CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761107Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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)

Date of This Memorandum:	October 30, 2018
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	BLA 761107
Product Name and Strength:	Gamifant (emapalumab-lzsg) injection, 10 mg/2 mL (5 mg/mL) 50 mg/10 mL (5 mg/mL)
Applicant/Sponsor Name:	Novimmune SA
FDA Received Date:	September 4, 2018, September 19, 2018, October 5, 2018, October 24, 2018, and October 26, 2018
OSE RCM #:	2018-619-01
DMEPA Safety Evaluator:	Casmir Ogbonna, PharmD, MBA, BCPS, BCGP
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Division of Hematology Products (DHP) requested that we review the revised container label and carton labeling for Gamifant (emapalumab-lzsg) injection, (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review[a] and teleconference[b] discussing the linear barcode on container labels and Compliance requirement for T3 data and serialization.

2 CONCLUSION

The revised carton labeling and container labels for Gamifant (emapalumab-lzsg) injection, are acceptable from a medication error perspective. We have no recommendations at this time.

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[a] Ogbonna, C. Label and Labeling Review for Gamifant (BLA 761107). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 AUG 21. RCM No.: 2018-619.

[b] Teleconference between the Applicant's team and the FDA Review team: Silver Spring (MD): FDA, CDER, OND, OHOP, DHP (US); 2018 OCT 16.

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/s/

CASMIR I OGBONNA
10/30/2018

HINA S MEHTA
10/31/2018

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: October 5, 2018

To: Natasha Kormanik, Regulatory Project Manager, Division of Hematology Products (DHP)

Virginia Kwitkowski, Associate Director for Labeling, DHP

From: Robert Nguyen, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for GAMIFANT™ (emapalumab-lzsg) injection, for intravenous use

BLA: 761107

In response to DHP's consult request dated March 26, 2018, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original BLA submission for Gamifant (emapalumab-lzsg).

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DHP (Katie Chon) on September 25, 2018 and are provided below.

Medication Guide: A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under separate cover on October 4, 2018.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on September 4, 2018 and September 19, 2018, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Robert Nguyen at (301) 796-0171 or Robert.Nguyen@fda.hhs.gov.

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/s/

ROBERT L NGUYEN
10/05/2018

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	October 3, 2018
To:	Ann Farrell, MD Director **Division of Hematology Products (DHP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Robert Nguyen, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	GAMIFANT (emapalumab-xxxx)
Dosage Form and Route:	injection, for intravenous use
Application Type/Number:	BLA
Supplement Number:	761107
Applicant:	Novimmune SA c/o Advyzom LLC

1 INTRODUCTION

On March 20, 2018, Novimmune SA, c/o Advyzom LLC, submitted for the Agency's review an original Biologics License Application (BLA) 761107 for GAMIFANT (emapalumab-xxxx) injection, for intravenous use, for the treatment of patients with primary hemophagocytic lymphohistiocytosis (HLH).

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 Hematology Products (DHP) on April 26, 2018, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG), for GAMIFANT (emapalumab-xxxx) injection, for intravenous use.

2 MATERIAL REVIEWED

- Draft GAMIFANT (emapalumab-xxxx) injection, for intravenous use, MG received on March 20, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 25, 2018.
- Draft GAMIFANT (empalumab-xxxx) injection, for intravenous use, Prescribing Information (PI) received on March 20, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 25, 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.

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.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20.
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006

4 CONCLUSIONS

The MG 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 MG 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 MG.

Please let us know if you have any questions.

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/s/

SUSAN W REDWOOD
10/03/2018

ROBERT L NGUYEN
10/03/2018

BARBARA A FULLER
10/03/2018

LASHAWN M GRIFFITHS
10/03/2018

Division of Hematology Products (DHP) Labeling Review

NDA/BLA Number	**BLA 761107 / SD1**
Application Type	**NME**
Proprietary Name **(nonproprietary name)**	**GAMIFANT** **(emapalumab)**
Receipt Date	**03/20/18**
PDUFA Goal Date **(Internal Goal Date)**	**11/20/18** **(09/28/18)**
Review Classification	**Expedited**
Proposed Indication (or current indication if unchanged)	**GAMIFANT is a fully human anti-interferon gamma (IFNγ) antibody indicated for the treatment of primary hemophagocytic lymphohistiocytosis (HLH).**
Dosing Regimen	**1 mg/kg by intravenous infusion over 1 hour twice a week (every 3 to 4 days) until HSCT is performed.**
From	**Virginia Kwitkowski, MS, ACNP-BC** **Associate Director for Labeling, DHP**

Background of Application: Novimmune SA has submitted an original BLA in accordances with PHS Act Section 351(a) for GAMIFANT (emapalumab) for the treatment of patients with primary hemophagocytc lymphohistiocytosis (HLH).

Documents Reviewed:

Module 1: Form 356h, Cover Letter, Labeling

Module 2: Clinical Overview, Clinical Summary

In this review, I propose labeling recommendations and edits in the GAMIFANT labeling to ensure that the prescribing information is a useful communication tool for healthcare providers and uses clear, concise language; is based on regulations and guidances; and conveys the essential scientific information needed for the safe and effective use of GAMIFANT.

The following pages contain the working version of the GAMIFANT labeling with my recommended edits and comments (identified as 'KV2' through 'KV95') and includes comments and edits from

other review team members. Given that the scientific review of the labeling is ongoing, my labeling recommendations in this review should be considered preliminary and may not represent DHP's final recommendations for the GAMIFANT labeling.

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/s/

VIRGINIA E KWITKOWSKI
09/12/2018

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*****

Date of This Review:	August 21, 2018
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	BLA 761107
Product Name and Strength:	Gamifant (emapalumab) injection, 10 mg/2 mL (5 mg/mL) 50 mg/10 mL (5 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription
Applicant/Sponsor Name:	Novimmune SA
FDA Received Date:	March 20, 2018
OSE RCM #:	2018-619
DMEPA Safety Evaluator:	Casmir Ogbonna, PharmD, MBA, BCPS, BCGP
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

This review responds to a request from the Division of Hematology Products (DHP) to review the Prescribing Information (PI), carton labeling, and container labels for Gamifant (emapalumab) injection for areas of vulnerability that may lead to medication errors. On March 20, 2018, Novimmune SA submitted an original BLA 761107 for Gamifant (emapalumab) injection, a fully human anti-interferon gamma (IFNγ) antibody indicated for the treatment of primary hemophagocytic lymphohistiocytosis (HLH).

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

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 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA evaluated the proposed Prescribing Information (PI), carton and container labeling for areas of vulnerability in regards to medication error. We note the use of the term (b) (4) in labels and labeling. We defer to the Office of Pharmaceutical Quality (OPQ) for the appropriateness of the terminology.

We identified areas of concern in the PI in addition to the carton and container labeling that should be revised to improve the clarity of the information presented.

We provide recommendations for the Division in Section 4.1 and for the Applicant in Section 4.2 to address these deficiencies.

4 CONCLUSION & RECOMMENDATIONS

DMEPA identified areas in the labels and labeling that can be improved to increase readability and prominence of important information and promote the safe use of the product. We

provide recommendations in Section 4.1 for the PI and 4.2 for the carton and container labels to address these deficiencies.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Highlights of Prescribing Information

1. Dosage and Administration Section

a. Remove the first statement as this can be combined with the first bulleted statement. In addition, combine the first two bullets. Revise to "Recommended starting dosage: 1 mg/kg as an intravenous infusion over 1 hour twice (b) (4) week (b) (4) (2.1)"

B. Full Prescribing Information

1. Section 2.4: Instructions for Preparation and Administration

a. As the product has weight based dosing we recommend adding "kg" in the parenthesis with the "mg" for calculation of dose. Thus, revise to "(mg/kg)".

b. We recommend putting the information regarding placement of diluted solution into appropriate infusion bag in a separate bullet so that this important information is not overlooked.

c. We recommend removing the last bullet under the preparation section (b) (4)

d. We recommend placing the administration instructions before the information on storage of diluted solution.

2. Section 16: How Supplied/Storage and Handling

a. As currently presented, the NDC is denoted by a placeholder NDC XXXXX-XXX-XX. We ask Applicant to submit the NDC number for review.

4.2 RECOMMENDATIONS FOR NOVIMMUNE SA

We recommend the following be implemented prior to approval of this BLA 761107:

A. Container Labels

1. As currently presented, the NDC is denoted by a placeholder NDC XXXXX-XXX-XX. Consider replacing with NDC number and submit for Agency review in accordance with 21 CFR 207.35(b)(3)(i).
2. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. We recommend using a format like either:
   DDMMMYYYY (e.g., 31JAN2013)
   MMMYYYY (e.g., JAN2013)
   YYYY-MMM-DD (e.g., 2013-JAN-31)
   YYYY-MM-DD (e.g., 2013-01-31)

3. As currently presented, the finished dosage form “injection” is missing. If space permits, revise to include the finished dosage form below the proper name. Per *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013* (lines 336-342, 344-349).
4. If space permits revise the route of administration for the 10 mg vial from “For IV infusion after dilution” to “For Intravenous infusion after dilution”. Dangerous abbreviations, symbols, and dose designations are included on the Institute of Safe Medication Practice’s List of Error-Prone Abbreviations, Symbols, and Dose Designations. As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone abbreviations in the approved labeling of products.
5. Ensure nonproprietary name is at least half as large as the proprietary name and has a commensurate prominence per 21 CFR 201.10(g)(2).
6. Consider debolding the “Rx Only” statement to increase the prominence of other critical information on the label.

B. Carton Labelings

1. See A.1 thru A.3, and A.5
2. In the Contents statement: Please correct the spelling of the active ingredient from “empalumab” to “emapalumab”.
3. Revise and bold the storage information to “**Refrigerate at 36°F to 46°F (2°C to 8°C)** in original carton to protect from light”.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Gamifant received on March 20, 2018, from Novimmune SA.

Table 2. Relevant Product Information for Gamifant	
Initial Approval Date	N/A
Active Ingredient	emapalumab
Indication	(b) (4)
Route of Administration	Intravenous infusion
Dosage Form	Injection
Strength	10 mg/2 mL (5 mg/mL) 50 mg/10 mL (5 mg/mL)
Dose and Frequency	For intravenous infusion only: • The recommended starting dose of GAMIFANT is 1 mg/kg administered over 1 hour. • GAMIFANT should be administered twice a week (every 3 to 4 days) until hematopoietic stem cell transplantation (HSCT) is performed. • Increase dose based on clinical and laboratory parameters from 1 to 3, then to 6 and up to 10 mg/kg (fever, platelets, ANC, ferritin, splenomegaly, coagulopathy). GAMIFANT should be given concomitantly with dexamethasone
How Supplied	One 10 mg/2 mL (5 mg/mL) single-dose vial One 50 mg/10 mL (5 mg/mL) single-dose vial
Storage	Refrigerate at 2ºC to 8ºC (36ºF to 46ºF) in original carton to protect from light. Do not freeze or shake.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On June 13, 2018, we searched DMEPA's previous reviews using the terms, Gamifant. Our search identified no previous reviews

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Gamifant labels and labeling submitted by Novimmune SA.

- Container label received on March 20, 2018
- Carton labeling received on March 20, 2018
- Prescribing Information (Image not shown) received on March 20, 2018 \\cdsesub1\evsprod\bla761107\0001\m1\us\114-labeling\draft\labeling\proposeddoc.doc

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[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

CASMIR I OGBONNA
08/21/2018

HINA S MEHTA
08/22/2018

CLINICAL INSPECTION SUMMARY

Date	July 24, 2018
From	Anthony Orencia M.D., F.A.C.P., GCPAB Medical Officer Janice Pohlman M.D., M.P.H., GCPAB Team Leader Kassa Ayalew, M.D., M.P.H., GCPAB Branch Chief Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Margret Merino, M.D., Medical Officer Tanya Wroblewski, M.D., Clinical Team Leader Natasha Kormanik, MSN, RN, Regulatory Project Manager Division of Hematology Products
BLA	761107 (IND 111015)
Applicant	Advyzom
Drug	emapalumab
NME	Yes
Therapeutic Classification/Status	human IgG1 anti-IFNγ monoclonal antibody
Proposed Indication	Treatment of primary hemophagocytic lymphohistiocytosis (HLH)
Consultation Request Date	March 23, 2018
Summary Goal Date	August 6, 2018 (Priority Review)
Action Goal Date	September 6, 2018
PDUFA Date	November 20, 2018

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical sites (Drs. Jordan and Locatelli) were selected by the Division of Hematology Products (DHP) for inspection in support of BLA 761107. The study data from these clinical sites, as reported by the sponsor to the BLA, are considered to be reliable in support of the requested indication.

The final inspectional classification of Dr. Jordan is No Action Indicated. The preliminary regulatory classification for Dr. Locatelli is No Action Indicated.

2. BACKGROUND

Emapalumab is a fully human IgG1 anti-IFNγ monoclonal antibody that binds both free and receptor-bound IFNγ and neutralizes its biological activity. IFNγ is thought to play an important role in the pathogenesis of primary hemophagocytic lymphohistiocytosis (pHLH). Therefore, neutralization of IFNγ by empalumab is proposed as a novel targeted treatment.

Primary hemophagocytic lymphohistiocytosis (pHLH) is a heterogeneous autosomal recessive disorder characterized by a severe impairment or absence of cytotoxic function by natural killer (NK) and CD8+ T cells with striking activation of the immune system. Primary HLH is mostly seen in infancy and early childhood with an estimated prevalence in Europe of 1/50,000 live births. The disease is invariably fatal if untreated, with a median survival of less than 2 months after diagnosis. Primary disease features include the following: prolonged fever, organomegaly, cytopenia, hypertriglyceridemia, hyperferritinemia, hypofibrinogenemia, lymphohistiocytic infiltrate, hypoplasia in the bone marrow, meningeal infiltrate, and hypercytokinemia.

Study NI-0501-04:

Study NI-0501-04 is an open-label, multicenter, single-arm Phase 2 study of emapalumab in the treatment of male and female pediatric patients (less than 18 years of age at the time of diagnosis) with suspected or confirmed primary hemophagocytic lymphohistiocytosis (pHLH). This study will continue as a Phase 2 to 3 study based on the positive benefit-risk profile observed in the patients enrolled in the study. The primary efficacy endpoint was Overall Response at the End of Treatment (EOT) in Study NI-0501-04 (EOT 04), defined as achievement of either a complete or partial response or HLH improvement based on a pre-specified algorithm. EOT was defined as 3 days after the last emapalumab infusion within protocol-specified time-windows.

This multicenter, multinational study enrolled subjects at 12 sites across four countries including the U.S., Germany, Italy, and Spain. In total, 35 subjects constituted the enrolled study population. The primary efficacy population consisted of 25 patients with relapsed or refractory disease. The first subject enrolled on July 28, 2013. The data cutoff date (EOT 04) for this report was July 20, 2017.

3. RESULTS (by site):

Name of Clinical Investigator/Sponsor Address	Protocol #/ Site #/# Subjects enrolled	Inspection Dates	Classification
Michael Jordan, M.D. Cincinnati Children's Hospital Division of Immunobiology Department of Pediatrics 3333 Burnet Avenue Cincinnati, OH 45229	Study NI-0501-04 Site #16 10 total	June 11 to 15, 2018	NAI

Name of Clinical Investigator/Sponsor Address	Protocol #/ Site #/# Subjects enrolled	Inspection Dates	Classification
Franco.Locatelli, M.D. Ospedale Pediatrico Bambino Gesu Dipartimento di Onco- Ematologia pediatrica e Medicina Trasfusionale Piazza S. Onofrio 4 Rome, Italy 00165	Study NI-0501-04 Site #7 7 total	June 18 to 22, 2018	*NAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data are 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.

Clinical Investigator

1. Michael Jordan, MD

A total of 20 subjects were screened and 10 subjects were enrolled prior to the data cutoff date and considered evaluable for Study NI-0501-04. Ten subjects completed the study.

For this inspection, a complete review of all regulatory documentation at the study site was performed, as well as the source records for 10 of 10 total subjects enrolled at the site prior to the database lock. A 100% review of informed consent forms, for both enrolled and screen failure subjects, was completed. The source records reviewed included medical records, source data worksheets, informed consent forms, and pharmacy records.

Source documents for all screened and enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary safety study endpoint were verifiable at the study site. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. A Form FDA 483 (Inspectional Observations) was not issued at the end of the inspection.

2. Franco Locatelli, M.D.

A total of seven subjects were screened and were enrolled. One subject died during the treatment phase of the study. Six subjects completed the study

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for seven enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. A comprehensive audit of the inclusion and

exclusion criteria for patient enrollment was evaluated at this site inspection. Source documents for the raw data used to assess the primary safety study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. No Form FDA 483 was issued.

{See appended electronic signature page}

Anthony Orencia, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}
Janice Pohlman, M.D., M.P.H.
Team Leader, Good Clinical Practice Assessment Branch
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Office of Scientific Investigations

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/s/

ANTHONY J ORENCIA
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07/24/2018

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