APPLICATION NUMBER:

208627Orig1s000

OTHER REVIEW(S)
PATIENT LABELING REVIEW

Date: June 7, 2018

To: Debra Birnkrant, MD
   Director
   Division of Antiviral Products (DAVP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
   Associate Director for Patient Labeling
   Division of Medical Policy Programs (DMPP)

From: Morgan Walker, PharmD, MBA, CPH
   Senior Patient Labeling Reviewer
   Division of Medical Policy Programs (DMPP)

Subject: Nima Ossareh, PharmD, RAC
   Regulatory Review Officer
   Office Of Prescription Drug Promotion (OPDP)
   Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): TPOXX (tecovirimat)

Dosage Form and Route: capsules, for oral use

Application Type/Number: NDA 208627

Applicant: SIGA Technologies, Inc.
1 INTRODUCTION

On December 8, 2017, SIGA Technologies, Inc. submitted for the Agency’s review an original New Drug Application (NDA) 208627 for TPOXX (tecovirimat) capsules. The proposed indication is for the treatment of human smallpox disease caused by variola virus in adults and pediatric patients weighing at least 13 kg.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Antiviral Products (DAVP) on December 22, 2017 for DMPP and OPDP to review the Applicant’s proposed Patient Package Insert (PPI) for TPOXX (tecovirimat) capsules.

2 MATERIAL REVIEWED

- Draft TPOXX (tecovirimat) capsules PPI received on December 8, 2017, and received by DMPP and OPDP on May 24, 2018.
- Draft TPOXX (tecovirimat) capsules Prescribing Information (PI) received on December 8, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 24, 2018.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:
- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA’s Guidance for Useful Written Consumer Medication Information (published July 2006)
4 CONCLUSIONS
The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.
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/s/

MORGAN A WALKER
06/07/2018

NIMA OSSAREH
06/08/2018

LASHAWN M GRIFFITHS
06/08/2018
Memorandum

Date: 6/5/2018

To: LCDR Andrew Gentles, PharmD, BCPS AQ-ID
   Regulatory Project Manager
   Division of Antiviral Products (DAVP)

From: Nima Ossareh, PharmD, RAC
   Regulatory Review Officer
   Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for TPOXX (tecovirimat) capsules, for oral use

NDA: 208627

In response to DAVP’s consult request dated December 22, 2017, OPDP has reviewed the proposed product labeling (PI) and patient package insert (PPI) for TPOXX (tecovirimat) capsules, for oral use.

PI: OPDP’s comments on the proposed labeling are based on the draft PI received by electronic mail from DAVP on May 23, 2018, and are provided below.

PPI: A combined OPDP and Division of Medical Policy Programs (DMPP) review of the PPI will be completed under a separate cover.

Thank you for your consult. If you have any questions, please contact Nima Ossareh at (240) 402-2769 or nima.ossareh@fda.hhs.gov.
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/s/

NIMA OSSAREH
06/05/2018
1 PURPOSE OF MEMORANDUM

The Division of Antiviral Products (DAVP) requested that we review the revised container label, tray labeling, shipper labeling and pallet labeling for Tpoxx (tecovirimat) (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSION

The revised container label, tray labeling, shipper labeling and pallet labeling for Tpoxx (tecovirimat) is acceptable from a medication error perspective. We have no further recommendations at this time.

¹ Johnson C. Label and Labeling Review for Tpoxx (tecovirimat) (NDA 208627). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 APR 05. RCM No.: 2017-2539.

Container label (for new lots of NDA approved drug)
DATE: April 26, 2018

TO: Debra Birnkrant, MD
Director
Division of Antiviral Products (DAVP)
Office of Antimicrobial Products

FROM: Ruben C. Ayala, Pharm.D.
Lead Pharmacologist
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Director
DNDBE, OSIS

SUBJECT: Amended EIR review covering the routine inspection of the clinical portion of study SIGA-246-008 (NDA 208627) conducted at New Orleans Center for Clinical Research, Knoxville, TN and Johnson County Clin-Trials Inc., Lenexa, KS.

**Inspection Summary**

The Office of Study Integrity and Surveillance (OSIS) is amending the EIR review finalized in DARRTS on 4/3/2018 to include the recently submitted correct randomization schedule, complete audit trails from the Interactive Web Response System (IWRS), and drug accountability logs. The submitted information supports that study subjects enrolled at both audited sites were given the correct treatment (test or placebo) and dietary conditions (fed or fasted). Therefore, I now recommend that DAVP accept all clinical data from study SIGA-246-008.

OSIS arranged inspections of New Orleans Center for Clinical Research, Knoxville, TN and Johnson County Clin-Trials Inc., Lenexa, KS. Both clinical sites participated in evaluating the pharmacokinetics of tecovirimat in study SIGA-246-008 submitted in support of NDA 208627.
Page 2 – Amended EIR review covering the routine inspection of the clinical portion of study SIGA-246-008 (NDA 208627) conducted at New Orleans Center for Clinical Research, Knoxville, TN and Johnson County Clin-Trials Inc, Lenexa, KS.

No objectionable conditions were observed and Form FDA 483 was not issued at the close-out of the inspections. The final inspection classification for both audited sites is No Action Indicated (NAI). However, both ORA investigators observed discrepancies between the study report submitted to the Agency and documentation at the site with treatment allocation, treatment identity and dietary conditions at both sites. Specifically, site documents showed that several study subjects (n=54) received opposite treatments (e.g., test instead of placebo), mixed treatments (test and placebo), or opposite dietary conditions (e.g., fed instead of fasted) during the study. Because the findings occurred at both audited sites, it was likely that other non-audited, clinical sites participating in study SIGA-246-008 were also affected. Thus, my recommendation in the EIR review finalized in DARRTS on 4/3/2018 was to reject data from 54 study subjects.

Upon DAVP’s request for information, the Sponsor submitted a series of supporting documents on 4/9/2018, 4/11/2018, 4/16/2018, and 4/18/2018 to clarify the reporting discrepancies. Apparently, the Sponsor’s CRO inadvertently submitted to FDA an incorrect randomization schedule which led to discrepancies in treatment allocation and dietary conditions across all clinical sites participating in study SIGA-246-008. A closer examination of submitted post-inspectional documents revealed supportive evidence that study subjects received the correct treatment and dietary conditions.

After reviewing inspectional findings and post-inspection documents from the Sponsor, I conclude that the clinical data generated by the two inspected clinical sites as well as the non-inspected clinical sites for study SIGA-246-008 (NDA 208627) are reliable and should be accepted for further Agency review. In addition, other clinical studies of similar design (Attachment 1) conducted by the two inspected sites between the start date of the audited study (6/29/2015) and the end of the current surveillance interval should be accepted for review by the Agency without an inspection.

**Inspected Study:**
NDA 208627

Study Number: SIGA-246-008
Study Title: “An expanded double-blind, randomized, placebo-controlled, multicenter trial to assess the safety, tolerability, and pharmacokinetics of the anti-orthopoxvirus compound tecovirimat when administered orally for 14 days in subjects”
Dates of conduct: 6/29/2015 to 8/24/2016

Site 1:
Site Name: New Orleans Center for Clinical Research
Street Address: 1928 Alcoa Highway, Suite 107
City, State: Knoxville, TN 37920
Investigator Name: William B. Smith, MD

Site 2:
Site Name: Johnson County Clin-Trials Inc.
Street Address: 16300 College Blvd
City, State: Lenexa, KS 66219-1376
Investigator Name: Carlos A. Fierro, MD

New Orleans Center for Clinical Research (Site 101)
ORA Investigator Ann B. Borromeo (BIMOE) inspected New Orleans Center for Clinical Research, Knoxville, TN from January 23 to 26, 2018.

The inspection included a thorough examination of study records, subject records, informed consent process, protocol compliance, institutional review board (IRB) approvals, sponsor and monitor correspondence, test article accountability and storage, randomization, adverse events, and case report forms (CRFs).

At the conclusion of the inspection, Investigator Borromeo did not observe objectionable conditions and did not issue Form FDA 483 to the clinical site. However, she noticed reporting discrepancies with treatment allocation and identity and dietary conditions. Specifically, site documentation showed that several subjects received:
Page 4 - Amended EIR review covering the routine inspection of the clinical portion of study SIGA-246-008 (NDA 208627) conducted at New Orleans Center for Clinical Research, Knoxville, TN and Johnson County Clin-Trials Inc, Lenexa, KS.

1. Placebo and test article when the protocol called for one treatment during the lead-in period;

2. Test article but were reported in the placebo group (and vice versa); and/or

3. The opposite dietary conditions during dosing days.

The following table displays examples of reporting discrepancies among site records and documents submitted to FDA. Additional examples are provided in Attachment 2.

<table>
<thead>
<tr>
<th>Site records</th>
<th>FDA reports</th>
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<tr>
<td>Sub ID</td>
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<td>1013</td>
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<td>1008</td>
<td>10146; 10622</td>
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<table>
<thead>
<tr>
<th>Site records</th>
<th>FDA reports</th>
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<tr>
<td>Sub ID</td>
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<tr>
<td>1013</td>
<td>Fasted cohort</td>
</tr>
</tbody>
</table>

*During the Lead-in period, the site dispensed two bottles each containing forty-two, 200-mg capsules to attain a dosing schedule of 600 mg BID for 14 days.

The above finding was discussed with site personnel during the inspection. In their response, they stated that IWRS generated an email containing two bottle numbers to be dispensed and communicated fed or fasted conditions. The site dispensed both treatment bottles to subjects at the same time and instructed subjects to finish one bottle before starting on the subsequent one. Per site personnel, there was no way to determine if subjects followed these instructions after leaving the clinic and completing the study at home.
Initial OSIS Evaluation: Based on the inspection findings, 30 out of 40 subjects enrolled at this site had reporting discrepancies (Attachment 2) which casted doubt on the reliability of study data.

Sponsor’s Response to DAVP’s IR letters: The sponsor stated that an incorrect randomization schedule submitted to FDA caused multiple discrepancies in actual treatment allocation, treatment identity, and dietary conditions. As a corrective action, they submitted the “correct” randomization schedule (Refer to IR response letter dated 4/09/2018), complete IWRS audit trails from sites 101 and 102 (refer to IR response letter dated 4/16/2018), and individual site drug accountability logs (refer to IR response letter dated 4/18/2018).

Revised OSIS Evaluation: After reviewing the Sponsor’s post inspection documents, I verified that the correct randomization schedule was used across study sites. Per audit trails obtained from IWRS, (CRO) uploaded a randomization schedule in IWRS prior to initiating the study on June 29, 2015. They later modified the schedule before enrolling the expanded cohort on April 18, 2016. appears to have added extra randomization numbers to the randomization schedule, but didn’t change treatment allocation or identity. Thus, submitted documents support that an incorrect randomization was inadvertently submitted to FDA instead of the live, “correct” randomization schedule.

In addition, I also successfully cross-linked randomization, subject, and bottle numbers (treatment identity) by reviewing IWRS audit trails from sites 101 and 102. The IWRS recorded these numbers contemporaneously as subjects were randomized into cohorts at both audited sites (Attachment 4). I verified bottle assignment and treatment identity by comparing audit trails to individual drug accountability logs, subject records collected by ORA investigators, and the correct randomization schedule (Attachment 5). Dietary conditions recorded in these documents also matched. Thus, there are no remaining concerns with treatment allocation and identity at site 101.
Johnson County Clin-Trials Inc (Site 102)

ORA Investigator Lori Gioia (BIMOW) inspected Johnson County Clin-Trials, Lenexa, KS from February 12 to 14, 2018. Upon OSIS’s request, Investigator Gioia returned to the site on April 16 to 17, 2018 to review site drug accountability and IWRS audit trails.

The initial inspection included a thorough examination of study records, subject files, informed consent process, protocol deviations, IRB approvals, sponsor and monitor correspondence, test article accountability and storage, randomization, adverse events, and CRFs. The inspection was re-opened and included an in-depth audit of drug disposition, accountability, and IWRS audit trails.

At the conclusion of the inspection, Investigator Gioia did not observe objectionable findings and did not issue Form FDA 483 to the clinical site. However, she noticed reporting discrepancies related to treatment allocation and identity. Specifically, some subjects were documented to have received:

1. Placebo and test article when the protocol called for one treatment during the expanded period; or

2. Test article but were reported in the placebo group (and vice versa)

The following table displays examples of reporting discrepancies among site records and documents submitted to FDA. Additional examples are provided in Attachment 3.
Page 7 - Amended EIR review covering the routine inspection of the clinical portion of study S1GA-246-008 (NDA 208627) conducted at New Orleans Center for Clinical Research, Knoxville, TN and Johnson County Clin-Trials Inc, Lenexa, KS.

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<tr>
<th>Sub ID</th>
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<th>Bottle #s dispensed per drug accountability log*</th>
<th>Bottle identity per CSR section 16.1.7 (T=Test; P=Placebo)</th>
<th>Randomization Scheme, CSR 16.1.7</th>
<th>Dosing per Exposure (EX) Dataset</th>
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<td>T; P</td>
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<tr>
<td>4541</td>
<td>10077; 10824</td>
<td>T; T</td>
<td>P</td>
<td>T all 14 days</td>
<td>Yes</td>
<td></td>
<td>Subject received opposite treatment? Reporting error at 16.1.??</td>
</tr>
</tbody>
</table>

*During the expanded period, the site dispensed two bottles each containing forty-two, 200-mg capsules to attain a dosing schedule of 600 mg BID for 14 days.

Investigator Gioia stated via email that she didn’t discuss the above finding with clinical site management because they correctly dispensed treatment bottles per the study’s IWRS. However, she informed them about a potential problem with randomization. The site didn’t comment on the finding.

**Initial OSIS Evaluation:** Based on the inspection findings, 24 out of 41 subjects enrolled at this site had reporting discrepancies (Attachment 3), which casted doubt on the reliability of study data.

**Sponsor’s Response to DAVP’s IR letters:** The Sponsor stated that an incorrect randomization schedule submitted to FDA caused multiple discrepancies in actual treatment allocation, identity, and dietary conditions. See page 5 above for more details.

**Revised OSIS Evaluation:** After reviewing the Sponsor’s post inspection documents, I successfully verified the randomization schedule, and cross-linked randomization numbers, subject numbers, and bottle numbers (treatment identity). See page 5 above for more details.

In addition, Investigator Gioia audited IWRS audit trails and drug accountability during her second site. She verified treatment allocation and identity in a handful of randomly
selected subjects at site 102. Thus, there are no remaining concerns with treatment allocation and identity at site 102.

**Conclusion:**

After reviewing the initial inspectional findings and post-inspection documents from the Sponsor, I conclude that the clinical data generated by both inspected sites as well as the non-inspected sites for study SIGA-246-008 (NDA 208627) are reliable and should be accepted for further Agency review.

In addition, other clinical studies of similar design (Attachment 1) conducted by both clinical sites between the start date of the audited study (June 29, 2015) and the end of the current surveillance interval should be accepted for review by the Agency without an inspection.

The final inspection classifications for both sites remains NAI because reporting discrepancies occurred beyond the control of the sites. The discrepancies appear to have stemmed from an incorrect randomization schedule inadvertently submitted to FDA by the Sponsor’s CRO.

Ruben C. Ayala, Pharm.D.
Lead Pharmacologist

**Final Classification:**

**Clinical Sites**

**NAI** - New Orleans Center for Clinical Research
Knoxville, TN 37920
FEI#: 3013166872

**NAI** - Johnson County Clin-Trials, Inc.
Lenexa, KS 66219-1376
FEI#: 3011592022

**cc:**
OTS/OSIS/Kassim/Choe/Kadavil/CDER-OSIS-BEQ
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Biswas/Ayala

Reference ID: 4254148
Page 9 - Amended EIR review covering the routine inspection of the clinical portion of study SIGA-246-008 (NDA 208627) conducted at New Orleans Center for Clinical Research, Knoxville, TN and Johnson County Clin-Trials Inc, Lenexa, KS.

OTS/OSIS/DGDBE/Cho/Jang/Choi/Skelly/Au
ORA/Gioia/Borromeo

Draft: RCA 4/22/2018; 4/25/2018
Edit: AD 04/23/2018; CB 4/25/2018

ECMS:
New Orleans Center for Clinical Research
http://ecmsweb.fda.gov:8080/webtop/drl/objectId/0b0026f8818057fc

Johnson County Clin-Trials, Inc.
http://ecmsweb.fda.gov:8080/webtop/drl/objectId/0b0026f8818046ab

OSIS File #: BE 7784

**FACTS:** 11809396

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### Attachment 1

**Studies in support of Pending Applications**

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<th>Study #</th>
<th>Drug Name(s)</th>
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<td>NDA 208627</td>
<td>SIGA-246-008</td>
<td>Tecovirimat</td>
<td>6/29/2015 to 8/24/2016</td>
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/s/

RUBEN C AYALA
04/26/2018

ARINDAM DASGUPTA
04/26/2018
Clinical Inspection Summary

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<tr>
<th>Date</th>
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<tbody>
<tr>
<td>From</td>
<td>Sharon Gershon, Pharm.D, Reviewer</td>
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<tr>
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<td>Susan Thompson, M.D., Team Leader,</td>
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<tr>
<td></td>
<td>Kassa Ayalew, M.D., M.P.H., Branch Chief,</td>
</tr>
<tr>
<td></td>
<td>OSI /DCCE/GCPAB</td>
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<tr>
<td>To</td>
<td>Kirk Chan-Tack, M.D, DAVP/Medical Officer</td>
</tr>
<tr>
<td></td>
<td>Andrew Sherwat, M.D, DAVP/Medical Team Leader</td>
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<tr>
<td></td>
<td>Debra Birnkam, M.D, DAVP/Division Director</td>
</tr>
<tr>
<td></td>
<td>Andrew Gentles, PharmD, DAVP/Regulatory Project Manager</td>
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<tr>
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<td>NDA 208627</td>
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<td>SIGA Technologies, Inc.</td>
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<td>Proposed Indication</td>
<td>Treatment of human smallpox disease caused by variola virus</td>
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<td>Summary Goal Date</td>
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<td>Action Goal Date</td>
<td>August 8, 2018</td>
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<td>PDUFA Date</td>
<td>August 8, 2018</td>
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I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATION

The data from study SIGA 246-008 was submitted to the Agency in support of NDA 208627. The BIMO inspections for this NDA were conducted at three domestic clinical investigator sites and the sponsor (SIGA) site. No regulatory violations were found during inspections at two clinical investigator sites (Hurley and Essink), and no regulatory violations were found during the sponsor inspection. These inspections are classified as No Action Indicated (NAI). The studies were conducted adequately, and data from these sites are acceptable in support of the pending application.

Regulatory violations were found during the inspection of Dr. Boone (Site #103) for failure to follow the investigational plan and failure to prepare or maintain accurate case histories with respect to data pertinent to the investigation. The final EIR is pending, but the findings do not appear to impact the validity of the data at the site.

The data from the CI sites and the sponsor in support of the pending application are acceptable, and the study was conducted adequately to support approval.

The Office of Study Integrity and Surveillance (OSIS) conducted inspections of New Orleans
Center for Clinical Research, Knoxville, Tennessee and Johnson County Clinical-Trials Inc. Lenexa, Kansas. Both sites conducted the portion of Study SIGA-246-008 which included the pharmacokinetics (PK) lead-in portion of the study. Although the final inspection classification for these two clinical investigator inspections was No Action indicated (NAI), ORA investigators observed GCP discrepancies with treatment allocation, treatment assignment, and dietary conditions at both audited sites when comparing source records at both sites with listings submitted to the FDA. Specifically, it appeared that 54 (of approximately 80) study subjects received opposite treatments, mixed treatments, or opposite dietary conditions than the data listings. Because those discrepancies could have occurred beyond control of the audited sites and they raised additional concerns regarding the data integrity at all sites for the study, the Applicant was asked to explain why those discrepancies have occurred through detailed Information Requests (IR) dated April 10, 2018. The sponsor response to the IR states the documentation discrepancies FDA had noted in their Information Request were due to an error in Appendix 16.1.7 of the Clinical Study Report for the SIGA-246-008 study. The randomization schedule initially provided to FDA in Appendix 16.1.7 was incorrect. The biostatistician at the Contract Research Organization had provided their medical writer with the “dummy/surrogate” randomization list to insert into the CSR instead of the list that was utilized during the conduct of the study. Comparison of the new randomization schedule (including for the remaining non-PK sites) provided by the Sponsor showed no irregularities. Additionally, the ORA Investigator conducting the Hurley inspection (Site #108) was requested to review the drug accountability log, the IWRS system, and treatment allocation, since this site was not yet complete. All logs, subject records, IWRS, and data listings matched at the site #108. Accountability logs were maintained and study drug was returned by the monitor. No other concerns were found, and the randomization tables were confirmed to match those at the CI sites.

Note: The final EIRs from the inspections of Dr. Boone and Dr. Hurley were not available at the time this clinical inspection summary was written. The final classifications for these two sites will be made later after receiving and reviewing the EIRs provided by the ORA investigators. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR. A response letter to the Form FDA 483, Inspectional Observations dated April 10, 2018 has been received and reviewed.

II. BACKGROUND

The sponsor SIGA Technologies seeks approval of oral tecovirimat in adult subjects for treatment of variola virus (VARV), the etiologic agent of smallpox. Smallpox is highly communicable and carries high morbidity and mortality. The smallpox vaccine is approved and is currently stockpiled for use in the event of a smallpox emergency, but is not universally used for prophylaxis due to a high risk of serious adverse events. There is a need for a safe and tolerable medication that can be taken by mouth and that is highly active against VARV. Tecovirimat appears to meet those qualifications, and has been included in the Strategic National Stockpile as a treatment for smallpox. Because there are no active cases of smallpox in humans in which to test the efficacy of tecovirimat, the product is being developed under the
FDA Animal Rule, and thus, there were no efficacy measures in the Phase 3 study - only the safety and the pharmacokinetic (PK) profile of the product were evaluated.

Investigators: Multicenter, 12 principal investigators, 12 sites in the United States

Study Period: June 29, 2015 – August 24, 2016

Tecovirimat inhibits an orthopoxviral protein whose activity is required for the exit of enveloped virions from the infected cell. This block in virus release is sufficient to stop the spread of infection.

The following protocol was conducted in support of efficacy under this NDA:

<table>
<thead>
<tr>
<th>Protocol Number</th>
<th>Study ID (Study Title)</th>
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<tr>
<td>SIGA 246-008</td>
<td>An Expanded Double-Blind, Randomized, Placebo-Controlled, Multicenter Trial to Assess the Safety, Tolerability and Pharmacokinetics of the Anti-Orthopoxvirus Compound Tecovirimat When Administered Orally for 14 Days in Subjects</td>
</tr>
</tbody>
</table>

This was a multicenter, double-blind, randomized, placebo-controlled, Phase 3 study to assess the safety, tolerability, and pharmacokinetics (PK) of the anti-orthopoxvirus compound oral tecovirimat 600 mg twice daily (BID) for 14 days in adult subjects.

The study was designed with a lead-in cohort of 40 subjects randomized at a 4:1 active drug/placebo ratio (32 active:8 placebo) over approximately two months, to evaluate the PK of oral tecovirimat 600 mg twice daily for 14 days in 20 fed subjects and 20 fasted subjects.

Approximately 382 additional subjects were enrolled into the expanded portion of the study at the determined dose. These subjects took study drug within 30 minutes of eating. The randomization ratio for the expanded study was 4:1 (306 active: 76 placebo). The study design allowed for approximately 322 subjects to receive tecovirimat at the targeted dose in the fed state and 80 subjects to receive placebo in the fasted state. The screening of subjects for the expanded study enrollment took place over approximately six months.

The primary outcome measure was the evaluation of the safety and tolerability of twice daily oral dosing of tecovirimat 600 mg for 14 days through assessments and procedures such as vital signs, complete and symptom-directed physical examinations, hematology and blood chemistry laboratory tests, pregnancy testing, electrocardiograms (ECGs), collection of adverse events (AEs), and review of concomitant medications.

Adult subjects from 18 to 80 years of age, inclusive, were eligible for this trial. Other inclusion criteria included availability for clinical follow-up for the duration of the study, in good general health without clinically significant medical history, able to comply with dietary requirements throughout the study drug dosing period, and physical examination and
laboratory test results without clinically significant findings within the 14 days before receipt of study drug.

**Reasons for Site Selection:**

This is a NME oral formulation for treatment of smallpox virus. Verification of data submitted in support of the requested indication was considered essential by the review division for this NDA application. The review division selected these study sites principally due to higher enrollment rates compared to other sites, and higher numbers of discontinued subjects.

Site #103 (Dr. Boone) has one IND in the CDER database and no prior history of inspections.

Site #106 (Dr. Essink) has 61 INDs in the CDER database. His last inspection was in December 2017 and was classified as NAI.

Site #108 (Dr. Hurley) has 33 INDs in the CDER database. He was inspected in January 2012, and the inspection was classified NAI.

**III. RESULTS (by site):**

<table>
<thead>
<tr>
<th>Name of CI, Address</th>
<th>Protocol #, Site #, and # of Subjects enrolled</th>
<th>Inspection Dates</th>
<th>Compliance Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gary Boone</strong></td>
<td>Protocol SIGA-246-008 Site #103 39 subjects randomized 5 discontinued</td>
<td>3/26-4/3/2018</td>
<td>*OAI</td>
</tr>
<tr>
<td>San Diego, CA 92117</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Brandon Essink</strong></td>
<td>Protocol SIGA-246-008 Site #106 40 subjects randomized 4 discontinued</td>
<td>3/12-15/2018</td>
<td>NAI</td>
</tr>
<tr>
<td>Omaha, NE 68134</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Donald Hurley</strong></td>
<td>Protocol SIGA-246-008 Site #108 22 subjects randomized 4 discontinued</td>
<td>4/9- 12/2018</td>
<td>NAI</td>
</tr>
<tr>
<td>Charleston, SC 29407</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SIGA Technologies, Inc.</strong></td>
<td>Sponsor</td>
<td>3/19-22/2018</td>
<td>NAI</td>
</tr>
<tr>
<td>Corvallis, OR 97333</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Clinical Inspection Summary
NDA 208627 tecovirimat

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
*Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Gary Boone
3737 Moraga Ave, Ste A1
San Diego, CA 92117

Note: The final EIR from the inspection of Dr. Boone was not available at the time this clinical inspection summary was written. The observations noted are based on the preliminary EIR and email communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR, and the response letter from Dr. Boone.

Dr. Gary Boone has one IND study in the CDER database, and no prior FDA inspections. For the current protocol, 39 subjects were randomized, and 35 subjects completed the study. The following documents were reviewed during this inspection: Informed Consent Documents (ICD); Subject Diaries; Source Documents for Office Visits and Telephone Contacts; Test Article Accountability Records; Randomization Documents: Electrocardiograms; Inclusion and Exclusion Criteria; Blood Chemistry Reports; Adverse Events; Protocol Deviations, Delegation Log; Electronic Case Report Forms (eCRFs); Monitoring Reports; IRB Approvals and Memberships. Other areas covered included dietary conditions; primary dose administration; supervision of study conduct; and adherence to protocol.

A Form FDA 483, Inspectional Observations was issued at the conclusion of the inspection for the following inadequacies: failure to properly supervise the conduct of this study, failure to keep adequate case histories, and under-reporting of adverse events. Dr. Boone provided a response letter dated April 10, 2018 to the Form FDA 483, Inspectional Observations.

Specifically,

1. Informed Consent was obtained by the clinical research coordinator, and not by the clinical investigator (CI) as required by the protocol for 34 of 34 subjects reviewed.

   Reviewer Comments: During the inspection, Dr. Boone stated that he spoke with the subjects to see if they had questions before signing the ICD. Although Dr. Boone failed to follow the protocol, and allowed the study coordinator to administrate the ICD, I do not think that this has a significant impact on the safety or welfare of the subjects. A response letter from Dr. Boone dated April 10, 2018 was received, in which he stated that this finding was incorrect because he was present during the consenting process, and that the study coordinator was instructed by him on how to provide any explanation of phrases or terms not understood by the subject.
2. For 11 of 17 subjects who experienced at least one adverse event (AE), the AE was entered into the eCRF before the clinical investigator assessed the seriousness or intensity of the AE prior to the CI assessing the AE. For example:

- For Subject [redacted], events of headache were documented in the AE log on June 4, 2016 and June 8, 2016, assessed by [redacted], a clinical coordinator, never signed off by the CI, and entered into the eCRF by [redacted] on June 16, 2016.

- Subject [redacted] experienced headache according to source documents which started and stopped on May 8, 2016. This was documented in the AE Log by [redacted], a clinical coordinator on May 20, 2016, and the CI signed his initials to the AE log on June 8, 2016. This AE was entered into the eCRF on May 25, 2016 by [redacted], a clinical coordinator.

- Subject [redacted] experienced headaches on May 10, 12, 15, 18, and 20, 2016. These events were assessed by [redacted], signed off by the CI on June 8, 2016, and entered into the eCRF by [redacted] on June 26, 2016.

**Reviewer Comments:** During the inspection, Dr. Boone stated that he relied on qualified study staff to make the initial assessments, and when he visited with subjects he would review the documents and sign off on the AE Log. In his response letter dated April 10, 2018, Dr. Boone stated that there were 8 (not 11) subjects whose AEs were entered into the eCRF prior to the Investigator's review. He assured corrective action. Headache is a known AE associated with the study drug, and while it is important to properly assess and document by the CI, these events were reported.

3. Protocol Version 1 required that EKGs at Day 6 Visit be done after the AM dose of study medications at 4 hours (± 1 hour) post-dose. The inspection found that for Subject [redacted], the dose on April 28, 2016 was administered at 9 am and the EKG was done at 10:46 am, 1 hour and 45 minutes later; and for Subject [redacted], the May 2, 2016 dose was administered 4:45 am and the EKG was done at 11:51 am, over 7 hours later.

**Reviewer Comments:** In his response letter dated April 10, 2018, Dr. Boone stated that he had discussed with and re-educated all site study coordinators to document the reason for any deviations. This is not a significant finding, and is unlikely to impact the safety of the subject. Protocol Amendment 2 no longer required the EKG to be conducted 4 hours (± 1 hour) post dose.

4. There were discrepancies between the protocol, the diary instructions, and the Informed Consent Document concerning if the language was “about”, “at least” or “approximately” 600 calories for dietary management.
Reviewer Comments: Subjects appeared to get a meal consisting of at least 600 calories. This is not a significant issue, because subjects who were “fed” did receive diets of 600 calories and 25 grams of fat.

Additional Comments: The response letter from Dr. Boone dated April 10, 2018 addressed each item listed on the Form FDA 483, and proposed corrective action. Dr. Boone stated that subject safety was never compromised during the study. Although Dr. Boone should have reviewed the AEs in a more timely manner, it seems likely that the study coordinators who evaluated them would have notified the CI if they were significant. The data is acceptable from this site is acceptable to use for this NDA.

2. Brandon Essink  
3319 N 107th Street  
Omaha, NE 08134

A prior inspection of this clinical investigator occurred January 29-February 1, 2018, and was classified No Action Indicated (NAI).

For the current protocol, 71 subjects were screened, 40 subjects enrolled, and 36 subjects completed the study. Of the four discontinued subjects, two were due to adverse events, and two subjects enrolled with low white blood counts and did not meet the inclusion criteria for WBC count. Dr. Essink stated that this laboratory had a higher than normal reference range for WBC, and that these two subjects had clinically normal WBC counts.

The current inspection reviewed the following: IRB approvals, study correspondence, monitoring, drug accountability records, informed consent documents, adverse events, and subject files for all 40 subjects. Source records for inclusion and exclusion criteria, protocol deviations, and adverse events were corroborated with data listings provided with the assignment. The protocol required that doses be administered every 12 hours ± 30 minutes, and there were some doses administered outside that range by one or two hours, and not reported as protocol deviations. This out of window time range is unlikely to significantly influence the outcome of the study.

Monitoring was done by [redacted], and occurred about once per month. Drug accountability records were reviewed, and the ORA field investigator verified that all subjects received the correct kit number and treatment assignment as assigned by the IWRS system used by [redacted]. The investigator confirmed that for the four meal options for subjects, all meals were at least 600 calories and 25 grams of fat, as per protocol.

No Form FDA-483 was issued. The inspection is classified as NAI.
3. **Donald Hurley**  
1481 Tobias Gadson Blvd., Ste 2  
Charleston, SC 29407

**Note:** The final EIRs from the inspection of Dr. Hurley’s site was not available at the time this clinical inspection summary was written. The observations noted are based on the preliminary email communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

Dr. Hurley has 33 INDs in the CDER database. He was last inspected in January 2012, and the inspection was classified No Action Indicated (NAI).

At this site, 44 subjects were screened and 22 subjects enrolled. There were 22 screen failures. Three subjects were lost to follow-up, and 19 subjects completed the study. The ORA investigator reviewed records for the 22 subjects enrolled. There was no evidence of underreporting of adverse events or protocol deviations. Drug accountability was well documented, and no concerns were noted during the inspection. All requested documents were collected and will be included in the EIR upon completion.

The data listings were consistent with the source documents. All logs, subject records, IWRS, and data listings matched at the site. Accountability logs were maintained and study drug was returned by the monitor. Four bottles were not accounted for, but they had been dispensed to four different subjects during the study, and the subject failed to return the empty bottles to the site. No other concerns were found.

No Form FDA-483 was issued, and the inspection is classified as No Action Indicated (NAI).

4. **SIGA Technologies, Inc.**  
4575 Southwest Research Way, Suite 110  
Corvallis, OR 97333

This was the first inspection of the sponsor SIGA Technologies. The following items were reviewed: sponsor and contract research organization (CRO) responsibilities; communication with the sites, monitors and FDA; monitoring; quality assurance; data management; adverse event reporting and adjudication by the data safety monitoring board (DSMB); primary endpoint data verification; information on clincialtrials.gov; investigational product accountability; IRB approvals, informed consent documents; signed Statements of Investigator; training of clinical investigators and clinical site personnel; sponsor’s identification and handling of noncompliance at sites; financial disclosure forms.
The sponsor contracted out most of the work for this study to CRO (b)(4). The sponsor appeared to retain adequate oversight of the clinical trial. The responsibilities of the CRO appeared to match those submitted to the FDA in the transfer of regulatory obligations documents. Responsibilities included, but were not limited to: write protocol, create Informed Consent Document (ICD), Case Report Form (CRF) design, site selection, monitoring plan and site monitoring, overall execution of study, investigator meetings and site trainings (with SIGA), medical monitoring wrote initial draft CSR, data management, SAE reconciliation, final database review, lock & transfer; randomization schedule, statistical review & analysis, PK analysis, putting together Trial Master File (TMF), vendors (central lab, imaging), selection of CIs & monitors, and control and shipping of Investigational Product (IP).

Only one SAE occurred in the Study SIGA-246-008, and it was reported to FDA. The autopsy report confirmed the findings of pulmonary embolism, and given the subject’s medical history, was not considered to be related to study drug. There was no evidence of under-reporting of adverse events. One AE of dry mouth for Subject # at Site #108 was found in a sponsor audit, after database lock, and included in an addendum to the CSR.

Data collection and management procedures appeared to have been followed. The electronic Case Report Forms (eCRFs) were electronically signed by the CIs and had audit trails.

Review of the Trial Master File (TMF), and all hard copy study information collected from clinical sites were stored in an access controlled document control room.

Test article procedures and documentation, including the certificate of analysis for the one lot of tecovirimat used in the study SIGA-246-008 and the lot of placebo were reviewed. No issues were found. Other drug accountability documents were reviewed and no issues found.

The ORA field investigator reviewed all available monitoring correspondence and information for the three inspected sites: #103 (Boone), #106 (Essink), and #108 (Hurley). Monitoring appeared adequate. Monitoring included ensuring that site personnel reviewed subject diaries with subjects at all visits to ensure that the subject was compliant and collecting the required information.

For the three inspected sites, the field investigator compared eCRFs to the data listings provided and observed they appeared to match regarding the primary endpoint data.

Protocol deviations included out-of-window visits between one and five days due to subject’s work schedules and holidays, for Site #106 (Essink) four subjects threw away one bottle each; Site #106 (Essink) and Site #108 (Hurley) enrolled two subjects, each with exclusionary low WBC count; two subjects at Site #103 (Boone) had positive urine opioids and one subject at Site #108 (Hurley) had positive amphetamine on Day
1, and were later withdrawn. All protocol deviations appeared to be appropriately reported.

No FDA 483 was issued, and the inspection is classified as NAI.

Issues Raised by the OSIS Inspections

The Office of Study Integrity and Surveillance (OSIS) conducted inspections of New Orleans Center for Clinical Research, Knoxville, TN and Johnson County Clin-Trials Inc., Lenexa, KS. Both sites conducted the portion of Study SIGA-246-008 which included the pharmacokinetics (PK) lead-in portion of the study. Although the final inspection classification for these two inspections was No Action indicated (NAI), ORA investigators observed reporting GCP discrepancies with treatment allocation, treatment assignment, and dietary conditions at both sites. During BEQ inspections, however, ORA investigators reported discrepancies with treatment allocation, treatment identity, and dietary conditions at both inspection sites (Knoxville and Kansas, the only sites where PK studies were done). Site documents showed that several study subjects (n=54) received opposite treatments, mixed treatments, or opposite dietary conditions from what was originally reported.

An IR was sent to the sponsor regarding OSIS’s findings. The documentation discrepancies FDA had noted in their Information Request were due to an error in Appendix 16.1.7 of the Clinical Study Report for the SIGA-246-008 study. The randomization schedule initially provided to in the datasets listed in Appendix 16.1.7 is incorrect. The biostatistician at the Contract Research Organization had provided their medical writer with the “dummy/surrogate” randomization list to insert into the CSR instead of the list that was utilized during the conduct of the study. Comparison of the new randomization schedule (including for the remaining non-PK sites) provided by the Sponsor showed no irregularities.

{See appended electronic signature page}

Sharon Gershon, Pharm.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:
Clinical Inspection Summary
NDA 208627 tecovirimat

{See appended electronic signature page}

Susan Thompson, M.D., Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H., Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:
Central Doc. Rm. NDA #208627
DAVP Division Director /Debra Birnkrant, MD
DAVP/Medical Team Leader/Andrew Sherwat, MD
DAVP/Medical Officer/Kirk Chan-Tack, MD
DAVP/Regulatory Project Manager/Andrew Gentles, Pharm.D.
OSI/Office Director /David Burrow
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew
OSI/DCCE/GCPAB/Team Leader/Susan Thompson
OSI/DCCE/GCP Reviewer/Sharon Gershon
OSI/ GCP Program Analysts/Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHARON K GERSHON
04/23/2018

SUSAN D THOMPSON
04/23/2018

KASSA AYALEW
04/23/2018

Reference ID: 4252179
**LABEL AND LABELING REVIEW**
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

<table>
<thead>
<tr>
<th>Date of This Review:</th>
<th>April 5, 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Requesting Office or Division:</td>
<td>Division of Antiviral Products (DAVP)</td>
</tr>
<tr>
<td>Application Type and Number:</td>
<td>NDA # 208627</td>
</tr>
<tr>
<td>Product Name and Strength:</td>
<td>Tpoxx (tecovirimat) capsule, 200 mg</td>
</tr>
<tr>
<td>Product Type:</td>
<td>Single Ingredient Product</td>
</tr>
<tr>
<td>Rx or OTC:</td>
<td>Rx</td>
</tr>
<tr>
<td>Applicant/Sponsor Name:</td>
<td>Siga Technologies, Inc.</td>
</tr>
<tr>
<td>Submission Date:</td>
<td>12/08/2017 and 2/23/2018</td>
</tr>
<tr>
<td>OSE RCM #:</td>
<td>2017-2539</td>
</tr>
<tr>
<td>DMEPA Safety Evaluator:</td>
<td>Cameron Johnson, PharmD</td>
</tr>
<tr>
<td>DMEPA Team Leader:</td>
<td>Otto L. Townsend, PharmD</td>
</tr>
</tbody>
</table>
1 PURPOSE OF REVIEW
As part of the approval process for Tpoxx (tecovirimat) capsule, 200 mg, the Division of Antiviral Products requested that we review the proposed packaging, label and labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND
Seventy-two lots of tecovirimat received approval to be stored in the Strategic National Stockpile (SNS) under IND 69019. These lots may be distributed under an Emergency Use Authorization prior to approval of NDA 208627 (subject of this review). The lots received label exceptions, in which an expiration date was not required on the unit of use bottle label.

A label exception, as per 21CFR 201.26 for the relabeling of drugs currently stocked in the SNS as well as drug that will be supplied to the SNS following NDA approval of tecovirimat, has been requested by the Applicant. The Applicant plans to supply tecovirimat in unit of use bottles of 42 tablets, that will be packaged in a tray containing containers. Trays will be placed in a shipper containers and shippers will be placed in a pallet containers. If approved, the label exception will only require the expiration date to be placed on the pallet and not the shipper, tray or immediate container (unit of use bottle) of drug. This request is to ease the labor and time that would be required for relabeling drug that is already stored in the SNS (i.e. unwrapping the pallets, shippers and trays to place an expiration date on each bottle) as well as in cases where the expiration date may be extended based on stability testing. A label exception would ensure that if the expiration can be extended in the future, only the label on the pallet would need to be changed. In the event of expiration date extensions, the Applicant plans to relabel the pallet package configuration only with the updated expiration date. Furthermore, the tecovirimat that is currently stored in the SNS does not contain the “Rx Only” statement. The company has requested that the FDA “exercise enforcement discretion regarding the requirement of this statement” since the “Rx only” statement is not an element that can be omitted per 21CFR 201.26.
2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

<table>
<thead>
<tr>
<th>Material Reviewed</th>
<th>Appendix Section (for Methods and Results)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Information/Prescribing Information</td>
<td>A</td>
</tr>
<tr>
<td>Previous DMEPA Reviews</td>
<td>B</td>
</tr>
<tr>
<td>ISMP Newsletters</td>
<td>C- N/A</td>
</tr>
<tr>
<td>FDA Adverse Event Reporting System (FAERS)*</td>
<td>D- N/A</td>
</tr>
<tr>
<td>Other</td>
<td>E- N/A</td>
</tr>
<tr>
<td>Labels and Labeling</td>
<td>F</td>
</tr>
</tbody>
</table>

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

As noted above, we are aware that the Applicant has submitted a labeling exception request. We did not identify any medication error concerns with the proposed exception and associated relabeling plan. Tables 2 and 3 below include the identified medication error issues with the submitted packaging, label and labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2: Identified Issues and Recommendations for Division of Antiviral Products

<table>
<thead>
<tr>
<th>Prescribing Information</th>
<th>IDENTIFIED ISSUE</th>
<th>RATIONALE FOR CONCERN</th>
<th>RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highlights of Prescribing Information</td>
<td>1. In the dosage and administration section, the weight is expressed (b)(4)</td>
<td>(b)(4)</td>
<td>Patient weights should be expressed in metric units (kilograms) (b)(4) should be consistent between the Highlights and FPI.</td>
</tr>
<tr>
<td>Full Prescribing Information</td>
<td>1. In Section 2, Dosage and Administration, (b)(4)</td>
<td>The amount of liquid needed to mix the contents of a</td>
<td></td>
</tr>
<tr>
<td>subsection 2.3 (Preparation for Administration to Pediatrics and Those Who Cannot Swallow Capsules),</td>
<td>capsule should be expressed “30 mL”).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>----------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>milliliters are used to express the amount of liquid or soft food to mix with the contents of a capsule.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. In Section 2 Dosage and Administration, subsection 2.3 Preparation for Administration to Pediatrics and Those Who Cannot Swallow Capsules may result in misinterpretation and confusion which could lead to a medication error. To prevent misinterpretation and confusion.

---


3. In Section 2 Dosage and Administration, subsections 2.1, 2.2 and 2.3 the weight based dosing could result in a prescribing medication error. Include the weight in metric units (kg).

4. In Section 2 Dosage and Administration, subsection 2.3 Preparation for Administration to Pediatrics and Those Who Cannot Swallow Capsules, there is not a unit of measurement following every numeral for the weight range and the dash symbol “-“ is used (e.g. kg). Confusion may occur if the unit of measure for each weight is not explicitly expressed and the dash symbol “-“ may result in misinterpretation which could lead to a medication error. To improve readability, we recommend adding a unit of measurement, kg, after each numeral in the weight range and use the word “to” instead of a dash (e.g. change (b) (4) to (b) (4)).

Table 3: Identified Issues and Recommendations for Siga Technologies, Inc. (entire table to be conveyed to Applicant)

<table>
<thead>
<tr>
<th>Container Labels</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
</tr>
</tbody>
</table>

Reference ID: 4244755
2. The net quantity statement “42 capsules” on the container label is Use [b][4] for the net quantity statement.

3. The pallet package configuration does not contain a barcode or NDC. The barcode is often used as an additional verification before drug distribution, dispensing and administration; therefore, it is an important safety feature that should be part of the label and labeling whenever possible. If the Smallpox Response Plan is implemented, during a smallpox outbreak, the pallet package configuration may be used to distribute the product. A barcode on the pallet may be beneficial in identifying and tracking the product. We recommend adding a linear barcode as well as an NDC to the pallet package configuration. If a barcode is added, an NDC is required per the barcode rule, 21 CFR 201.25.

4 CONCLUSION
DMEPA’s evaluation of the proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. We provided recommendations in Table 2 above for the Division. We also have provided recommendations in Table 3 above and ask that the Division conveys Table 3 in its entirety to Siga Technologies, Inc. so that recommendations are implemented prior to approval of this NDA.
APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Tpoxx that Siga Technologies, Inc. submitted on 2/23/2018.

<table>
<thead>
<tr>
<th>Table 4. Relevant Product Information for Tpoxx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Approval Date</td>
</tr>
<tr>
<td>Active Ingredient</td>
</tr>
<tr>
<td>Indication</td>
</tr>
<tr>
<td>Route of Administration</td>
</tr>
<tr>
<td>Dosage Form</td>
</tr>
<tr>
<td>Strength</td>
</tr>
</tbody>
</table>
| Dose and Frequency    | Adults and pediatrics greater than \( \text{(b) (4)} \): 600 mg twice daily for 14 days  
                        | Pediatric dosing:  
                        | o between \( \text{ (b) (4)} \): 200 mg twice daily for 14 days  
                        | o between \( \text{ (b) (4)} \): 400 mg twice daily for 14 days |
| How Supplied          | 200 mg hard gelatin capsules packaged in bottles of 42 capsules |
| Storage               | Store at 20-25°C (68-77°F) excursions permitted 15-30°C (59-86°F) |
| Container Closure     | 75 cc high-density polyethylene (HDPE) bottles fitted with heat induction seal and child-resistant screw cap closure system. |

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On 1/29/2018, we searched the L:drive and AIMS using the term, tecovirimat, to identify reviews previously performed by DMEPA. The reviews and summary of recommendations from these reviews are provided in Table 5.
B.2 Results

Our search identified 2 previous reviews, and we confirmed that our previous recommendations have not yet been implemented primarily due to changes in product characteristics.

<table>
<thead>
<tr>
<th>OSE RCM #</th>
<th>Review Date</th>
<th>Summary of Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-851</td>
<td>October 3, 2013</td>
<td>This review evaluated the instructions for use (IFU) entitled submitted by the Centers for Disease Control and Prevention (CDC) under IND 116039. DMEPA found areas of vulnerability within the instructions and provided comments and recommendations in the form of tracked changes. There was no further correspondence from CDC with regards to these recommendations.</td>
</tr>
<tr>
<td>2016-397</td>
<td>September 16, 2016</td>
<td>This memorandum review of revised label and labeling evaluated the protocol, “Study to Observe and Evaluate Home Preparation of Tecovirimat Mixed in Liquid and Soft Foods” submitted by SIGA pharmaceuticals under IND 69019. The protocol was reviewed by DMEPA and found to have deficiencies. DMEPA requested that the company provide a use related risk analysis (URRA) and submit information regarding the clinical implications related to incorrect mixing time of the food/drug mixture in the infant population. After submitting the risk analysis, the sponsor company stated that the purpose of the study was designed to be a label comprehension study as well as to assess the homogeneity of the product and not human factors. FDA recommended that the company conduct and submit an analytical study to assess the homogeneity and mixing instructions and then submit a human factors validation study for review. A human factors study has not been submitted and the current labeling does not include infant dosing.</td>
</tr>
</tbody>
</table>


Table 5. Summary of Previous DMEPA Reviews for Tpoxx

<table>
<thead>
<tr>
<th>OSE RCM #</th>
<th>Review Date</th>
<th>Summary of Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017-1175</td>
<td>July 20, 2017</td>
<td>An internal PreNDA meeting was held in response to a Siga Pharmaceuticals request for a Type B Meeting. Siga submitted a meeting package and DMEPA was consulted to review the HF questions and provide comments. In the meeting package, SIGA asked if it should “remove pediatrics from the indication and the dosing for pediatrics instructions from the FPI until Agency review and concurrence on the Human Factors results...?“ DMEPA responded that “in the absence of results from a human factor (HF) usability validation study, you should only propose dosing recommendations in the original NDA for pediatric patients who would not require partial (i.e. less than 1 capsule) dosing”. DMEPA also provided additional comments that the company should use their comprehensive use related risk analysis (URRA) to inform the design of a human factors validation study protocol. The meeting request was withdrawn by the applicant after receipt of the preliminary comments⁶.</td>
</tr>
</tbody>
</table>

APPENDIX C. N/A

APPENDIX D. N/A

APPENDIX E. Other

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,⁷ we reviewed the following Tpoxx labels and labeling submitted by Siga Technologies, Inc. on 12/08/2017 and 2/23/2018.

- Container label for new lots of NDA Approved Drug received on 2/23/2018
- Current label on container of drug currently contained in the SNS received on 12/08/2018

⁶ Wilson, V. Type B Internal PreNDA Meeting Preliminary Comments for Tecovirimat IND 69019. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JUL 20. RCM No.: 2017-1175

• Schematic for pallet Label for all future lots for SNS received on 12/08/2018
• Schematic for Tray and Shipper Labels for all future lots for SNS received on 12/08/2018
• Medication Guide received on 2/23/2018
• Prescribing Information (Image not shown) received on 2/23/2018

F.2 Label and Labeling Images

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CAMERON D JOHNSON
04/05/2018

OTTO L TOWNSEND
04/05/2018
DATE: April 3, 2018

TO: Debra Birnkrant, MD
   Director
   Division of Antiviral Products (DAVP)
   Office of Antimicrobial Products

FROM: Ruben C. Ayala, Pharm.D.
   Lead Pharmacologist
   Division of New Drug Bioequivalence Evaluation (DNDBE)
   Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
   Deputy Director
   DNDBE, OSIS

SUBJECT: Routine inspection of the clinical portion of study SIGA-246-008 (NDA 208627) conducted at New Orleans Center for Clinical Research, Knoxville, TN and Johnson County Clin-Trials Inc., Lenexa, KS.

**Inspection Summary**

The Office of Study Integrity and Surveillance (OSIS) arranged inspections of New Orleans Center for Clinical Research, Knoxville, TN and Johnson County Clin-Trials Inc., Lenexa, KS. Both sites conducted the clinical portion of study SIGA-246-008 submitted in support of NDA 208627.

No objectionable conditions were observed and Form FDA 483 was not issued at the close-out of the inspections. The final inspection classification for both audited sites is No Action Indicated (NAI).

However, ORA investigators observed reporting discrepancies with treatment allocation, treatment identity and dietary conditions at both sites. Specifically, site documents showed that several study subjects (n=54) received opposite treatments (e.g., test instead of placebo), mixed treatments (test and placebo), or opposite dietary conditions (e.g., fed instead of fasted) during the study. Because the findings occurred at both audited sites,
Page 2 - Routine inspection of the clinical portion of study SIGA-246-008 (NDA 208627) conducted at New Orleans Center for Clinical Research, Knoxville, TN and Johnson County Clin-Trials Inc, Lenexa, KS.

It’s likely that other non-audited, clinical sites participating in study SIGA-246-008 were also affected.

After reviewing the inspectional findings, I conclude that a large portion of the clinical data generated by both sites for study SIGA-246-008 (NDA 208627) are not reliable and should not be accepted for further Agency review. I recommend that DAVP rejects data from 30 subjects enrolled at New Orleans Center for Clinical Research and 24 subjects from Johnson County Clin-Trials. The Applicant should rectify the reporting issues if possible, and determine if the issues affected other non-audited, clinical sites involved with study SIGA-246-008.

The current inspections at each site covered one study only and didn’t reveal whether the adverse finding was systemic or isolated in nature. Therefore, DAVP should scrutinize information on treatment allocation, treatment identity, and dosing conditions in other studies (Attachment 1) in which the two audited sites participated before accepting their clinical data for review.

**Inspected Study:**

**NDA 208627**

**Study Number:** SIGA-246-008  
**Study Title:** “An expanded double-blind, randomized, placebo-controlled, multicenter trial to assess the safety, tolerability, and pharmacokinetics of the anti-orthopoxvirus compound tecovirimat when administered orally for 14 days in subjects”  
**Dates of conduct:** 6/29/2015 to 8/24/2016

**Site 1:**

**Site Name:** New Orleans Center for Clinical Research  
**Street Address:** 1928 Alcoa Highway, Suite 107  
**City, State:** Knoxville, TN 37920  
**Investigator Name:** William B. Smith, MD

**Site 2:**

**Site Name:** Johnson County Clin-Trials Inc.  
**Street Address:** 16300 College Blvd
New Orleans Center for Clinical Research (Site 101)

ORA Investigator Ann B. Borromeo (BIMOE) inspected New Orleans Center for Clinical Research, Knoxville, TN from January 23 to 26, 2018.

The inspection included a thorough examination of study records, subject records, informed consent process, protocol compliance, institutional review board (IRB) approvals, sponsor and monitor correspondence, test article accountability and storage, randomization, adverse events, and case report forms (CRFs).

At the conclusion of the inspection, Investigator Borromeo did not observe objectionable conditions and did not issue Form FDA 483 to the clinical site. However, she noticed reporting discrepancies with treatment allocation and identity and dietary conditions. Specifically, site documentation showed that several subjects received:

1. Placebo and test article when the protocol called for one treatment during the lead-in period;

2. Test article but were reported in the placebo group (and vice versa); and/or

3. The opposite dietary conditions during dosing days.

The following table displays examples of reporting discrepancies among site records and documents submitted to FDA. Additional examples are provided in Attachment 2.
Page 4 - Routine inspection of the clinical portion of study SIGA-246-008 (NDA 208627) conducted at New Orleans Center for Clinical Research, Knoxville, TN and Johnson County Clin-Trials Inc, Lenexa, KS.

<table>
<thead>
<tr>
<th>Sub ID</th>
<th>Rand #</th>
<th>Bottle s dispensed on day 1 per site records</th>
<th>Bottle identity per CSR section 16.1.7 (T=Test; P=Placebo)</th>
<th>Dosing per Exposure (EX) dataset</th>
<th>Measurable drug conc per FC dataset</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1013</td>
<td>10554; 10562</td>
<td>F; T</td>
<td>T all 14 days</td>
<td>Yes</td>
<td>Sub received mixed treatments? Reporting error?</td>
<td></td>
</tr>
<tr>
<td>1008</td>
<td>10146; 10622</td>
<td>T; T</td>
<td>P all 14 days</td>
<td>No</td>
<td>Sub received opposite treatment? Reporting error?</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sub ID</th>
<th>Rand #</th>
<th>IWRS instructions</th>
<th>Randomization scheme CSR 16.1.7</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1013</td>
<td>Fasted cohort</td>
<td>Fed cohort</td>
<td>Sub received opposite dietary condition? Reporting error?</td>
<td></td>
</tr>
</tbody>
</table>

*During the Lead-in period, the site dispensed two bottles each containing forty-two, 200-mg capsules to attain a dosing schedule of 600 mg BID for 14 days.

The above finding was discussed with site personnel during the inspection. In their response, they stated that the Interactive Web Response System (IWRS) generated an email containing two bottle numbers to be dispensed and communicated fed or fasted conditions. The site dispensed both treatment bottles to subjects at the same time and instructed subjects to finish one bottle before starting on the subsequent one. Per site personnel, there was no way to determine if subjects followed these instructions after leaving the clinic and completing the study at home.

**OSIS Evaluation:** Per inspection findings, 30 out of 40 subjects enrolled at this site had reporting discrepancies (Attachment 2) which cast doubt on the reliability of study data. In contrast, data from subjects appear to be reliable because information is consistent among data collected at the site and reports submitted to FDA. Therefore, I recommend that DAVP accept data from these 10 subjects only. The Applicant should rectify reporting discrepancies from the remaining 30 subjects, if possible.
Page 5 - Routine inspection of the clinical portion of study SIGA-246-008 (NDA 208627) conducted at New Orleans Center for Clinical Research, Knoxville, TN and Johnson County Clin-Trials Inc, Lenexa, KS.

**Johnson County Clin-Trials Inc (Site 102)**

ORA Investigator Lori Gioia (BIMOW) inspected Johnson County Clin-Trials, Lenexa, KS from February 12 to 14, 2018.

The inspection included a thorough examination of study records, subject files, informed consent process, protocol deviations, IRB approvals, sponsor and monitor correspondence, test article accountability and storage, randomization, adverse events and CRFs.

At the conclusion of the inspection, Investigator Gioia did not observe objectionable findings and did not issue Form FDA 483 to the clinical site. However, she noticed reporting discrepancies related to treatment allocation and identity. Specifically, some subjects were documented to have received:

1. Placebo and test article when the protocol called for one treatment during the expanded period; or

2. Test article but were reported in the placebo group (and vice versa)

The following table displays examples of reporting discrepancies among site records and documents submitted to FDA. Additional examples are provided in **Attachment 3**.

<table>
<thead>
<tr>
<th>Sub ID</th>
<th>Rand #</th>
<th>Bottle #s dispensed per drug accountability log*</th>
<th>Bottle identity per CSR section 16.1.7 (T=Test; P=Placebo)</th>
<th>Randomization Scheme, CSR 16.1.7</th>
<th>Dosing per Exposure (EX) Dataset</th>
<th>Measurable drug conc per FC dataset</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0046</td>
<td>3531</td>
<td>10503; 11385</td>
<td>T; P</td>
<td>T</td>
<td>T all 14 days</td>
<td>Yes</td>
<td>Sub received mixed treatment?</td>
</tr>
<tr>
<td>4541</td>
<td>10077; 10824</td>
<td></td>
<td>T; T</td>
<td>P</td>
<td>T all 14 days</td>
<td>Yes</td>
<td>Subject received opposite treatment? Reporting error at 16.1.7?</td>
</tr>
</tbody>
</table>
Page 6 - Routine inspection of the clinical portion of study SIGA-246-008 (NDA 208627) conducted at New Orleans Center for Clinical Research, Knoxville, TN and Johnson County Clin-Trials Inc, Lenexa, KS.

During the expanded period, the site dispensed two bottles each containing forty-two, 200-mg capsules to attain a dosing schedule of 600 mg BID for 14 days.

Investigator Gioia stated via email that she didn’t discuss the above finding with clinical site management because they correctly dispensed treatment bottles per the study’s IWRS. However, she informed them about a potential problem with randomization. The site didn’t comment on the finding.

**OSIS Evaluation:** Per inspection findings, 24 out of 41 subjects enrolled at this site had reporting discrepancies (*Attachment 3*), which cast doubt on the reliability of study data. In contrast, data from subjects appear to be reliable because information is consistent among data collected at the site and reports submitted to FDA. Therefore, I recommend that DAVP accept data from these 17 subjects only. The Applicant should rectify reporting discrepancies from the remaining 24 subjects, if possible.

**Conclusion:**

After reviewing the inspectional findings, I conclude that clinical data from 30 and 24 subjects generated by New Orleans Center for Clinical Research and Johnson County Clin-Trials Inc, respectively, for study SIGA-246-008 (NDA 208627) are not reliable and should not be accepted for further Agency review. The Applicant should rectify treatment allocation, identity and dosing conditions at both audited sites, and determine if the findings affected other non-audited clinical sites involved with the study.

The final inspection classifications for both sites is NAI because reporting discrepancies may have occurred beyond the control of the sites. The discrepancies were discovered only after comparing documents at the site and those submitted to FDA.
Page 7 – Routine inspection of the clinical portion of study SIGA-246-008 (NDA 208627) conducted at New Orleans Center for Clinical Research, Knoxville, TN and Johnson County Clin-Trials Inc, Lenexa, KS.

The current inspections at each site covered one study only and didn’t reveal whether the adverse finding was systemic or isolated in nature. Therefore, DAVP should scrutinize information on treatment allocation, treatment identity, and dosing conditions in other studies in which the two audited sites participated before accepting their clinical data for review.

Ruben C. Ayala, Pharm.D.
Lead Pharmacologist

Final Classification:

Clinical Sites

NAI - New Orleans Center for Clinical Research
Knoxville, TN 37920
FEI#: 3013166872

NAI - Johnson County Clin-Trials, Inc.
Lenexa, KS 66219-1376
FEI#: 3011592022

cc:
OTS/OSIS/Kassim/Choe/Mitchell/CDER-OSIS-BEQ
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Biswa/Ayala
OTS/OSIS/DGDBE/Cho/Kadavil/Choi/Skelly/Au
ORA/Gioia/Borromeo

Draft: RCA 4/02/2018; 4/03/2018
Edit: AD 04/03/2018

ECMS:
New Orleans Center for Clinical Research
http://ecmsweb.fda.gov:8080/webtop/drl/objectId/0b0026f8818057fc

Johnson County Clin-Trials, Inc.
http://ecmsweb.fda.gov:8080/webtop/drl/objectId/0b0026f8818046ab

OSIS File #: BE 7784

FACTS: 11809396
Page 8 - Routine inspection of the clinical portion of study SIGA-246-008 (NDA 208627) conducted at New Orleans Center for Clinical Research, Knoxville, TN and Johnson County Clin-Trials Inc, Lenexa, KS.

Attachment 1

Studies in support of Pending Applications

<table>
<thead>
<tr>
<th>Application #</th>
<th>Study #</th>
<th>Drug Name(s)</th>
<th>Dates of conduct</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDA 208627</td>
<td>SIGA-246-008</td>
<td>Tecovirimat</td>
<td>6/29/2015 to 8/24/2016</td>
</tr>
</tbody>
</table>

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/s/

RUBEN C AYALA
04/03/2018

ARINDAM DASGUPTA
04/03/2018
Date: February 1, 2018

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

To: Andrew Gentles, RPM
DAVP

Subject: QT-IRT Consult to NDA 208627

Note: Any text in the review with a light background should be inferred as copied from the sponsor’s document.

This memo responds to your consult to us dated 12/14/2017 regarding QT related information included in the NDA submission in response to a previous request from the QT-IRT. The QT-IRT reviewed the following materials:

- Previous QT-IRT reviews under IND 69019 dated 04/27/2016; 08/16/2017 in DARRTS;
- “Electrocardiographic Effects of Tecovirimat and Metabolites: M4, M5 and TF MBA” submitted to sequence 0003 dated 12/5/2017; and

1. QT-IRT Responses

We have reviewed the results of study SIGA 246-008 and together with the results of the thorough QT study we have concluded that small mean increases (i.e. 10 ms) in the QTc interval can be excluded at the therapeutic exposure for tecovirimat.

2. BACKGROUND

SIGA Technologies, Inc. is developing tecovirimat as an oral capsule for treatment of smallpox and other human orthopoxvirus disease (e.g., monkeypox, as well as post-exposure treatment of orthopoxvirus infection.
A thorough QT study (SIGA-246-010) was conducted for tecovirimat, which has been reviewed by the QT-IRT (DARRTs 08/16/2017). No significant QTc prolongation was observed in the study for a single dose of 1000 mg tecovirimat, which corresponds to the therapeutic exposure of tecovirimat (DARRTs 04/27/2017). However, significant accumulation is expected for three metabolites (2 to 5-fold) and the exposure after a single dose of 1000 mg of tecovirimat does therefore not cover the expected steady-state exposure for these three metabolites. Moreover, there is only limited information about the preclinical signal for QT prolongation for any of the three metabolites.

The focus of the current submission is to review the data collected in study 246-008 and evaluate if the steady-state ECG data from that study can close the gap in the thorough QT study for the three major metabolites.

**SIGA 246-008**
This was a multicenter, double-blind, randomized, placebo-controlled, Phase 3 study to assess the safety, tolerability, and PK of oral tecovirimat 600 mg BID for 14 days in adult subjects. The study was designed as a two-stage study with a lead-in cohort of 40 subjects to evaluate the PK of oral tecovirimat 600 mg BID for 14 days in 20 fed subjects and 20 fasted subjects. The lead-in cohort was followed by the expanded phase of the study which included an additional 319 fed subjects with a PK subset of 40 subjects. Overall, the study included 359 subjects treated with tecovirimat and 90 with placebo.

**PK collection**
Blood was collected at specific time points to determine the PK of tecovirimat and metabolites vs placebo in humans. Blood samples from approximately 80 subjects were to be evaluated for PK analysis at the targeted dose level identified by the Lead-in cohort of the study. This included 40 subjects from the Lead-in cohort and 40 subjects from the PK subset in the expanded study. Pharmacokinetic collection and data analysis were evaluated from 20 subjects in the Lead-in cohort who took study drug in a fasted state and 20 subjects who took study drug in a fed state. All PK samples collected from the expanded study PK subset were from subjects who took study drug in a fed state.

Pharmacokinetic evaluations were performed at each of the following time points:

- **Days 1-2:** Day 1 at Baseline (before dosing), at 0.5, 1, 2, 4, 6, and 8 hours (± 5 minutes), and at 12, 14, 16, 18, 20, and 24 hours (± 15 minutes) after the Day 1 AM dose,
- **Day 6:** Before the AM dose and at 4 hours (± 15 minutes) after the Day 6 AM dose,
- **Day 14:** Before the AM dose, at 0.5, 1, 2, 4, 6, and 8 hours (± 5 minutes), and at 12, 14, 16, 18, 20, and 24 hours (± 15 minutes) after the Day 14 AM dose,
- **The 12 and 24 hour (± 15 minutes) PK samples were to be collected before PM and AM dosing, respectively.**

**Lead-in Cohort ONLY:**
- **Samples collected at 48, 72, 96, 120, and 144 hours (± 1 hour) after the Day 14 AM dose.**

Reference ID: 4215674
ECG collection

ECGs were digitally recorded using an Eli 150c ECG machine (Mortara) provided by the corelab (1). A paper copy of the tracing was printed on-site and an electronic copy was sent to the corelab. The screening ECGs were read locally and the post-screening ECGs were reviewed by a single cardiologist who measured the cardiac intervals on the Global Superimposed Median Beat in a semi-automated manner and provided a morphological waveform assessment on each ECG.

For subjects participating in the PK portion of the study, an ECG was done at:
- Screening,
- Day -1 Check-in Visit before Dose 1,
- Day 2 Visit after Dose 3,
- Day 6 (± 1 day) Visit after the AM dose, and
- Day 15 Dosing Complete/Early Termination Visit after study drug dosing was complete.

For non-PK subjects enrolled in the expanded study, ECGs were done at:
- Screening,
- Day 1 Visit before Dose 1,
- Day 6 (± 1 day) Visit after the AM dose, and
- Day 15 Dosing Complete/Early Termination Visit after study drug dosing was complete.

PK results

This section focuses on the PK results in fed subjects because tecovirimat is being developed for oral administration in the fed state. In this study, tecovirimat was given at 600 mg BID for 14 days and the PK samples were collected at various time points on Day 1, at pre- and 4 hours post-morning dose on Day 6, and at various time points from Day 14 to Day 20 (4.3.1.1 Pharmacokinetic Evaluations).

Table 2 presents the percentage of total exposure of tecovirimat and metabolites M4, M5, and TFMB in plasma in fed subjects on Day 1 and Day 14.

Table 1: Plasma exposure for tecovirimat and metabolites (M4, M5 and TFMB) in fed subjects on day 1 and 14

<table>
<thead>
<tr>
<th></th>
<th>C_{max} (μg/mL)</th>
<th>AUC_{0-24} (h·μg/mL)</th>
<th>% of Total Exposure Day 1</th>
<th>Day 14</th>
<th>% of Total Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tecovirimat</td>
<td>1591.00</td>
<td>2208.75</td>
<td>25875.94</td>
<td>24.0</td>
<td>30632.18</td>
</tr>
<tr>
<td>M4</td>
<td>906.96</td>
<td>1289.52</td>
<td>13634.28</td>
<td>12.6</td>
<td>23486.76</td>
</tr>
<tr>
<td>M5</td>
<td>109.11</td>
<td>665.48</td>
<td>929.11</td>
<td>0.9</td>
<td>13066.87</td>
</tr>
<tr>
<td>TFMB</td>
<td>5135.63</td>
<td>7955.83</td>
<td>67597.04</td>
<td>62.6</td>
<td>159582.68</td>
</tr>
</tbody>
</table>

Source: ECG Report, Table 2, Page 11

Of note, the ECGs collected on day 15 were not matched to a PK sample. However, based on the available PK information in the fed population, it is unlikely that this would impact the interpretation of the ECG information for the three major metabolites (M4, M5, TFMB).
Figure 1: M4, M5 and TFMBPA plasma concentration-time profiles. Green arrows indicate approximate ECG collection time.

Source: ECG Report, Figure 1, Page 12

ECG results

QTcF changes from baseline for the placebo and tecovirimat treatment group and change from baseline and placebo in the safety population are shown in Table 4.

Table 2: Change from baseline on day 6 and 15 for tecovirimat and placebo

<table>
<thead>
<tr>
<th>ECG Parameter</th>
<th>Visit</th>
<th>Statistic</th>
<th>Tecovirimat 600 mg</th>
<th>Placebo</th>
<th>Tecovirimat 600 mg (Placebo-Adjusted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTcF Interval (msec)</td>
<td>Day 6</td>
<td>n=349</td>
<td>349</td>
<td>89</td>
<td>349</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean (SD)</td>
<td>-0.5 (13.43)</td>
<td>-0.2 (11.49)</td>
<td>-0.2 (13.43)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Min Max</td>
<td>-82.47</td>
<td>-32.28</td>
<td>-82.47</td>
</tr>
<tr>
<td></td>
<td></td>
<td>90% CI of Mean</td>
<td>-1.6, 0.7</td>
<td>-2.2, 1.8</td>
<td>-1.4, 1.0</td>
</tr>
<tr>
<td></td>
<td>Day 15</td>
<td>n=342</td>
<td>342</td>
<td>86</td>
<td>342</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean (SD)</td>
<td>-1.5 (11.56)</td>
<td>-0.0 (11.91)</td>
<td>-1.5 (11.56)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median</td>
<td>-2</td>
<td>1</td>
<td>-2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Min Max</td>
<td>-48.38</td>
<td>-24.30</td>
<td>-48.38</td>
</tr>
<tr>
<td></td>
<td></td>
<td>90% CI of Mean</td>
<td>-2.5, -0.5</td>
<td>-2.2, 2.1</td>
<td>-2.5, -0.4</td>
</tr>
</tbody>
</table>

Source: ECG Report, Table 4, Page 15

None of the subjects had a QTcF above 480 ms or an increase from baseline above 60 ms. Subjects with a QTcF above the normal range (450 ms for males, 470 ms for females) and increase from baseline greater than 30 ms are shown in Table 5.
Table 3: Listing of subjects with change from baseline in QTcF >30 ms or ECG above normal range

<table>
<thead>
<tr>
<th>Subject ID (b)</th>
<th>Treatment</th>
<th>Normal Range (ms)</th>
<th>Visit</th>
<th>Baseline</th>
<th>Response</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tecovirimat 600 mg</td>
<td>(320,470)</td>
<td>Day 6</td>
<td>390.67</td>
<td>425.67</td>
<td>35.00</td>
</tr>
<tr>
<td></td>
<td>Tecovirimat 600 mg</td>
<td>(320,470)</td>
<td>Day 15</td>
<td>390.67</td>
<td>426.00</td>
<td>35.33</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>(320,450)</td>
<td>Day 15</td>
<td>397.67</td>
<td>428.00</td>
<td>30.33</td>
</tr>
<tr>
<td></td>
<td>Tecovirimat 600 mg</td>
<td>(320,450)</td>
<td>Day 15</td>
<td>366.33</td>
<td>404.67</td>
<td>38.33</td>
</tr>
<tr>
<td></td>
<td>Tecovirimat 600 mg</td>
<td>(320,470)</td>
<td>Day 6</td>
<td>420.33</td>
<td>453.67</td>
<td>33.33</td>
</tr>
<tr>
<td></td>
<td>Tecovirimat 600 mg</td>
<td>(320,470)</td>
<td>Day 6</td>
<td>384.67</td>
<td>417.00</td>
<td>32.33</td>
</tr>
<tr>
<td></td>
<td>Tecovirimat 600 mg</td>
<td>(320,470)</td>
<td>Day 6</td>
<td>385.00</td>
<td>432.00</td>
<td>47.00</td>
</tr>
<tr>
<td></td>
<td>Tecovirimat 600 mg</td>
<td>(320,470)</td>
<td>Day 6</td>
<td>406.00</td>
<td>442.33</td>
<td>36.33</td>
</tr>
<tr>
<td></td>
<td>Tecovirimat 600 mg</td>
<td>(320,450)</td>
<td>Day 15</td>
<td>450.67</td>
<td>456.67</td>
<td>6.00</td>
</tr>
<tr>
<td></td>
<td>Tecovirimat 600 mg</td>
<td>(320,450)</td>
<td>Day 15</td>
<td>438.33</td>
<td>453.33</td>
<td>15.00</td>
</tr>
</tbody>
</table>

Source: ECG Report, Table 5, Page 16

Reviewer’s Comments:

- The PK data collected in this study suggest that steady-state levels are reached by day 14 and that little fluctuation is expected between the last dose and the timing of the ECG collection.
  - Additionally, the PK data suggests that the M4 and M5 metabolites are minor metabolites and the Cmax of TFMBA, the most abundant metabolite, is ~1.87-fold higher than what was observed in the thorough QT study.
- The statistical reviewer could reproduce the results of Table 2, which does not suggest the presence any significant difference between tecovirimat and placebo.
- Taken altogether, the data collected in the thorough QT study and the results of this study supports the absence of small mean increases (i.e. 10 ms) on the QTc interval at therapeutic exposure.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderderpqt@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LARS JOHANNESEN
02/01/2018

CHRISTINE E GARNETT
02/01/2018
Inspection Assignment Memorandum

User Fee: Yes, PDUFA
Surveillance: Yes
Directed: No

Application: Yes
Submission: Premarket Original

Entity: Contract Research Organization (CRO)
Date: 1/19/2018

From: Yiyue Zhang, Ph.D.
Visiting Associate
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993

To: Division of Bioresearch Monitoring Operations East (BIMOE)-Division 1
Division of Bioresearch Monitoring Operations West (BIMOW)-Division 2

Preannounce: No
Priority: Yes
ORA Due Date: 4/2/2018

Compliance Program: 7348.001 (BE)
Program Assignment Code: 48001A (NDA)
Operation Code: 12 (Domestic)

Application Number: NDA 208627
Product Name: Tecovirimat Capsules

Sponsor: Siga Technologies Inc
4575 SW Research Way, Corvallis, OR 97333

Study/Protocol Number: SIGA-246-008

Center Participation: □ Yes or ☒ No

Joint Regulatory Agency Participation: □ Yes or ☒ No

Reference ID: 4209318
<table>
<thead>
<tr>
<th>Establishments for inspection</th>
<th>FEI Numbers</th>
<th>FACTS Number</th>
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<tbody>
<tr>
<td>New Orleans Center for Clinical Research</td>
<td>3013166872</td>
<td>11809396</td>
</tr>
<tr>
<td>1924 Alcoa Highway</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4th and 5th Floors North Tower</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knoxville, TN 37920</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEL: (865) 305-9100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAX: (865) 305-8381</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Johnson County Clin-Trials, Inc</td>
<td>3011592022</td>
<td>11809396</td>
</tr>
<tr>
<td>16300 College Blvd</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lenexa, KS 66219</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEL: (913) 825-4400</td>
<td></td>
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</tr>
</tbody>
</table>

**NOTE**

Please contact the OSIS scientific point of contact (POC) at [CDER-OSIS-SCIPOC-BE@fda.hhs.gov](mailto:CDER-OSIS-SCIPOC-BE@fda.hhs.gov) prior to the beginning of the inspection to verify the focus and intent of the inspection. We frequently receive real-time information from the review team that may change the focus of the inspection.

Please follow the compliance program with emphasis on the specific instructions in the memorandum.

If significant deviations are found during the inspection that may have impact on the safety of study subjects or accuracy and reliability of the data, we request that you expand the scope of your inspection as necessary and contact the OSIS scientific POC at [CDER-OSIS-SCIPOC-BE@fda.hhs.gov](mailto:CDER-OSIS-SCIPOC-BE@fda.hhs.gov) and cc [CDER-OSIS-BEQ@fda.hhs.gov](mailto:CDER-OSIS-BEQ@fda.hhs.gov) immediately.

Send the following information to the respective email in the table.

<table>
<thead>
<tr>
<th><a href="mailto:CDER-OSIS-SCIPOC-BE@fda.hhs.gov">CDER-OSIS-SCIPOC-BE@fda.hhs.gov</a></th>
<th><a href="mailto:CDER-OSIS-BEQ@fda.hhs.gov">CDER-OSIS-BEQ@fda.hhs.gov</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>Scientific questions/comments</td>
<td>Not applicable</td>
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</tbody>
</table>

Significant deviations found during the inspection that may have impact on the safety of study subjects or accuracy and reliability of the data

<table>
<thead>
<tr>
<th>EIR (when available in OSAR)</th>
<th>Form FDA 483 and 483 responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not applicable</td>
<td></td>
</tr>
</tbody>
</table>

Inspection findings at end of inspection

| Post inspection correspondence from establishment | |
|---------------------------------------------------| |
| Not applicable                                    | |
If the endorsed EIR and exhibits are paper, send the documents to Angel Johnson, OSIS Project Specialist. 
Ms. Angel Johnson 
Project Specialist 
FDA/CDER/OTS/OSIS 
WO22 RM1471 
10903 New Hampshire Ave. 
Silver Spring, MD 20993-0002

Important: All post-inspection correspondence must be reviewed prior to issuing any post-inspection notification of compliance status.

BACKGROUND INFORMATION

This inspection memo provides pertinent information to conduct the inspection of the clinical portion of the following bioavailability (BA) study. Background materials are available in ECMS under the ORA folder.

IMPORTANT REMINDERS:
1. Inspections should be scheduled for no more than one week unless otherwise noted.
2. A 100% audit of the studies is not required unless noted (refer to the DATA AUDIT CHECKLIST section of this memo). If specific audit instructions are not provided, please audit as much as possible during the one week inspection.
3. If the assignment contains more than 3 studies, instructions to audit specific sections of the study will be included in the DATA AUDIT CHECKLIST section of this memo.
4. Please note that additional studies for the site may be added to the assignment no later than 2 weeks prior to the inspection start date. The additional studies may be added because more significant, complex or recent studies are received by OSIS, or specific study issues are identified after the initial assignment is issued. Addition of these additional studies SHOULD NOT extend the inspection duration at the site.

Do not reveal the study to be inspected, drug name, or the study investigators to the site prior to the start of the inspection. You should provide this information during the inspection opening meeting. Please note that the inspection will be conducted under Bioresearch Monitoring Compliance Program CP 7348.001, not under CP 7348.811 (Clinical Investigators).

At the completion of the inspection, please send a scanned copy of completed sections A and B of this memo to the OSIS scientific POC at CDER-OSIS-SCIPOC-BE@fda.hhs.gov.

Required study to be audited (Refer to DATA AUDIT CHECKLIST in Section B-Clinical Data Audit for additional information.)
NDA 208627

Study Number: SIGA-246-008
Study Title: “An Expanded Double-Blind, Randomized, Placebo-Controlled, Multicenter Trial to Assess the Safety, Tolerability, and Pharmacokinetics of the Anti-Orthopoxvirus Compound Tecovirimat When Administered Orally for 14 Days in Subjects”

Clinical Site #1: New Orleans Center for Clinical Research (Site 101)
1924 Alcoa Highway
Knoxville, TN 37920
Investigator: William B. Smith, M.D.
# of Subjects: 40

Clinical Site #2: Johnson County Clin-Trials, Inc. (Site 102)
16300 College Blvd
Lenexa, KS 66219
Investigator: Carlos A. Fierro, M.D.
# of Subjects: 41

Please collect a list of bioequivalence studies performed at the site in the last 5 years. The list should include information on test and reference reserve samples retained at the site or at a third party for the bioequivalence studies. Refer to Table 1 for an example. Please do spot checks to verify that the lot number(s) listed in the table match the reserve samples in the clinical site storage.

Table 1

<table>
<thead>
<tr>
<th>SL NO.</th>
<th>Study number</th>
<th>Drug Name</th>
<th>Fast/Ted</th>
<th>Sponsor</th>
<th>Submission</th>
<th>Study Conduct Dates</th>
<th>Reserve Samples</th>
<th>Quantity</th>
<th>Lot for Test and Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>XXXXXXX</td>
<td>Acyclovir + Dipyridamole Capsules</td>
<td>Fast</td>
<td>USDA</td>
<td>Dec 24-Dec 31, 2014</td>
<td>At Site</td>
<td>300 for test, 300 for reference</td>
<td>X000 and X000</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>XXXXXXX</td>
<td>Montelukast</td>
<td>Fed</td>
<td>unknown</td>
<td>X0000</td>
<td>Third Party</td>
<td>two lots</td>
<td>X000 and X000</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>XXXXXXX</td>
<td>XXXXXXXXXX</td>
<td>Fast</td>
<td>Pilot</td>
<td>X00000</td>
<td>Not retained</td>
<td>two bottles for test, two bottles for reference</td>
<td>X000 and X000</td>
<td></td>
</tr>
</tbody>
</table>

SECTION A – RESERVE SAMPLES

Reserve samples are not required for study SIGA-246-008. However, if the capsule formulation was retained, do not collect it, but verify that the lot number on the containers match those in the study report for the study mentioned above.
SECTION B – CLINICAL DATA AUDIT

Please remember to collect relevant exhibits for all findings, including discussion items at closeout, as evidence of the findings.

Data Audit Checklist:

☐ Confirm that informed consent was obtained prior to the study procedures for all subjects enrolled in Study SIGA-246-008.

☐ Audit the study records for all subjects enrolled in Study SIGA-246-008 at each site.

☐ Compare the randomization schedule with the Case Report Forms or dosing records and verify that 100% of the subjects received their intended treatment (i.e., test or reference) in each period.

☐ Compare the study report submitted to FDA with the original documents at the site.

☐ Check for under-reporting of adverse events (AEs).

☐ Check for evidence of inaccuracy in the electronic data capture system.

☐ Check reports for the subjects audited.
  o Number of subject records reviewed during the inspection:______
  o Number of subjects screened at the site:______
  o Number of subjects enrolled at the site:_____
  o Number of subjects completing the study:_____

☐ Confirm that site personnel conducted clinical assessments in a consistent manner and in accordance with the study protocols.

☐ Confirm that site personnel followed SOPs during study conduct.

☐ Examine correspondence files for any applicant or monitor-requested changes to study data or reports.

☐ Confirm that adequate corrective actions were implemented for observations cited during the last inspection (if applicable).

☐ Include a brief statement summarizing your findings including IRB approvals, study protocol and SOPs, protocol deviations, AEs, concomitant medications, adequacy of records, inclusion/exclusion criteria, drug accountability documents, and case report forms for dosing of subjects, etc.

☐ Other comments:
Additional instructions to the ORA Investigator:

In addition to the compliance program elements, other study specific instructions may be provided by the OSIS scientific POC prior to commencement of the inspection. Therefore, we request that the OSIS scientific POC be contacted at CDER-OSIS-SCIPOC-BE@fda.hhs.gov for any further instructions, inspection related questions or clarifications before the inspection and also regarding any data anomalies or questions noted during review of study records on site.

If you issue Form FDA 483, please forward a copy to CDER-OSIS-BEQ@fda.hhs.gov, if electronic or please forward a copy to the OSIS Project Specialist contact at the address below, if paper. If it appears that the observations may warrant an OAI classification, send notification to the OSIS scientific POC at CDER-OSIS-SCIPOC-BE@fda.hhs.gov and cc CDER-OSIS-BEQ@fda.hhs.gov, as soon as possible.

Remind the inspected site of the 15 business-day timeframe for submission of a written response to the Form FDA 483. In addition, please forward a copy of the written response as soon as it is received to CDER-OSIS-BEQ@fda.hhs.gov, if electronic or if paper, forward a copy to the OSIS Project Specialist contact at the address below.

If the endorsed EIR and exhibits are in OSAR or submitted in another electronic format, send an email to CDER-OSIS-BEQ@fda.hhs.gov for the assignment.

If the endorsed EIR and exhibits are submitted in paper format, send the endorsed EIR and exhibits to the OSIS Project Specialist at the address below.

**OSIS Project Specialist:** Ms. Angel Johnson
Project Specialist
FDA/CDER/OTS/OSIS
WO22 RM1471
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002
Tel: 301-796-3374

Email cc:
ORA BIMO Inspection POC
OSIS/Kassim/Taylor/Choe/CDER-OSIS-BEQ@fda.hhs.gov
OSIS/DNDBE/Bonapace/Dasgupta/Biswas/Ayala/Zhang
OSIS/DGDBE/Cho/Kadavil/Choi/Skelly/Au
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YIYUE ZHANG
01/19/2018

RUBEN C AYALA
01/19/2018