vectored subunit vaccines for Mpox in rhesus macaques. Sci Transl Med. 2024 Mar 27;16(740):eadl4317.

Interim results from study 25-06 were provided and the final report is expected in April 2026. The objective of this study was to define the therapeutic window for use of tecovirimat following intravenous (IV) challenge of cynomolgus macaques with Clade IIb MPXV. This new NHP study of tecovirimat in clade IIb is considered the most representative model for mpox.

Tecovirimat treatment was initiated at intervals chosen to model distinct, clinically relevant stages of disease progression: group1 - pre-symptomatic (day 2), group 2 - early symptomatic with rising viremia (day 5), group 3 - peak symptomatic disease (day 9), and group 4 - early natural resolution (day 13). Group 5 were untreated controls. Intravenous challenge is defined as study day 0.

Tecovirimat administration produced clear, time-dependent effects on quantitative disease measures. The most pronounced antiviral activity, as measured by suppression of progressive lesions (see Figure 1), maximal total lesion formation, and viral loads occurred when treatment was initiated on Day 2. Animals treated at the onset of early symptoms on day 5 exhibited reductions in both peak lesion counts and AUC, although these effects were less pronounced than in the day 2 cohort. Treatment on day 5 had no significant effect on plasma viremia. However, lesions were not confirmed in all treatment groups until day 5, and progressive lesions were observed in all treatment groups by day 13. There was no reduction in lesion counts or viral load relative to controls for animals treated on day 9 or 13.

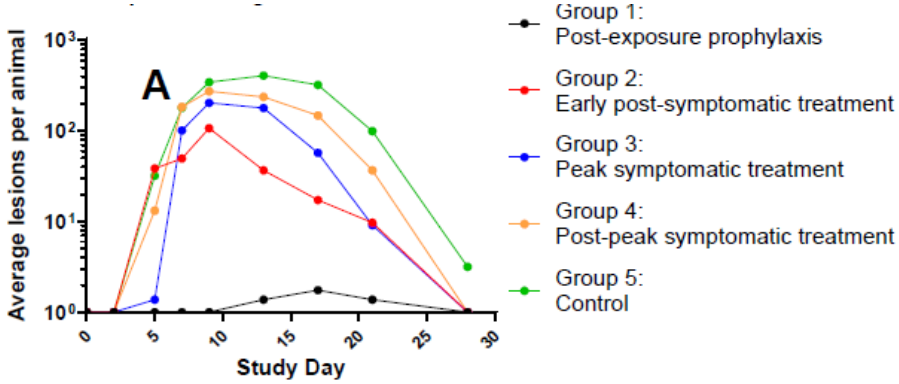

Figure 1. Mean progressive mpox lesion counts over time per study group – study 25-06

The study results demonstrate that tecovirimat's antiviral effects in this Clade IIb MPXV model were strongly dependent on the timing of administration with most benefit achieved when treatment was initiated prior to the appearance of lesions. However, these data cannot be a substitute for demonstrated clinical efficacy in RCTs.

2.2.4. Discussion on efficacy

All RCTs were of a similar general double blind, placebo-controlled trial design. STOMP and UNITY also included open label arms for higher risk subjects, for which there is no outcome data available at the time of this assessment report.

The baseline demographics of the patients recruited differed significantly amongst the RCTs with outcome data. PLATINUM-UK, STOMP and UNITY trials predominantly recruited male (>98%) adults (median age 34 – 38 years) with clade II mpox. Co-morbidity with HIV was also a feature of these trials. Overall, the cohorts of subjects recruited to these trials reflected the 2022 outbreak patterns of mainly sexual transmission of mpox between men who have sex with men.

In contrast, PALM007 recruited a similar number of male and female subjects with a median age of 11 years. Subjects had clade I mpox and were hospitalised. PALM007 took place in the DRC where clade I mpox is endemic. HIV was reported in only 1% of subjects while malaria was reported in 19% of

subjects. This made PALM007 the first large-scale clinical trial to evaluate a therapeutic for mpox in a predominantly paediatric population.

Overall, baseline demographics were well balanced between tecovirimat and placebo arms in all 4 RCTs with outcome data.

Results across the RCTs

Overall, there were no significant differences between the tecovirimat and placebo arms across the RCTs for lesion resolution and other endpoints such as mortality, virological outcomes and pain/use of analgesia.

It is noted that some positive trends favouring tecovirimat treatment over placebo were observed for subgroup analyses in some of the RCTs. In PALM007, a trend towards earlier lesion resolution was observed in patients with more than 100 lesions at baseline, indicative of severe disease (HR 1.20; 95% CI 0.98,1.48). In STOMP, a higher percentage of patients treated with tecovirimat had negative lesion swabs for MPXV at day 8 compared to placebo (48% v 37%). Post-hoc and exploratory analyses of viral load suggested that tecovirimat may accelerate viral clearance in specific subgroups, particularly among patients with severe disease, younger age, or without malnutrition. However, there are numerous limitations/weaknesses to these analyses (see also below), and the results were not statistically significant.

Limitations across the RCTs

Limitations of the lesion assessments include different variations of the primary endpoint across the RCTs which limits direct comparisons between trials. As some RCTs relied on subjects self-swabbing (PLATINUM-UK) and self-reporting on lesions and symptoms (STOMP, PLATINUM-UK), there is the possibility that the key clinical and virological outcomes may not have been accurately and consistently recorded across the recruited subjects. In UNITY there was only weekly assessment of lesions which limits the accuracy of assessing lesion resolution. No RCT included patients from both mpox clades, so direct comparison of clade impact is not possible. Time from symptom onset to treatment initiation was defined as when symptoms began, however trial protocols did not require further specification regarding which symptoms were first noted. The limitation regarding specification of symptom presentation introduces recall bias and variability in defining "early treatment", potentially misclassifying patients and weakening subgroup analyses.

Immunocompromised patients and other groups considered more at risk for severe illness

Immunocompromised patients are of particular interest as they are at greater risk of a more severe and protracted viral course. In immunocompromised patients, viral dynamics and viraemia timings may be different than for otherwise well, immunocompetent subjects. Immunocompromised subjects were not recruited to randomised arms of the mpox/tecovirimat trials. The UNITY trial includes a small subset of patients living with HIV and lower CD4 cell counts (100-500 cells/mm^3), which may provide further insight into safety and efficacy in this population, however it will not provide a robust efficacy dataset. The available data does not help identify patient groups that may be more likely to gain benefit from tecovirimat, as also noted by the SAG. Immunocompromised patients are a group in which tecovirimat resistance has been reported which could considerably impact on efficacy in this subgroup (see also below discussion on resistance). Further, data from animal studies indicated that tecovirimat may have reduced efficacy in immunocompromised patients. It is understood from the MAH that patient populations at increased risk of severe outcomes, including immunocompromised patients, pregnant, and paediatric patients, are expected to be included in any future clinical trial.

Resistance

Tecovirimat has a relatively low resistance barrier, and certain amino acid substitutions in the target VP37 protein can confer large reductions in tecovirimat antiviral activity. The product information prompts prescribers to consider the possibility of resistance to tecovirimat in patients either who fail to respond to therapy, or who develop recrudescence of disease after an initial period of responsiveness. Antiviral resistance is not a plausible explanation for the lack of efficacy observed in PALM007 and STOMP. Prolonged use of tecovirimat in severely immunocompromised patients receiving treatment courses beyond the recommended duration may result in the emergence or amplification of resistance (Garrigues, 2023a[13]; Garrigues, 2023b[14]; Griffith, 2024[15]; Mertes, 2023[16]; Smith, 2023 [17]). It is reassuring that resistance remains <1% and largely confined to severely immunocompromised patients receiving prolonged treatment. Nevertheless, when resistance does occur, the SAG noted that it may be associated with severe clinical failure, including persistent or progressive disease despite therapy. In the view of the SAG, these observations raise important considerations regarding the treatment regimen for tecovirimat in severely immunocompromised patients and the need for targeted virological monitoring, particularly in cases of delayed clinical response or prolonged infection. The CHMP also noted that, ongoing use of tecovirimat in settings where efficacy has not been demonstrated (in particular for example, immunocompetent patients with mild or moderate mpox, or late presenters) could contribute to wider selection or amplification of resistant variants. While current data suggest the absolute risk remains low, the potential for avoidable selective pressure warrants acknowledgement in the context of repeated or unnecessary prescribing.

Expanded access programmes and observational studies

Regarding the expanded access programmes and observational studies, in the only one that included a large number of patients, there was a high recovery without sequelae rate overall (> 76%). It is noted that the recovery without sequelae rate was significantly lower for the severely immunocompromised group. Due to the inherent limitations of expanded access programme data and observational studies, these data are of limited relevance to the present assessment.

Population pharmacokinetics

The popPK model 883, demonstrated good predictive performance and fit for the totality of the data used to develop it (healthy volunteers and patients with mpox from the PALM007 study), as well as predicting external data from the STOMP study. The data from PALM007 suggests that the PK is similar in individuals with mpox to what is observed in healthy volunteers. The MAH was unable to perform any meaningful exposure-response analysis given the limited data available from the PALM007 and STOMP studies, so no conclusions can be drawn on the PK-PD of tecovirimat.

The CHMP considered that for clarity, the paediatric age group in which no dose recommendations have been established (i.e. for children less than 13 kg body weight) should be specified in 4.2, in line with the authorised indications.

[13] Garrigues JM, Hemarajata P, Espinosa A, Hacker JK, Wynn NT, Smith TG, et al. Community spread of a human monkeypox virus variant with a tecovirimat resistance-associated mutation. Antimicrob Agents Chemother. 2023 Nov 15;67(11):e0097223.
[14] Garrigues JM, Hemarajata P, Karan A, Shah NK, Alarcón J, Marutani AN, et al. Identification of Tecovirimat Resistance-Associated Mutations in Human Monkeypox Virus - Los Angeles County. Antimicrob Agents Chemother. 2023 Jul 18;67(7):e0056823.
[15] Griffith DC, Fall A, Carter M, Traut CC, Sop J, Hansoti B, et al. Mpox Recurrence and Tecovirimat Resistance in a Patient With Advanced Human Immunodeficiency Virus Disease. Open Forum Infect Dis. 2024 Sep 23;11(10):ofae549.
[16] Mertes H, Rezende AM, Brosius I, Naesens R, Michiels J, deBlock T, et al. Tecovirimat Resistance in an Immunocompromised Patient With Mpox and Prolonged Viral Shedding. Ann Intern Med. 2023 Aug;176(8):1141-1143.
[17] Smith TG, Gigante CM, Wynn NT, Matheny A, Davidson W, Yang Y, et al. Tecovirimat Resistance in Mpox Patients, United States, 2022-2023. Emerg Infect Dis. 2023 Dec;29(12):2426-2432.

Non-clinical data

Study 25-06, the new nonlethal NHP study, demonstrated that tecovirimat's antiviral effects were strongly dependent on the timing of administration, with most benefit achieved when treatment was initiated prior to the appearance of lesions. The results of study 25-06, are consistent with those of study SR10-0037F that supported the initial marketing authorisation. Overall, the non-clinical data indicated that the timing of tecovirimat treatment may be critical. However, in the non-clinical studies, treatment was administered at given time points post IV challenge, rather than post symptom onset. Whereas, as also noted by the SAG, dating the infection in humans is complicated.

The CHMP considered that for clarity it should be specified under section 5.1 of the summary of product characteristics (SmPC) that the efficacy studies in cynomolgus macaques infected with MPXV virus used a lethal model broadly accepted as a model for human smallpox.

The SAG also discussed the limitations of the NHP models, relying largely on intravenous challenge, whereas in humans MPXV replicates primarily at mucosal sites and not in blood (at least for clade IIb). Furthermore, there are no data on the temporal correlation between intravenous exposure and infection at the mucosal surface.

Timing of treatment

Of the four RCTs with outcome data, median time from symptom onset to treatment initiation was balanced across placebo and tecovirimat arms but varied between trials (PALM007 median 6 days, STOMP 8 days, UNITY 9 days, PLATINUM-UK 7 days). This indicates that most of the patients were advanced in their illness at the time of starting trial treatment. In PALM007, which had the largest number of subjects treated early (89 subjects treated with tecovirimat ≤ 4 days), earlier treatment with tecovirimat suggested benefit if started within 4 days of symptom onset (HR 1.30, 95% CI 0.97–1.73). However, this result was derived from post hoc sensitivity analysis and was not statistically significant.

Longitudinal analysis of lesion count (mean +/- SEM) demonstrated (nominally) statistically significant lower lesion counts for the tecovirimat arm compared to the placebo arm, in particular for patients treated ≤4 days and 5 days from symptom onset and in patients with baseline lesion counts ≥100. Overall, while these new PALM007 analyses suggest positive effects, these results are post-hoc and exploratory in nature, limiting their utility in determining efficacy. In addition, these findings have not been corroborated in other trials. For most of the trials there were too few subjects for which tecovirimat treatment was administered at < 5 days, < 4 days and < 3 days from symptoms onset to conclude on any potential trends towards a better outcome with earlier treatment.

The MAH argues that in these four RCTs the patients received tecovirimat treatment too late in their illness (i.e. past peak viraemia). In this context the MAH refers to the NHP mpox studies that supported the initial marketing authorisation that showed efficacy with tecovirimat, but that also showed a drop off in efficacy when treatment was started on the sixth day post IV monkeypox virus challenge. Additionally, the MAH refers to the expected timing of the peak viraemia in mpox, and outlines that a broad range of literature reports support that by the time mpox lesions are present, the peak viraemia has often passed in contrast with smallpox (see Figure 2) (Behbehani, 198318; Fenner,

[18] Behbehani AM. The smallpox story: life and death of an old disease. Microbiol Rev. 1983 Dec;47(4):455-509

198819; Reynolds, 200620; Huhn, 200521; Marziano, 202422; Tarín-Vicente, 202223; Adler, 202224; Kim, 202325; Srivastava, 202526; Yang, 202427; Thornhill, 202228; Patel, 202229; Pittman, 202330; Nishiyama, 202531). The overarching premise that peak viraemia in mpox tends to occur early is agreed by CHMP. It has been shown that MPXV DNA tends to be lower in blood samples than in other samples (e.g. skin lesion samples) and also that MPXV DNA clears faster from blood than from other samples. However, this remains a generalised conceptual graph (Figure 2), it is noted that analysis of viral load was generally performed after subjects had already developed a rash. The SAG also concurred that overall, available evidence indicates that viraemia occurs early in infection and has usually passed at the time of lesion onset, while the current understanding of the evolution of viraemia in mpox remains partial and incompletely characterised, particularly when comparing different viral clades. Further, the SAG highlighted the lack of clear correlation between viraemia levels and the presence, number or severity of lesions in humans, unlike in animal models. As MPXV viral replication is mostly located in the mucosal surface, the group considered that viraemia was not the most reliable marker for mpox lesion onset or progression.

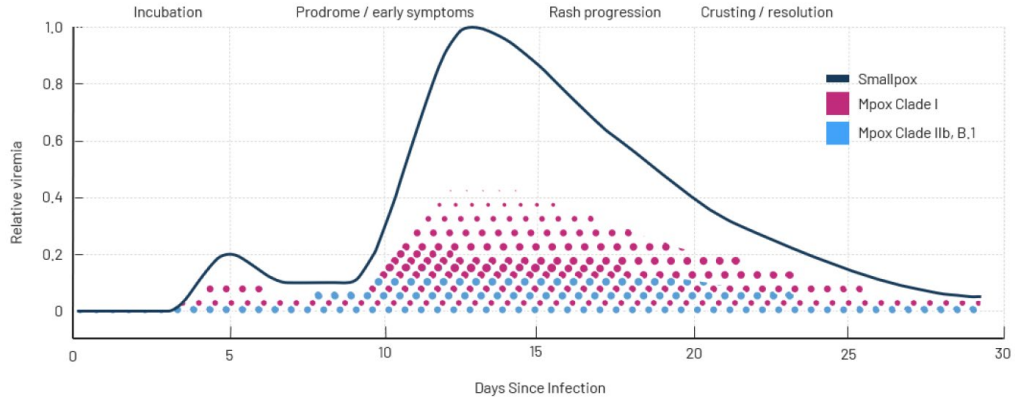

Figure 2. Generalised conceptual graph comparing the viremia envelope for smallpox, Clade I and Clade IIb mpox

[19] Fenner, Frank, Henderson, Donald A, Arita, Isao, et al. (1988). Smallpox and its eradication. World Health Organization.
[20] Mary G. Reynolds, Krista L. Yorita, Mathew J. Kuehnert, Whitni B. Davidson, Gregory D. Huhn, Robert C. Holman, Inger K. Damon, Clinical Manifestations of Human Monkeypox Influenced by Route of Infection, The Journal of Infectious Diseases, Volume 194, Issue 6, 15 September 2006, Pages 773–780
[21] Huhn GD, Bauer AM, Yorita K, Graham MB, Sejvar J, Likos A, et al. Clinical characteristics of human monkeypox, and risk factors for severe disease. Clin Infect Dis. 2005 Dec 15;41(12):1742-51.
[22] Marziano V, Guzzetta G, Longini I, Merler S. Epidemiologic Quantities for Monkeypox Virus Clade I from Historical Data with Implications for Current Outbreaks, Democratic Republic of the Congo. Emerg Infect Dis. 2024 Oct;30(10):2042-2046.
[23] Tarín-Vicente EJ, Alemany A, Agud-Dios M, Ubals M, Suñer C, Antón A, et al. Clinical presentation and virological assessment of confirmed human monkeypox virus cases in Spain: a prospective observational cohort study. Lancet. 2022 Aug 27;400(10353):661-669.
[24] Adler H, Gould S, Hine P, Snell LB, Wong W, Houlihan CF, et al. Clinical features and management of human monkeypox: a retrospective observational study in the UK. Lancet Infect Dis. 2022 Aug;22(8):1153-1162.
[25] Kim H, Kwon R, Lee H, Lee SW, Rahmati M, Koyanagi A, et al. Viral load dynamics and shedding kinetics of mpox infection: a systematic review and meta-analysis. J Travel Med. 2023 Sep 5;30(5):taad111.
[26] Srivastava, S., Sharma, D., Sridhar, S.B. *et al.* Comparative analysis of Mpox clades: epidemiology, transmission dynamics, and detection strategies. BMC Infect Dis 25, 1290 (2025).
[27] Yang, Y., Niu, S., Shen, C. et al. Longitudinal viral shedding and antibody response characteristics of men with acute infection of monkeypox virus: a prospective cohort study. Nat Commun 15, 4488 (2024).
[28] Thornhill JP, Barkati S, Walmsley S, Rockstroh J, Antinori A, Harrison LB, et al. Monkeypox Virus Infection in Humans across 16 Countries - April-June 2022. N Engl J Med. 2022 Aug 25;387(8):679-691.
[29] Patel A, Bilinska J, Tam JCH, Da Silva Fontoura D, Mason CY, Daunt A, et al. Clinical features and novel presentations of human monkeypox in a central London centre during the 2022 outbreak: descriptive case series. BMJ. 2022 Jul 28;378:e072410.
[30] Pittman PR, Martin JW, Kingebeni PM, Tamfum JM, Mwema G, Wan Q. Clinical characterization and placental pathology of mpox infection in hospitalized patients in the Democratic Republic of the Congo. PLoS Negl Trop Dis. 2023 Apr 20;17(4):e0010384.
[31] Nishiyama, T., *et al.* (2025). Modeling lesion transition dynamics to clinically characterize patients with clade I mpox in the Democratic Republic of the Congo. Science Translational Medicine.

On this basis, and considering the above-mentioned results of the new NHP study 25-06, the MAH proposed to include in section 4.2 of the SmPC a statement that "*For the treatment of mpox, tecovirimat should be administered as early as possible, and no later than 5 days after symptom onset. Since the initial symptoms of mpox may be non-specific, attention should be given to the clinical setting including the likelihood of exposure to others with mpox. The benefit of tecovirimat in lesional mpox is greatest in patients with Severe or Very Severe (formerly "Grave") mpox (≥ 100 lesions) by World Health Organization (WHO) criteria".* The MAH considers that initiation of treatment within 5 days of symptoms onset is possible and would be aided by public health awareness and the use of point-of-care testing, several of which are under development (Cavuto, 2025[32]; Madihi & Benani, 2025[33]; Yu, 2025[34]).

CHMP noted that until there is a standard, widely available point-of-care test available, early patient identification will remain challenging. Public health awareness of early symptoms will also be challenging given the non-specific nature of the prodromal symptoms but will be most beneficial in early identification of household transmission cases. The SAG also noted that the absence of a clear prodromal phase in a significant proportion of cases further complicates the temporal alignment between systemic viral replication and important clinical stages. However, it was considered that better engagement with communities affected by mpox and education of general practitioners may contribute to earlier diagnosis.

More importantly, in the PALM007 and STOMP studies, rates of blood PCR positivity were not high at trial entry suggesting that the viraemia stage may have passed. As such it is plausible that the reason for tecovirimat not showing efficacy in the treatment of mpox in the RCTs may have been the design and treatment conditions (specifically the timing of starting tecovirimat). However, Tecovirimat SIGA was authorised under exceptional circumstances, and therefore, there was no comprehensive evidence of efficacy at the time of initial authorisation, whereas the new data assessed in this procedure call into question the previously predicted efficacy of tecovirimat in the treatment of mpox. Furthermore, there is currently no convincing clinical evidence to support the efficacy of tecovirimat given at an earlier timepoint, and no convincing data to identify what might be the correct therapeutic window, if any. The SAG also considered that appropriate treatment window for treatment of mpox with tecovirimat cannot be defined based on the currently available clinical data. It was further noted that the absence of a clear prodromal phase in a significant proportion of cases further complicates the temporal alignment between systemic viral replication and important clinical stages. A theoretical clinical recommendation proposed by the SAG was to start treatment as soon as possible within 24 hours of diagnosis, however in the absence of conclusive data to support such recommendation, the CHMP noted that this remained hypothetical.

The MAH has outlined potential future strategies for generating new clinical data with tecovirimat in patients with mpox, however, the outcome of such trial(s) remains hypothetical; and this proposal in has no bearing on the conclusion based on the data available at present.

Whilst the current epidemiological situation may limit the possibility for further RCT, the CHMP and the SAG considered that further trials would be of value, in particular, the MAH may consider investigating the efficacy and safety of tecovirimat in post-exposure prophylaxis.

[32] Cavuto, M.L., Malpartida-Cardenas, K., Pennisi, I., et al. (2025). Portable molecular diagnostic platform for rapid point-of-care detection of mpox and other diseases. *Nat Commun, 16*(1), 2875.
[33] Madihi, S., & Benani, A. (2025). A comprehensive review of current diagnostic techniques for Monkeypox virus detection. *Biologicals: journal of the International Association of Biological Standardization, 91*, 101841.
[34] Yu, J., Di, B., Zhou, L., et al. (2025). A point-of-care testing device for monkeypox virus integrating recombinase polymerase amplification and lateral flow assay. *BMC Medicine, 23*(1), 641.

Other indications

The authorisation of these indications was based on in vitro and preclinical efficacy data which supported antiviral activity of tecovirimat against a range of orthopoxviruses, and safety data from healthy volunteers. While there are now negative clinical data on the use of tecovirimat in mpox under the conditions studied in the RCTs, the viral dynamics and disease courses of smallpox, cowpox, and vaccina virus are each different to mpox, despite their structural similarities. Differences are also noted in potential circumstances of exposure to these viruses, e.g. through deliberate release of variola (smallpox) virus. Therefore, the efficacy results from the mpox RCTs are not considered of direct relevance for the demonstration of efficacy of tecovirimat in the three other authorised indications. Overall, the in vitro and animal data that supported the initial marketing authorisation smallpox, cow pox and vaccina virus indications are still considered relevant and should be predictive of the efficacy of tecovirimat in treating these viruses in humans. Further the early timing of treatment in the animal studies reflects a realistic human scenario for smallpox where rapid diagnosis and treatment are prioritised.

It is noted that clinical studies remain currently not possible in these indications due to eradication (smallpox), or very low incidences (cowpox, vaccinia). In addition, there is an unmet need for these indications as there are no or limited available treatments for these viruses. Further each indication, smallpox in particular, can result in considerable morbidity or mortality in the event of an outbreak (or of bioterrorism).

Considering the lack of clinical data on resistance in other indications, the above-described findings on resistance relate to mpox are considered to be of potential relevance generally for tecovirimat use in the treatment of orthopoxvirus infections. Indeed, the VP37 protein is highly conserved in among orthopoxviruses and it is therefore plausible that the same VP37 resistance mutations may also arise in other indications. Therefore, updates to the SmPC section 5.1 are considered needed to reflect emerging information on resistance, namely that resistance have been documented in <1% of isolates, that resistance mutations have arisen in patients receiving prolonged tecovirimat treatment for mpox, particularly in immunocompromised patients, such as HIV patients with low CD4 T-cell counts. These updates align with ongoing monitoring under the periodic safety update report (PSUR) topic "Use in immunocompromised subjects (including resistance development)," which remains the appropriate framework for continued surveillance given the overall low prevalence of resistance and the limited evidence for broader population-level amplification.

The CHMP considered that for clarity it should be specified under section 5.1 of the SmPC that there is no human efficacy data available for the treatment of smallpox, cowpox or complications due to replication of vaccinia virus following vaccination against smallpox.

Conclusion on efficacy

Across all RCTs with outcome data, results were consistently negative despite the variability in the subjects recruited and trial designs and regardless of whether subjects had clade I or II. The CHMP concluded that the trials failed to show any efficacy in patients diagnosed with mpox based on established skin or mucosal lesions. While there were some of positive trends (without statistical significance) favouring tecovirimat treatment over placebo in certain scenarios and in particular if treatment is started earlier, the post hoc nature of these analyses, combined with inconsistent and poorly controlled evaluation of important methodological considerations, such as, symptom onset and clinical resolution, limits the utility of these secondary findings. The complete dataset was available for the PALM007 trial in Clade I in which most of these trends were observed. Likewise, data and analyses from the STOMP trial in Clade II are reasonably complete. Overall, it is considered unlikely that the future and final data of the RCT trials would alter the assessment conclusions.

The premise that the reason for tecovirimat not showing efficacy in the treatment of mpox may have been a possible mismatch between disease biology, timing of treatment, and endpoint selection, not inconsistency of antiviral action could be plausible, however there is currently no conclusive evidence to support the efficacy of tecovirimat given at an earlier timepoint post symptom onset or to identify what might be the therapeutic window for treatment of mpox.

While the new NHP study of tecovirimat in clade IIb is considered the most representative model for mpox and demonstrates that tecovirimat's antiviral effects in this model are strongly dependent on the timing of administration, these data cannot be a substitute for demonstrated clinical efficacy in RCTs.

There are no new clinical data concerning the efficacy of the other three authorised therapeutic indications and the basis for their authorisation is still considered valid.

2.3. Data on safety

The MAH provided an overview of safety data from clinical trials, observational studies, expanded access programmes, and post-marketing surveillance.

Across the four RCTs with outcome data (PALM007, UNITY, STOMP, and PLATINUM-UK) the incidence of treatment-emergent adverse events (TEAEs) was broadly similar between tecovirimat and placebo groups and suggested that the safety profile of tecovirimat is consistent across different clades and demographic groups. Serious adverse events (SAEs) were also infrequent and generally balanced between treatment arms. In several studies, including PALM007 and STOMP, relatedness was either not assessed or not reported, which limits the ability to draw firm conclusions about causality. Furthermore, no stratified safety data by age, sex, HIV status, or pregnancy, was provided. In general, patients with the demographics/clinical characteristics that are associated with a more severe disease course were not recruited into the randomised parts of the RCTs (pregnancy, elderly, children [except in PALM007 where 64% of recruited patients were aged less than 18 years], severe skin disease). As such the safety of tecovirimat in these subgroups is less well characterised.

Data collection procedures varied significantly: RCTs employed structured AE reporting, while expanded access and observational studies relied on voluntary reporting, outcome forms, or physician discretion, introducing potential biases and underreporting.

No new safety signals were identified from data from post-marketing sources (including adverse reactions from spontaneous reports (originating from healthcare professionals, consumers, scientific literature, competent authorities, worldwide) and from non-interventional studies and other non-interventional solicited sources. This was also true in high-risk groups such as children, pregnant women, and immunocompromised patients.

Reduced drug efficacy in immunocompromised populations is a known risk, supported by preclinical data from animal models. However, based on the cumulative review of available clinical and observational data, no new or unexpected safety signals were identified in this population. It was noted that randomized controlled trials to date have not comprehensively studied individuals with severe immunocompromise. The UNITY trial includes a subset of patients living with HIV and CD4 cell counts of 100 - 500 cells/mm^3, which may provide further insight into safety and efficacy in this population once data are available. However, it will not provide a robust efficacy dataset for severely immunocompromised individuals.

In the last PSUSA (PSUSA/00010971/202501) PRAC noted concerns regarding the implications of emerging resistance and referred to the ongoing assessment of the RCT data in this Article 20 procedure, and updates to 5.1 are now considered warranted as discussed above under efficacy discussion.

Overall, no new safety signals were identified, and the safety profile for tecovirimat is considered broadly reassuring. The continued requirement for annual PSUR submissions for tecovirimat is appropriate and supported.

3. Expert consultation

The CHMP consulted the SAG on vaccine and therapies for infectious diseases supplemented with additional experts which provided advice on a number of issues as summarised below.

First, the experts were asked whether the evolution of viremia following the time of infection in mpox for the clades was well characterised, and if the onset of lesions necessarily indicates that peak viraemia has already passed.

The SAG concluded that the current understanding of the evolution of viraemia in mpox remains partial and incompletely characterised, particularly when comparing different viral clades. Overall, available evidence indicates that viraemia occurs early in infection and has usually passed at the time of lesion onset.

Current data show that Clade Ia in endemic settings has higher viremia levels compared to Clade II. However, data for clade II is scarcer. Further, there is no data for sub-clade Ib, which may become increasingly relevant. In addition, the mode of transmission differs depending on the network of contacts in which the virus is found which likely influences viraemia dynamics, complicating comparisons. Overall, the ability to fully characterise viraemia remains limited due to important differences between clades, transmission modes, insufficient data availability, including the absence of study comparing the different clades in the same setting.

The group also discussed that correlation between viral load and disease severity is only defined in animal models. In human data, there is no clear correlation between viraemia levels and the presence, number or severity of lesions. Consequently, the experts concluded that viraemia is not considered a reliable marker for mpox lesion onset or progression. Considering that MPXV viral replication is mostly located in the mucosal surface, rapid DNA testing of samples from mucosal sites of infection could be more clinically relevant than detecting viral load in the blood.

Second, the experts were asked if an appropriate time window from symptoms onset to initiation of treatment with tecovirimat could be defined, and if yes, whether it would be possible to implement in clinical practice

The SAG agreed that an appropriate treatment window for tecovirimat in mpox cannot be defined based on the currently available clinical data.

While a trend was noted towards faster resolution in PALM007 in particular in patients treated within 4 days of symptom onset (HR 1.30, 95% CI: 0.97–1.73), clinical trial results with tecovirimat do not allow to define a clear treatment window, a significant and clinically relevant difference in outcomes based on timing of treatment was not observed. It was also mentioned that the available randomised clinical trials were not designed for this purpose (e.g. primary endpoints, possible bias due to recollection and lack of definition of the type of symptoms).

The only evidence of a treatment window for tecovirimat has been determined in NHP models using time from infection, rather than from symptom onset. In the non-lethal NHP model, the most pronounced antiviral activity occurred when treatment was initiated on day 2 following exposure. It would therefore be necessary to be able to date the infection in humans, which is difficult. Treatment should then be started when the first symptoms of infection appear. However, the initial symptoms

induced by MPXV are often non-specific and can be confused with those of other infectious diseases such as influenza, dengue fever, and malaria. The absence of a clear prodromal phase in a significant proportion of cases further complicates the temporal alignment between systemic viral replication and important clinical stages. Treatment with Tecovirimat was initiated in clinical trials at the onset of skin signs, but these occur much later. Furthermore, a recent study in the murine severe combined immunodeficiency (SCID) model confirmed the efficacy of early treatment (D2 post-infection) but showed the ineffectiveness of tecovirimat treatment on established skin lesions, probably because their progression was based more on an immune-mediated mechanism (Cao, 2026[35]). Limitations of the NHP models were also discussed, since they rely largely on intravenous challenge, which does not represent MPXV behaviour in humans, since this replicates primarily at mucosal sites and not in blood (at least for clade IIb).

The group considered that the implementation of the theoretical therapeutic window for NHP (i.e., 2 days after intravenous exposure) in clinical practice would not be possible due to the uncertainty of early diagnosis of mpox and the variability of clinical manifestations. Furthermore, there are no data on the temporal correlation between intravenous exposure and infection at the mucosal surface.

The theoretical clinical recommendation would be to start treatment as soon as possible within 24 hours of diagnosis.

The patient representative emphasised that better engagement with communities, which are affected by mpox, and education of general practitioners may improve early diagnosis and therefore success rate of treatment.

Third, the experts were asked if data supported the efficacy of tecovirimat in any subset of patients with mpox

The group concluded that the data currently available do not allow the identification of a subset of mpox patients for whom efficacy of tecovirimat has been demonstrated.

It was mentioned that in PALM007 study, there was a trend of 1-day faster resolution of lesions in a subset of patients who have more than 100 lesions (HR: 1.2, 95%CI: 0.98-1.48).

The group also highlighted that even though there is a medical need in high-risk individuals, such as immunosuppressed individuals, there is not enough evidence supporting the benefit of tecovirimat in this subset at present. Of note, tecovirimat has known drug-drug interactions with some antiretroviral agents.

Fourth, the SAG was asked to discuss the feasibility of conducting a clinical trial of early treatment with tecovirimat feasible, what time-window between symptom onset and treatment initiation might be of interest to study, what would be the optimal design of such a trial, and the feasibility of such a clinical trial based on current mpox surveillance and situation reports

The experts agreed that a clinical trial evaluating early treatment with tecovirimat would be relevant. However, this does not appear feasible at present due to the current epidemiological conditions. In Europe, the low case numbers and the widespread mpox vaccination of individuals at risk would make recruitment very slow. In Africa, although in some regions (notably parts of DRC) still report household transmission, case numbers are now declining, and capacity and logistic constraints pose additional challenges.

In the future, should a new mpox wave emerge, conducting an early treatment clinical study could be feasible. In this situation, the experts and patient representative agreed that clinical trials should be

[35] Cao, X., Shi, N., Qiu, X. et al. Intervention timing and disease stage shape tecovirimat and cidofovir efficacy in male SCID mice. Nat Commun 17, 843 (2026).

conducted both in Europe and Africa, as the circulating clades and transmission can be different. Community engagement would be required for early enrolment, since public awareness has decreased since the 2022 outbreak.

The experts reiterated that there is no evidence-based treatment window between symptom onset and treatment initiation that could be proposed to be implemented in the study. If viremia is still considered a determining factor, it seems important to be able to implement rapid detection of it. It would also be desirable to study the use of tecovirimat in a more suitable NHP model, for example using rectal inoculation instead of intravenous injection (see the model developed by D. Barouch in the US or R. Le Grand in France), in order to mimic transmission in humans more closely. However, NHP models alone will not suffice, and the results will need to be confirmed by clinical trials.

Should an early treatment randomised controlled clinical trial be considered, the group also highlighted the possibility of including an open-label subset for immunocompromised patients. Endpoints to consider include resolution of skin lesions, replication in mucosa, decrease in severity, transmission rate and, as highlighted by the patient representative, quality of life taking into account the occurrence of pain, body image and impact of scaring. History of childhood smallpox vaccination would not constitute an exclusion criterion as the immune response declines overtime, but data on vaccination status should be collected.

Operationally, it was mentioned that the current diagnostic test by PCR takes time and requires presence of lesions; and these may appear after the desired treatment window. Rapid diagnostic tests are needed; the point-of-care PCR is currently limited and inconsistent.

To avoid bias and building on from the PALM007 study where the two sites showed large inter-centre variability, the trials should be conducted in a large number of centres.

Human challenge study design is not recommended as an ethical requirement of this type of study is to have an alternative effective therapeutic option which is currently not available.

The experts considered that in the future a post-exposure prophylaxis (PEP) trial to be more feasible and interesting given the benefit demonstrated by the NHP data. Possible settings for a PEP trial include household contacts in endemic African provinces (despite the low secondary attack rate), or sexual contacts in European sexually transmitted infections (STI) clinics. Experts also noted that this type of trial could compete with a ring vaccination strategy. It should be noted that in this context, tecovirimat does not appear to have an impact on the response to modified vaccinia Ankara (MVA) vaccination but could have an impact on the response to LC16m8 (now also used in Africa), which, unlike MVA, is a replication-competent vaccine.

Lastly, the SAG was asked for its view on the feasibility of a RCT to establish the efficacy of tecovirimat in the treatment of mpox in immunosuppressed patients or other patient groups at increased risk of severe outcomes.

In alignment with the views expressed above, the experts agreed that the feasibility of conducting a RCT to establish the efficacy of tecovirimat specifically in immunosuppressed individuals appears extremely limited at this time in view of the declining number of cases. Other patient groups at increased risk of severe outcomes other than immunocompromised patients are not identified at present. As mentioned above, the group considered that it would be interesting to include these in mpox trials, for sensitivity analyses, possibly in an open label arm. Finally, it should be kept in mind that tecovirimat resistance mutations have been reported in patients with profound immunosuppression, most commonly in individuals with advanced or uncontrolled HIV infection. Their emergence appears to require prolonged viral replication under sustained antiviral pressure, typically in the setting of persistent high viral loads and extended treatment courses. To date, such mutations

remain rare and have been documented only in a limited number of cases. Nevertheless, when they do occur, they may be associated with severe clinical failure, including persistent or progressive disease despite therapy. These observations raise important considerations regarding the treatment regimen for tecovirimat in severely immunocompromised patients and the need for targeted virological monitoring, particularly in cases of delayed clinical response or prolonged infection.

4. Benefit-risk balance

At the time of marketing authorisation, it was not possible to provide comprehensive data on the efficacy and safety of tecovirimat under normal conditions of use, because the indications in which it became authorised were encountered too rarely, and it would have been contrary to generally accepted principles of medical ethics to collect such information. The authorisation was therefore predominantly based on non-clinical (animal) studies, supported by PK and safety studies. The benefits of Tecovirimat SIGA in humans were predicted from studies in animal models of orthopoxvirus diseases. These studies, combined with the mechanism of action of tecovirimat, in vitro pharmacology evaluations demonstrating antiviral activity against a number of orthopoxviruses, and the highly conserved drug target, provided the basis for including the four indications. The non-clinical studies demonstrated significant survival benefit, reduced lesion burden and lowered viremia with tecovirimat treatment. The lethal NHP models, originally developed to mimic smallpox in humans and powered for mortality, demonstrated efficacy even once lesions had developed. However, these data indicated that tecovirimat should be used as soon as possible after diagnosis, in accordance with official recommendations.

In order to ensure adequate monitoring of safety and efficacy of tecovirimat in its authorised indications, the MAH was required as a specific obligation to provide yearly updates on any new related information. In the present review, the CHMP considered all available data, including from randomised controlled trials (PALM007, STOMP, UNITY, PLATINUM UK), access programmes (CAR and CDC) and an observational study (MOSAIC), PK data, preclinical efficacy data (in vitro and in vivo, including new interim results of a Clade II intravenous MPXV challenge in NHPs) and the literature. Complete data was available from PALM007, and reasonably complete data from STOMP. Therefore, while the complete data was not available from all trials, in view of the results available, it is considered unlikely that the future and final data of the RCT trials would alter the assessment conclusions. The CHMP also considered the views expressed by the Scientific Advisory Group (SAG) on Vaccines and Therapies for Infectious Diseases.

All RCTs were of a similar general double blind, placebo-controlled trial design based on WHO core protocol. No outcome data was available to date from the open label arms of the trials that included higher risk patients. PALM007 recruited a similar number of hospitalised male and female patients with a median age of 11 years, with clade I mpox. The three other trials recruited predominantly adult male patients with clade II mpox, overall reflecting the 2022 outbreak patterns of mainly sexual transmission between men who have sex with men. Most of the patients were advanced in their illness at the time of starting trial treatment (median time from symptom onset to treatment initiation was 6 days in PALM007, 8 days in STOMP, 9 days in UNITY and 7 days in PLATINUM-UK).

Overall, there were no significant differences between the tecovirimat and placebo arms across the RCTs for lesion resolution and other endpoints such as mortality, virological outcomes and pain/use of analgesia. There were positive trends favouring tecovirimat treatment over placebo observed across some of the RCTs, such as earlier lesion resolution in patients with more than 100 lesions at baseline or when treatment was started within 4 days of symptom onset in PALM007. However, these results

were derived from post-hoc sensitivity analyses and were not statistically significant. It is also important to recognise the methodological limitations of the RCTs, such as limited control over identification of symptom onset and determination of clinical resolution.

Immunocompromised patients are considered most at risk of a severe or protracted viral course, and therefore most likely to require antiviral treatment. However, there are data from animal studies that suggest that tecovirimat may have reduced efficacy in immunocompromised patients, while data from the open label arms of the studies are not yet available. Furthermore, resistance mutations have arisen in patients receiving prolonged tecovirimat treatment for mpox, particularly in immunocompromised patients. While current data suggest the absolute risk remains low, the potential for avoidable selective pressure warrants acknowledgement in the context of repeated or unnecessary prescribing. Whilst these findings relate to mpox, they are considered of potential relevance generally for tecovirimat use in the treatment of orthopoxvirus infections, and the product information is updated accordingly.

Across the four RCTs the incidence of TEAEs was broadly similar between tecovirimat and placebo groups. SAEs were infrequent and generally balanced between treatment arms. Despite limitations in the collection of some of this safety data (e.g. relatedness was not assessed or reported, safety data not provided by demographic subgroups), the data available provide a broadly reassuring safety profile for tecovirimat in the treatment of mpox across diverse clinical settings, with no new safety signals identified. The safety of tecovirimat in subgroups with demographics/clinical characteristics that are associated with a more severe disease course is less well characterised.

Benefit-risk balance in mpox

Considering that tecovirimat is expected to block the dissemination of the virus, the MAH argues that in order to see an effect, treatment should be initiated on or before peak viremia. By inclusion criteria, most patients in the trials had active lesions suggesting peak-viral load had passed. Tecovirimat was administered on average 6-9 days after reported symptom onset.

In support of this hypothesis, the MAH performed post-hoc longitudinal analyses of lesion count in PALM007, which demonstrated nominally statistically significant lower lesion counts for the tecovirimat arm compared to the placebo arm, in particular for patients treated ≤4 days and 5 days from symptom onset and patients with baseline lesion counts ≥100. The MAH proposed to specify in section 4.2 of the SmPC that for the treatment of mpox, tecovirimat should be administered as early as possible, and no later than 5 days after symptom onset. However, while these results suggest positive effects, they are exploratory, and these subgroups were not prespecified. Further, these findings have not been corroborated in the other trials. In most trials there were too few patients dosed early after symptom onset to conclude on any potential trends towards a better outcome with earlier treatment. In addition, some uncertainty is noted across the trials regarding the definition of symptom onset, and the accuracy of self-reported lesion assessment, which weakens the subgroup analyses.

The results of the new nonlethal NHP study 25-06 conducted in a new model using clade II MPXV characterised by low mortality (<1%) and lesional disease, better reflecting the human mpox phenotype, showed that tecovirimat's antiviral effects were strongly dependent on the timing of administration. Most benefits were achieved when treatment was initiated prior to the appearance of lesions. The most pronounced antiviral activity, as measured by suppression of progressive lesions, maximal total lesion formation, and viral loads occurred when treatment was initiated on day 2, before lesions appeared. Study SR10-0037F that supported the initial marketing authorisation had shown a drop off in efficacy when treatment was started in NHPs on the sixth day post intravenous MPXV challenge. Therefore, CHMP agreed that the non-clinical data indicate that the timing of tecovirimat treatment may be critical. However, in the non-clinical studies, treatment was administered at given time points post IV challenge, rather than post symptom onset. Whereas, as also noted by the SAG,

dating the infection in humans is complicated. Furthermore, there are no data on the temporal correlation between intravenous exposure and infection at the mucosal surface. Therefore, while informative, these data are insufficient to define a therapeutic window for tecovirimat administration in the treatment of mpox, considering the clinical results available.

Further, the CHMP and the SAG agreed that peak viraemia in mpox tends to occur early and has generally passed by the time of lesions onset. However, as mpox viral replication is mostly located in the mucosal surface (at least for clade IIb), viraemia is not the most reliable marker for mpox lesion onset or progression, as flagged by the SAG and agreed by CHMP.

Therefore, whilst the CHMP considered plausible that the reason for tecovirimat not showing efficacy in the treatment of mpox in the RCTs may have been the design and treatment conditions (specifically the timing of starting tecovirimat), the evidence currently available is insufficient to establish the efficacy of tecovirimat given at an earlier timepoint, or to identify what might be the correct therapeutic window (provided that there is one). The SAG was also of the view that an appropriate treatment window for treatment of mpox with tecovirimat cannot be defined based on the currently available clinical data.

The CHMP and the SAG also noted that while increased public awareness (e.g. through engagement of the community) could quicken treatment initiation, starting treatment within 5 days of symptom onset was mostly not feasible in the clinical trials, and would remain challenging in clinical practice as there is currently no standard point of care testing for rapid diagnosis.

The CHMP concluded that the benefit-risk balance of Tecovirimat SIGA was no longer favourable in the mpox indication.

Benefit-risk balance in the other indications

The viral dynamics and disease courses of smallpox, cowpox, and vaccina virus are each different to mpox, despite their structural similarities. Therefore, the efficacy results from the mpox RCTs are not considered of direct relevance for the demonstration of efficacy of tecovirimat in the three other authorised indications. Overall, in the absence of negative clinical efficacy data, as is now available for mpox, the in vitro and animal data that supported the initial marketing authorisation in the smallpox, cowpox and vaccina virus indications are still considered relevant and should be predictive of the efficacy of tecovirimat in treating these viruses in humans. It is noted that currently, clinical studies continue not to be possible in these indications due to eradication (smallpox), or very low incidences (cowpox, vaccinia). Further the early timing of treatment in the animal studies reflects a realistic human scenario for smallpox where rapid diagnosis and treatment are prioritised.

The CHMP concluded that the benefit-risk balance of Tecovirimat SIGA remains favourable in these indications, subject to annual reassessment and satisfactory adherence to the specific obligations in place. Early onset of treatment for all viruses is considered important and the current general advice in the SmPC section 4.2 to start treatment as soon as possible is considered adequate in the absence of clinical data with these viruses, given that the viral kinetics and clinical course of these viruses are not the same as those of human mpox virus.

The CHMP considered that minor clarifications were needed in section 4.2 and 5.1 of the SmPC, and typographic errors were corrected.

Conclusion

Overall, the CHMP considers that the benefit-risk balance of Tecovirimat SIGA in the treatment of mpox is no longer favourable. No new significant information has become available regarding the benefit-risk balance of Tecovirimat SIGA for the treatment of adults and children with body weight at

least 13 kg with smallpox, cowpox, and complications due to replication of vaccinia virus following vaccination against smallpox. Therefore, the committee recommends the variation to the terms of the marketing authorisation.

5. Summary of new activities and measures

5.1. Risk management

The MAH should operate a risk management system described in a Risk Management Plan, which has been revised to remove mpox related plans, and endorsed as part of the current review procedure.

5.1.1. Risk minimisation measures

5.1.1.1. Amendments to the product information

The CHMP considered that amendments to sections 4.1 and 5.1 of the SmPC were necessary to remove the mpox indication and related information, in line with the outcome of this review. Information on resistance was updated under 5.1, and the type of data available or not, clarified. The paediatric age group in which no dose recommendations have been established was clarified under 4.2.

The opportunity was taken to correct typographic errors.

The annex II and the package leaflet were amended accordingly (see section 6 of this report for more information on annex II).

5.1.2. Pharmacovigilance activities

5.1.2.1. Routine pharmacovigilance activities

The MAH will continue to conduct routine signal detection and cumulative reviews of all reports related to off-label use and highlight specifically in a separate section of the PSUR off-label use for the treatment of mpox.

5.2. Direct Healthcare Professional Communication (DHPC) and Communication plan

The Committee adopted the wording of a DHPC, to inform HCP of the fact that the indication of Tecovirimat SIGA is being restricted based on data from clinical trials, showing that Tecovirimat SIGA lacked efficacy in generally immunocompetent patients with active mpox lesions under the settings studied. The Committee also agreed on a communication plan.

6. Condition(s) to the marketing authorisation

The specific obligation to complete post-authorisation measures for the marketing authorisation under exceptional circumstances, should be revised to remove reference to the mpox indication. Therefore, the SOB002, is revised as below, whilst SOB001 remains unchanged.

SOB002: In order to ensure adequate monitoring of safety and efficacy of tecovirimat in the treatment of the Smallpox, Cowpox viral infections and complications due to replication of vaccinia virus following vaccination against smallpox in adults and children with body weight at least 13 kg, the MAH shall provide yearly updates on any new information concerning the safety and efficacy of tecovirimat.	Annually (with annual reassessment)

7. Grounds for Opinion

Whereas,

- The Committee for Medicinal Products for Human Use (CHMP) considered the procedure under Article 20 of Regulation (EC) No 726/2004 for Tecovirimat SIGA (tecovirimat).
- The CHMP reviewed the available data from clinical trials, taking into account all available data submitted by the MAH, as well as the views expressed by the Scientific Advisory Group on Vaccines and Therapies for Infectious Diseases.
- The CHMP noted the in vitro data and studies in animal models of orthopoxvirus diseases that predicted the benefits of Tecovirimat SIGA in humans for the initial marketing authorisation.
- Across the randomised clinical trials, CHMP noted the absence of significant differences between the tecovirimat and placebo arms for mpox lesion resolution and other endpoints such as mortality, virological outcomes and pain. The CHMP concluded that Tecovirimat SIGA lacks efficacy under the conditions studied in these mpox trials.
- The CHMP considered it plausible that this is due to the late timing of treatment administration in these trials. However, the evidence currently available is insufficient to establish the efficacy of tecovirimat in the authorised indication for the treatment of mpox in any therapeutic window.
- Therefore, the CHMP concluded that the benefit-risk balance of Tecovirimat SIGA is not favourable in the mpox indication.
- The CHMP also concluded that no new significant information has become available regarding the benefit-risk balance of tecovirimat for the treatment of adults and children with body weight at least 13 kg with smallpox, cowpox, and complications due to replication of vaccinia virus following vaccination against smallpox. Nevertheless, information on resistance development with mpox, considered potentially relevant to the use in these indications, is updated in the product information.

In view of the above, the Committee considers that the benefit-risk balance of Tecovirimat SIGA remains favourable subject to the revision to the agreed conditions to the marketing authorisation and taking into account the agreed amendments to the product information.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisation for Tecovirimat SIGA (tecovirimat).