CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761102Orig1s000

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:	December 20, 2018
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	BLA 761102
Product Name and Strength:	Calaspargase Pegol – mknl (Asparlas) 3,750 units/5 mL (750 units/mL) Injection
Applicant/Sponsor Name:	Servier Pharmaceuticals
FDA Received Date:	December 17, 2018
OSE RCM #:	2017-2619-2
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Hematology Products (DHP) requested that we review the revised container labels and carton labeling for Asparlas (Appendix A) to determine if it is acceptable from a medication error perspective. BLA 761102 ownership was transferred from Baxalta US, Inc to Servier Pharmaceuticals. Thus, Servier Pharmaceuticals is submitting revised carton and container labels with updated manufacturer information.

2 CONCLUSION

The revised carton labeling and container labels for Asparlas are acceptable from a medication error perspective. We have no further recommendations at this time.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON DECEMBER 17, 2018

Container labels

Carton Labeling

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/s/

HINA S MEHTA
12/20/2018

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:	November 30, 2018
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	BLA 761102
Product Name and Strength:	Calaspargase Pegol – mknl (Asparlas) 3,750 units/5 mL (750 units/mL) Injection
Applicant/Sponsor Name:	Baxalta US, Inc.
FDA Received Date:	November 19, 2018
OSE RCM #:	2017-2619-1
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Hematology Products (DHP) requested that we review the revised container labels and carton labeling for Asparlas (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] In addition, we provided advice to the Applicant on November 16, 2018 to revise the usual dosage statement and move to the principal display panel the 'discard unused portion' statement on the carton labeling.

2 CONCLUSION

The revised carton labeling and container labels for Asparlas are acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Rahimi L. Label and Labeling Review for Asparlas (BLA 761102). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JUN 22. RCM No.: 2017-2619.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON NOVEMBER 19, 2018

Container labels

Carton Labeling

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/s/

HINA S MEHTA
11/30/2018

MEMORANDUM

NONPROPRIETARY NAME SUFFIX

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:	October 2, 2018
Responsible OND Division:	Division of Hematology Products (DHP)
Application Type and Number:	BLA 761102
Product Name and Strength:	Asparlas (calaspargase pegol-mknl) Injection 3,750 Units/5 mL (750 Units/mL)
Product Type:	Single Ingredient Product
Applicant/Sponsor Name:	Baxalta US Inc. (Baxalta)
FDA Received Date:	April 06, 2018
OSE RCM #:	2018-712
DMEPA Primary Reviewer:	Carlos M Mena-Grillasca, BS Pharm
DMEPA Deputy Director:	Danielle Harris, PharmD, BCPS

1 PURPOSE OF MEMO

This memorandum summarizes our evaluation of the four-letter suffix for inclusion in the nonproprietary name and communicates our recommendation for the nonproprietary name for BLA 761102.

1.1 Regulatory History

Baxalta was notified of the Agency's intention to designate a nonproprietary name that includes a four-letter distinguishing suffix that is devoid of meaning for their product in an Advice Letter[a].

2 ASSESSMENT OF THE NONPROPRIETARY NAME

calaspargase pegol-mknl

FDA generated a four-letter suffix, -mknl. This suffix was evaluated using the principles described in the applicable guidance[b].

We determined that the FDA-generated suffix -mknl, is not too similar to any other products' suffix designation, does not look similar to the names of other currently marketed products, that the suffix is devoid of meaning, does not include any abbreviations that could be misinterpreted, and does not make any misrepresentations with respect to safety or efficacy of this product.

3 COMMUNICATION OF DMEPA'S ANALYSIS

These findings were shared with OPDP. In email correspondence dated October 2, 2018, OPDP did not identify any concerns that would render this suffix unacceptable. DMEPA also communicated our findings to the Division of Hematology Products (DHP) via e-mail on October 2, 2018.

4 CONCLUSION

We find the suffix -mknl acceptable and recommend the nonproprietary name be revised throughout the draft labels and labeling to calaspargase pegol-mknl.

4.1 Recommendation for Baxalta

We find the nonproprietary name, calaspargase pegol-mknl, conditionally acceptable for your proposed product. Should your 351(a) BLA be approved during this review cycle, calaspargase pegol-mknl will be the proper name designated in the license and you should revise your proposed labels and labeling accordingly. However, please be advised that if your application receives a complete response, the acceptability of this suffix will be re-evaluated when you respond to the deficiencies. If we find the suffix unacceptable upon our re-evaluation, we would inform you of our finding.

---

[a] Harris, D. General Advice Letter for BLA 761102. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US) 2018 APR 23.

[b] See Section VI which describes that any suffixes should be devoid of meaning in Guidance for Industry: Nonproprietary Naming of Biological Products. 2017. Available from:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf

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/s/

CARLOS M MENA-GRILLASCA
10/02/2018

DANIELLE M HARRIS
10/03/2018

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 14, 2018

TO: Ann Farrell, MD
Director, Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs

FROM: Hasan A. Irier, Ph.D.
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: [redacted] (b) (4)

Inspection Summary

The Office of Stu[redacted]nged n of [redacted] (b) (4) FEI# [redacted] (b) (4) for the audit of study AALL07P4 (BLA 761102).

Form FDA 483 was issued at the inspection close-out. The final inspection classification is Voluntary Action Indicated (VAI).

Some objectionable conditions were observed during this inspection. However, the inspectional findings did not impact the reliability of the data from the audited studies. Thus, I recommend that the data from study AALL07P4 (BLA 761102) be accepted for further Agency review.

Inspected Studies:

BLA 761102

Study Number: AALL07P4

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Study Title: "A Pilot study of Intravenous EZN-2285 (SC PEG E. coli L. asparaginase, IND 100594) or Intravenous Oncaspar® in the Treatment of Patients with High-Risk Acute Lymphoblastic Leukemia (ALL): A Limited Institution Pilot Study"

Dates of clinical sample analysis: 10/14/2008 - 12/15/2011

Clinical site: [redacted]

[redacted] investigators, [redacted] inspected [redacted]

The inspection included a thorough examination of study records (both paper based and digital), subject sample records, protocol compliance, subject sample accountability and storage. OSIS requested ORA investigators to [redacted] assays conducted at [redacted] under the study AALL07P4 (**Attachment 1**). The **Attachment 1** contains detailed information about the [redacted] (such as site ID, subject ID) and the type of assays [redacted] conducted to analyze blood samples from all 23 study sites participated in the study AALL07P4.

At the end of the inspection, the ORA investigators observed objectionable conditions and Form FDA 483 was issued to the clinical site. The Form FDA 483 observation(s) (**Attachment 2**), the firm's response dated July 11, 2018 (**Attachment 3**), and my evaluation are presented below.

[redacted]

[redacted] (b) (4)

Conclusion:

Some objectionable conditions were observed during this inspection and Form FDA 483 was issued. The final inspection classification is Voluntary Action Indicated (VAI).

After reviewing the inspectional findings and the firm's response to Form FDA 483, the objectionable conditions did not impact the reliability of the data from the audited studies.

Note that the **Attachment 1** contains detailed information about the assay results, such as site ID and subject ID, that were collected during the inspection.

[redacted] (b) (4) ducted at [redacted] (b) (4) FEI Number [redacted] (b) (4)) in support of study AALL07P4 (BLA 761102) be accepted for further Agency review.

Hasan A. Irier, Ph.D.
Pharmacologist

Final Classification:

VAI- (b) (4)

FEI#: (b) (4)

cc:
OTS/OSIS/Kassim/Choe/Mitchell/Fenty-Stewart/Nkah
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/
OTS/OSIS/DGDBE/Cho/Kadavil/Choi/Skelly/Au/Irier

Draft: HAI, 8/21/2018; 9/13/2018, 9/14/2018
Edit: YMC 9/6/2018, 9/12/2018, 9/14/2018; SA 9/6/2018, 9/11/2018; JC 9/12/2018, 9/14/2018

ECMS: Cabinets/CDER_OC/OSI/OSIS--Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/CLINICAL SITES/ (b) (4) (b) (4) /BLA 761102_ASPARLAS (calaspargase pegol) injection

OSIS File #: BE 7831

FACTS: (b) (4)

ATTACHMENTS:

Attachment 1. AALL07P4_03May2012_Assay_Results sorted by site ID numbers*
Attachment 2. FDA Form 483 Observations
Attachment 3. FDA Response Letter Final-July 11-2018
Attachment 4. Exhibit JRC9 List of affected FDP results

**(Available as Excel file upon request)*

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/s/

HASAN A IRIER
09/14/2018

YOUNG M CHOI
09/14/2018

SEONGEUN CHO
09/14/2018

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

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

Memorandum

Date: 8/2/18

To: Suria Yesmin, Regulatory Project Manager, DHP

Virginia Kwitkowski, Associate Director for Labeling, DHP

From: Rachael Conklin, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Mathilda Fienkeng, Team Leader, OPDP

Subject: OPDP Labeling Comments for ASPARLAS™ (calaspargase pegol - XXXX) injection, for intravenous use

BLA: 761102

In response to DHP's consult request dated January 8, 2018, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original BLA submission for ASPARLAS™ (calaspargase pegol - XXXX) injection, for intravenous use.

PI: OPDP's comments on the proposed labeling, based on the draft PI emailed to OPDP on July 19, 2018, are provided below.

Carton and Container Labeling: OPDP has reviewed the proposed carton and container labeling and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Rachael Conklin at (240) 402-8189 or (b) (6)

PI

Section	Statement from Draft (if applicable)	OPDP Comment
HIGHLIGHTS OF PRESCRIBING INFORMATION: ADVERSE REACTIONS **6.1 Clinical Trials Experience**	(b) (4) [redacted]	OPDP notes that certain adverse reactions that are included in the highlights (e.g., (b) (4) [redacted] (b) (4) [redacted] OPDP recommends (b) (4) [redacted] so that the information in the HL is reflected in section 6.1. If this information is not pertinent for the safe use of the drug, we recommend revising the HL section to reflect only the risk information presented in Table 1. Additionally, we recommend that the ARs in the HL section be presented in descending order.
5 WARNINGS AND PRECAUTIONS		OPDP recommends revising the WARNINGS AND PRECAUTIONS subsections to include numerical estimates of the AR rates, consistent with the recommendation made in the Labeling Review Tool for "How to describe an AR or risk information in the WARNINGS AND PRECAUTIONS section."
5.1 Hypersensitivity	"Grade 3 and 4 hypersensitivity reactions have been reported in clinical trials with ASPARLAS *[see Contraindications (4) and Adverse Reactions (6.1)]*. Hypersensitivity reactions **observed with other** asparaginases include angioedema, lip swelling, eye swelling, erythema, blood	OPDP recommends revising this statement regarding hypersensitivity reactions to include a listing of hypersensitivity reactions observed with Asparlas in clinical trials prior to the presentation of reactions observed with other products.

	pressure decreased, bronchospasm, dyspnea, pruritus and rash." (emphasis added)	Given that Grade 3 and 4 hypersensitivity reactions were observed with this product, presentation of the specific reactions only related to "other" products may distance the risk from the drug. Eg., Grade 3 and 4 hypersensitivity reactions have been reported in clinical trial with ASPARLAS including [insert reactions]. Additional hypersensitivity reactions observed with other asparaginases include [insert reactions not seen in the clinical trials with ASPARLAS].
5.2 (b) (4)	"Hemorrhagic or necrotizing pancreatitis have been reported with other asparaginases."	Were either hemorrhagic or necrotizing pancreatitis observed in trials with Asparlas? If so, OPDP recommends communicating this information.
5.5 (b) (4)	(b) (4)	(b) (4)
5.5 (b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)

	(b) (4)	(b) (4)
6.1 Clinical Trials Experience	(b) (4)	(b) (4)

6.1 Clinical Trials Experience		(b) (4)
12.1 Mechanism of Action	(b) (4)	(b) (4)
14.1 Acute Lymphoblastic Leukemia	(b) (4)	(b) (4)

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/s/

RACHAEL E CONKLIN
08/02/2018

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 31, 2018

TO: Ann Farrell, MD
Director, Division of Hematology Products(DHP)
Office of Hematology and Oncology Products (OHOP)

Dale Conner, Pharm.D.
Director (Acting)
Office of Bioequivalence
Office of Generic Drugs

FROM: Himanshu Gupta, Ph.D.
Staff Fellow
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Science

Amanda Jones, Ph.D.
Pharmacologist
Division of Bioequivalence 1
Office of Bioequivalence
Office of Generic Drugs

THROUGH: Seongeun Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

SUBJECT: Surveillance inspection of (b) (4) (b) (4)

Inspection Summary

The Office of Study Integrity and Surveillance (OSIS), Office of Translational Sciences (OTS), conducted an analytical inspection at (b) (4) (b) (4)) and BLA 761102 (study AALL07P4).

Form FDA 483 was not issued at the inspection close-out.

Based on the inspection results and the firm's response, we recommend accepting the data from study [redacted] (b) (4)

For BLA 761102, there were no data integrity issues for the asparagine method validation and sample analysis from study AALL07P4. However, more information is required to confirm the [redacted] (b) (4) Therefore, we cannot ensure the reliability of reported L-asparagine concentrations in plasma samples from study AALL07P4. We recommend that the review division discuss with the applicant whether there is any documentation or source document from clinical site that can determine [redacted] (b) (4) for study AALL07P4.

The final inspection classification is No Action Indicated (NAI).

Inspected Studies

[redacted] (b) (4)

BLA 761102:	EZN-2285 (SC PEG E. coli L asparaginase)
Study Project#:	AALL07P4
Study Title:	A Pilot study of Intravenous EZN-2285 (SC PEG E. coli L asparaginase, IND 100594) or Intravenous Oncaspar® in the Treatment of Patients with High-Risk Acute Lymphoblastic Leukemia (ALL): A Limited Institution Pilot Study
Sample analysis dates:	January 27, 2009 to April 29, 2011
Analytical site:	[redacted] (b) (4)

[redacted] (b) (4)

OSIS scientist Himanshu Gupta, OGD reviewer Amanda Jones and Captain Joseph L. Despins from ORA audited the analytical portions of the above studies at [redacted] (b) (4) from [redacted] (b) (4)

The inspection included examining facilities and site operations, study records for laboratory equipment, method validation and sample analyses, and interviews with the firm's management and staff.

At the conclusion of the inspection, no objectionable conditions were observed and Form FDA 483 was not issued to the analytical site.

Discussion item

The following issue that impacts BLA 761102 (study #AALL07P4) was discussed with the firm's management during the inspection.

[redacted] (b) (4)

[redacted] (b) (4)

OSIS Evaluation:

[redacted] (b) (4)

[redacted] (D) (4) We recommend that the review division discuss with the applicant whether there is any documentation or source document from clinical site that can determine [redacted] (b) (4) for study AALL07P4. [redacted] (b) (4)

Conclusion

Based on the inspection results and the firm's response, we recommend accepting the data from study [redacted] (b) (4) (b) (4)

For BLA 761102, there were no data integrity issues for the asparagine method validation and sample analysis from study AALL07P4. However, more information is required to confirm the [redacted] (b) (4) (b) (4) Therefore, we cannot ensure the reliability of reported L-asparagine concentrations

in plasma samples from study AALL07P4. We recommend that the review division discuss with the applicant whether there is any documentation from clinical site that can determine [redacted] (b) (4) for study AALL07P4.

Studies using similar methods conducted between April 2017 and the end of the current surveillance interval can be further reviewed by the FDA without an inspection.

Himanshu Gupta, Ph.D.
Staff Fellow
OSIS, DGDBE

Amanda Jones, Ph.D.
Pharmacologist
OGD, DBI

Stanley Au, Pharm.D., BCPS
Team Lead
OSIS, DGDBE

Seongeun (Julia) Cho, Ph.D.
Director
OSIS, DGDBE

Final Site Classification:

NAI– [redacted] (b) (4)

FEI: [redacted] (b) (4)

cc:

OSIS/Kassim/Choe/Mitchell/Nkah/Fenty-Stewart/
OSIS/DGDBE/Cho/Jang/Choi/Skelly/Au/Gupta
OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas

Draft: HG 5/5/2018, 5/15/18, 6/13/18, 6/15/18, 6/20/18, 7/10/18, 7/11/18, 7/13/18, 7/17/18, 7/20/18, 7/23/18, 7/27/18, 7/31/18
Edit: AJ 5/14/2018, SA 5/14/2018, 6/14/2018, 06/15/18,7/5/18, 7/9/18, 7/10/18, 7/11/18, 7/16/18, 7/17/18, 7/18/18, 7/19/18, 7/20/18, 7/23/18, 7/27/18; JC 6/18/2018; 6/21/2018; 7/13/2018; 7/17/2018; 7/27/2018

ECMS: Cabinets/ CDER_OC/OSI/OSIS--Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/ANALYTICAL SITES/ (b) (4) (b) (4) BLA 761102

OSIS file number: (b) (4) 7831 (BLA 761102)

FACTS: (b) (4)

Attachment:

Attachment 1- Email communication between firm and sponsor/applicant regarding (b) (4)
Attachment 2- Lab manual excerpt for an instruction (b) (4) (b) (4)

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/s/

HIMANSHU GUPTA
07/31/2018

AMANDA JONES
08/01/2018

STANLEY AU
08/01/2018
Team Lead

SEONGEUN CHO
08/01/2018

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 27, 2018

TO: Ann Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Office of New Drugs

FROM: Amanda Lewin, Ph.D.
Pharmacologist
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

Kara Scheibner, Ph.D.
Pharmacologist
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Charles Bonapace, Pharm.D.
Director
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: [redacted] (b) (4)

Inspection Summary

The Office of Study Integrity and Surveillance (OSI [redacted] d (b) (4)

Form FDA 483 was issued at the inspection close-out. The final inspection classification is Voluntary Action Indicated (VAI).

Significant objectionable conditions were observed during this inspection that impacted the reliability of the audited study. Specifically:

[redacted] (b) (4)

[redacted] (b) (4)

We conclude that the data from study DCFI-11-001 are unreliable to support a regulatory decision and should not be accepted for agency review.

Inspected Studies:

BLA 761102

Study Number: **DFCI 11-001**
Study Title: "Randomized Study of Intravenous Calaspargase Pegol (SC-PEG asparaginase) and Intravenous Oncaspar in Children and Adolescents with Acute Lymphoblastic Leukemia or Lymphoblastic Lymphoma"
Dates of conduct: 07/30/2012 – 03/14/2016

Analytical site: [redacted] (b) (4)

OSIS scientists Amanda Lewin, Ph.D. and Kara Scheibne[redacted]. e anal[redacted]ve study at [redacted] (b) (4) from [redacted] (b) (4)

The inspection included a thorough examination of study records, facility, method validation, sample analysis, and interviews with the firm's management and staff.

At the conclusion of the inspection, we observed objectionable conditions and Form FDA 483 was issued to the analytical site. In addition, three discussion items were discussed during inspection close out. The Form FDA 483 observations (**Attachment 1**), the discussion items, the firm's response dated 05/15/2018 (**Attachment 2**), and our evaluation are presented below.

(b) (4)

[redacted]

(b) (4)

(b) (4)

Conclusions:

Significant objectionable conditions were observed during this inspection and Form FDA 483 was issued. The final inspection classification is Voluntary Action Indicated (VAI).

After reviewing the inspectional findings and the firm's response to Form FDA 483, there was evidence that the objectionable conditions impacted the reliability of the data for study DFCI 11-001 (BLA 761102) and the findings may be systemic in nature.

The data from study DFCI-11-001 are not reliable and should not be accepted for review until additional stability and selectivity data are received from the sponsor.

After receiving stability and selectivity data to support the analytical method, the review division should consider the following recommendations:

(b) (4)

[redacted]

Amanda Lewin, Ph.D.
Pharmacologist

Kara Scheibner, Ph.D.
Pharmacologist

Final Classification:

VAI– [redacted]

FEI#: [redacted]

cc:
OTS/OSIS/Kassim/Choe/Kadavil/Mitchell/Fenty-Stewart/Nkah
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Lewin
OTS/OSIS/DGDBE/Cho/Jang/Choi/Skelly/Au/Scheibner

Draft: AL 06/05/2018, 7/20/2018; KS 06/06/2018, 07/24/2018, 07/25/2018
Edit: GB 06/14/2018, 7/11/2018, 7/24/2018, 7/26/2018; AD 7/17/2018; CB 7/25/2018;7/26/2018

ECMS: Cabinets/CDER_OTS/Office of Study Integri [redacted]

OSIS File #: BE 7831

FACTS: [redacted]

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/s/

KARA A SCHEIBNER
07/27/2018

AMANDA E LEWIN
07/27/2018

GOPA BISWAS
07/27/2018

CHARLES R BONAPACE
07/27/2018

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:	June 22, 2018
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	BLA 761102
Product Name and Strength:	Asparlas (calaspargase pegol-xxxx*) injection 3,750 Units/5 mL (750 Units/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription
Applicant/Sponsor Name:	Baxalta
FDA Received Date:	December 22, 2017, January 24, 2018, March 12, 2018, and April 20, 2018
OSE RCM #:	2017-2619
DMEPA Safety Evaluator:	Leeza Rahimi, Pharm.D.
DMEPA Team Leader:	Hina Mehta, Pharm.D.

***** The nonproprietary name for Teva's proposed biologic product includes a distinguishing suffix (see Guidance on Nonproprietary Naming of Biological Products). We are using "-xxxx" as a placeholder until an acceptable suffix has been designated.

1 REASON FOR REVIEW

Baxalta submitted an original Biological License Application (BLA 761102) on December 22, 2017 for Calaspargase pegol. Calaspargase pegol is an asparagine specific enzyme indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia (ALL).

The Division of Hematology Products (DHP) requested DMEPA to review the proposed label and labeling to evaluate for areas of vulnerability that may lead to medication error.

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 submitted PI, carton and container labeling for areas of vulnerability in regards to medication error. Our review identified areas in the labels and labeling that can be improved to increase readability and prominence of important information.

We provide our recommendations in Sections 4.1 and 4.2 and recommend their implementation prior to approval of this application.

4 CONCLUSION & RECOMMENDATIONS

We identified areas on the PI, carton and container labels that can be improved to increase clarity and prominence of important information to promote the safe use of this product.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Highlights of Prescribing Information (HPI) and Full Prescribing Information (FPI)

1. We recommend adding placeholder for non-proprietary name suffix (calaspargase pegol-xxxx) throughout the Prescribing Information. FDA has not yet designated a distinguishing suffix for the proposed biologic product (see Guidance on Nonproprietary Naming of Biological Products). FDA is using "-xxxx" as a placeholder for the suffix. "-xxxx" is not intended to be included in the final printed labels and labeling.

2. The Prescribing Information includes the error prone abbreviation "U" and "IV". The abbreviations "U" and "IV" appear on ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations because it is often misinterpreted and poses risk of medication dosing errors [a]. Replace "U" with "units" and "IV" with "intravenous" throughout PI.

B. Prescribing Information (PI)

1. Dosage and Administration Section
    a. For clarity of information, we recommend revising and re-arranging the information presented in section 2 of the PI. See Appendix G.2 for our recommendations.

2. Dosage Forms and Strengths
    a. Include the concentration per mL (750 Units/mL) following the total quantity per total volume strength presentation of "3,750 Units/5 mL" per USP General Chapter <7> Labeling.

3. How Supplied/Storage and Handling Section
    a. Consider removing the statement (b) (4) because this information does not provide any Storage/Handling Information.

4.2 RECOMMENDATIONS FOR BAXALTA

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

A. Carton Labeling

1. The proprietary name ASPARLAS is presented (b) (4) We recommend revising the name (b) (4) to prevent confusion. (b) (4) Please consider moving the graphic away from the proprietary name to prevent confusion. Please refer to 21 CFR 201.10 (a), 21 CFR 202.1(a)(1) and Draft Guidance: Container and Carton, April 2013 (line 219-222).

2. Consider stating numbers greater than 1,000 with a comma (i.e. 3,750 Units/5 mL) to prevent the reader from misinterpreting thousands "1000" as hundreds "100" or ten-thousands "10000" per Draft Guidance: Container and Carton April 2013 (lines 475-476), and ISMP' s List of Error-Prone Abbreviations, Symbols, and Dose Designations.
3. Consider adding the statement "Must dilute before use" on the principal display panel to minimize the risk of the product being administered without dilution per Draft Guidance: Container and Carton, April 2013 (lines 491-492).
4. Revise and bold the statement storage statement to "**Must be refrigerated, store at 2°C to 8°C (36°F to 46°F).**". We recommend this to increase the prominence of this important information and minimize the risk of the storage information being overlooked.
5. As currently presented, the carton labeling lacks a linear drug barcode. The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label whenever possible. Therefore, we request you add the product's linear barcode to carton labeling as required per 21CFR 201.25(c)(2) and 21 CFR 610.67.
6. Lot number statement is required on the immediate carton labeling when there is sufficient space per 21 CFR 610.61(c). As currently presented there is no placeholder for the lot number.
7. Expiration date is required on the immediate carton labeling per 21 CFR 610.61(d). As currently presented there is no placeholder for the expiration. In addition, 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)

B. Container Labels

1. See A.1, A.2, and A.4
2. Decrease the prominence of the statement "Rx Only" as this information appears more prominent than the established name on the principal display panel per Draft Guidance: Container and Carton, April 2013 (line 146-149).
3. Consider reorienting the linear barcode to a vertical position to improve the scannability of the barcode. Barcodes placed in a horizontal position may not scan due to vial curvature.[a]
4. Clarify if the placeholder XXXXXX below the linear barcode is an internal product code placeholder. We recommend removing and/or relocating this number to

[a] Neuenschwander M. et al. Practical guide to bar coding for patient medication safety. Am J Health Syst Pharm. 2003 Apr 15;60(8):768-79.

ensure there is sufficient white space to allow scanners to read the barcode properly in accordance with 21 CFR 201.25 (c)(1)(i).

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Asparlas received on December 22, 2017, January 24, 2018, March 12, 2018, and April 20, 2018 from Baxalta.

Table 2. Relevant Product Information for Asparlas	
Initial Approval Date	N/A
Active Ingredient	Calaspargase pegol
Indication	Indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with ALL.
Route of Administration	Intravenous infusion
Dosage Form	Injection
Strength	3,750 Units/5mL (750 Units/mL)
Dose and Frequency	2,500 Units/m^2 intravenously no more frequently than every 21 days.
How Supplied	Sterile solution in a single-dose vial containing 3,750 Units of L-asparaginaser per 5 mL solution
Storage	(b) (4) Do not shake or freeze product. (b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On June 01, 2018, we searched DMEPA's previous reviews using the terms, Asparlas and calaspargase pegol. Our search did not identify any previous labeling 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,[b] along with postmarket medication error data, we reviewed the following Asparlas labels and labeling submitted by Baxalta.

- Prescribing Information received on December 22, 2017, January 24, 2018, March 12, 2018, and April 20, 2018
- Container label received on December 22, 2017
- Carton labeling received on December 22, 2017

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

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/s/

LEEZA RAHIMI
06/22/2018

HINA S MEHTA
06/22/2018

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 22, 2018

TO: Richard Pazdur, M.D.
Director
Office of Hematology and Oncology Products (OHOP)
Office of New Drugs (OND)

FROM: Yiyue Zhang, Ph.D.
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Director
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Surveillance inspection of (b) (4) covering BLA 761102.

Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) and ORA conducted an inspection of the analytical portion of **Studies AALL07P4** and **DFCI 11-001** (**BLA 761102**) conducted at (b) (4) (b) (4)

Form FDA 483 was issued at the inspection close-out. The final inspection classification is Voluntary Action Indicated (VAI).

Although objectionable conditions were observed during this inspection, the findings did not impact the reliability of the data from the audited studies. Thus, I recommend that the analytical data from **Studies AALL07P4** and **DFCI 11-001** (**BLA 761102**) and other studies using similar methods (**Attachment 1**) be accepted for further Agency review.

Inspected Studies:

BLA 761102

Study #1: **AALL07P4**

Study Title: "A Pilot study of Intravenous EZN-2285 (SC PEG E. coli L asparaginase, IND 100594) or Intravenous Oncaspar® in the Treatment of

Patients with High-Risk Acute Lymphoblastic Leukemia (ALL): A Limited Institution Pilot Study"

Dates of conduct: November 2008 – June 2011

Study #2: **DFCI 11-001**

Study Title: "Randomized Study of Intravenous Calaspargase Pegol (SC-PEG-L-asparaginase) and Intravenous Oncaspar® in Children and Adolescents with Acute Lymphoblastic Leukemia or Lymphoblastic Lymphoma"

Dates of conduct: March 2013 – April 2016

Analytical site: [redacted] (b) (4)

OSIS scientist Yiyue Zhang, Ph.D. and ORA investigator Craig A. Garmendia (DBIMOI) audited the analytical portion of the above studies at [redacted] (b) (4) from [redacted] (b) (4)

During the inspection, we learned that [redacted] (b) (4) was not present and had authorized a former employee to facilitate the inspection (**Attachment 2**). Since the firm is no longer operational, we were unable to tour the facility and examine the laboratory equipment.

The inspection included a thorough review of available study records including method validation and sample analyses. The firm conducted the PK analysis (Asparaginase activity in plasma) for **Study AALL07P4,** and immunogenicity analysis (anti-drug and anti-PEG antibodies in plasma) for **Studies AALL07P4** and **DFCI 11-001.** However, no bioanalytical reports were compiled for the above analyses at the time of study completion. Per the sponsor's request, [redacted] (b) (4)

The current inspection also covered Study [redacted] submitted [redacted] The inspection findings and my evaluation are presented in a separate EIR review.

At the conclusion of the inspection, we observed objectionable conditions and Form FDA 483 was issued to [redacted] We are yet to receive a response to Form 483 at the time of the writing of this review which is beyond 15 business days from inspection closeout date. The Form FDA 483 observation pertinent to the above studies (**Attachment 3**) and my evaluation are presented below.

OBSERVATION 3:

Original records and raw documents were missing and/or incomplete for several analysis and method validations. Specifically, the firm was unable to provide all the original records and raw documents related to sample analyses of Study AALL07P4 and method validations [redacted]

Firm's Response: None provided.

OSIS Evaluation: Since the firm was no longer operational and there was no active QA unit, the complete original records and raw documents were unable to be located during the inspection. However, **Study AALL07P4** was previously submitted to the Agency under **BLA** [redacted] in September 2012 and a clinical pharmacology review was completed in November 2013. The application was withdrawn by the sponsor in May 2013. However, there appeared no change of the study documents from last submission.

For PK portion of **Study AALL07P4** and associated method validation, an analytical inspection was conducted by the Office of Scientific Investigations (OSI) [redacted] under the original application BLA [redacted] and the final classification was No Action Indicated (NAI) with no objectionable findings identified (**Attachment 4**). And since there appeared no change of the study documents from last submission, the PK data are acceptable for further Agency review.

For immunogenicity portion of **Study AALL07P4** and associated method validation, some scanned copies of study documents were available for review during the current inspection. No discrepancies were noted when available copies were compared to submitted documents. Although not all records were available for review, the sparse records we reviewed matched information

submitted to FDA. Therefore, there's no indication of discrepancies that could affect the reliability of study data.

Conclusion:

Some objectionable conditions were observed during this inspection and Form FDA 483 was issued. The final inspection classification is Voluntary Action Indicated (VAI).

Although objectionable conditions were observed during this inspection, the findings did not impact the reliability of the data from the audited studies. Thus, I recommend that the analytical data from **Studies AALL07P4** and **DFCI 11-001** (**BLA 761102**) and other studies using similar methods (**Attachment 1**) be accepted for further Agency review.

Yiyue Zhang, Ph.D.
Visiting Associate

Final Classification:

Analytical

VAI – (b) (4)
FEI#: (b) (4)

cc:
OTS/OSIS/Kassim/Choe/Kadavil/Fenty-Stewart/Nkah/CDER-OSIS-BEQ
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Zhang
OTS/OSIS/DGDBE/Cho/Jang/Choi/Skelly/Au
ORA/OMPTO/OBIMO/DBIMOI/Garmendia

Draft: YZ 6/20/2018, 6/21/2018, 6/22/2018
Edit: RCA 6/20/2018, 6/22/2018; AD 06/21/2018, 06/22/2018

ECMS: Cabinets/CDER_OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/ANALYTICAL/(b) (4)

OSIS File#: BE 7831
FACTS: (b) (4)

Attachments:

Attachment 1. Studies in support of pending applications.
Attachment 2. Authorization letter and affidavit.
Attachment 3. Form FDA 483 issued to (b) (4)
Attachment 4. EIR review of Study AALL07P04 (BLA (b) (4)) dated 04/19/2013

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/s/

YIYUE ZHANG
06/22/2018

RUBEN C AYALA
06/22/2018

ARINDAM DASGUPTA
06/22/2018

CLINICAL INSPECTION SUMMARY

Date	June 12, 2018
From	Anthony Orencia M.D., F.A.C.P., GCPAB Medical Officer Susan D. Thompson, M.D., GCPAB Team leader, for 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	Patricia Dinndorf, M.D., Medical Officer Donna Przepiorka, M.D., Ph.D., Clinical Team Leader Suria Yesmin Regulatory Project Manager Division of Hematology Products
BLA	761102
Applicant	Baxalta US, Inc
Drug	Calaspargase Pegol
NME	No
Therapeutic Classification/Status	pegylated asparaginase biologic
Proposed Indication	chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia
Consultation Request Date	January 26, 2018
Summary Goal Date	August 15, 2018
Action Goal Date	October 1, 2018
PDUFA Date	December 22, 2018

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three clinical sites (Drs. Silverman, Athale, and Michon) were selected by the Division of Hematology Products (DHP) for inspection in support of BLA 761102. The sponsor, Baxalta US, Inc. (Shire, PLC), was also inspected. 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 regulatory compliance classification for the sponsor is No Action Indicated (NAI). The final regulatory classification for Drs. Silverman, Athale, and Michon is NAI.

2. BACKGROUND

Acute lymphoblastic leukemia is the most common cancer diagnosed in children, representing approximately 25% of cancer diagnoses among children younger than 15 years. L-asparaginase is an essential component of treatment for acute lymphoblastic leukemia, but is associated with multiple toxicities. Because asparaginase preparations are bacterially-derived, they have the potential to be highly immunogenic. Hypersensitivity reactions to asparaginase occur in up to 30% of patients treated with native *E. coli* asparaginase. Clinical allergy is frequently associated with the development of neutralizing antibodies, so that even if symptoms are controlled, there is little therapeutic benefit after drug administration. Pancreatitis may occur in 5-10% of patients, and thrombosis may occur in up to 5% of patients.

Calaspargase Pegol (SC-PEG-asparaginase) is a new pegylated asparaginase preparation which utilizes a novel linkage between the PEG-moiety and the native *E.coli* L-asparaginase protein. Calaspargase Pegol utilizes the same *E.coli* L-asparaginase and the same size PEG that is used in the currently available form of PEG asparaginase (Oncaspar®), but the new linkage utilized in Calaspargase Pegol is felt to be more hydrolytically stable. The mechanism of action is probably related to the selective killing of leukemic cells due to the depletion of plasma asparagine. The sponsor submitted this BLA as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia.

Study DFCI 11-001

Study DFCI 11-001was a Phase 2 open label study of calaspargase pegol 2500 IU/m^2 given as a single dose during remission induction and then every 3 weeks for 30 consecutive weeks during post-induction therapy in children and adolescents with newly diagnosed acute lymphoblastic leukemia.

The primary objective of this study was to assess the safety and feasibility associated with the administration of calaspargase pegol 2500 IU/m^2 given IV as a single dose during remission induction and then every 3 weeks for 30 weeks during post-induction therapy in children and adolescents with newly diagnosed acute lymphoblastic leukemia.

Pediatric subjects were enrolled into the study for those with confirmed diagnosis of acute lymphoblastic leukemia or lymphoblastic lymphoma and no prior therapy, except short courses of corticosteroid, a single dose of intrathecal cytarabine at the time of diagnostic lumbar puncture, and/or emergent radiation to the mediastinum or other life-threatening masses. This study included the following treatment phases: (a) steroid prophase (3 days); (b) remission induction (29 days); (c) consolidation I phase (3 weeks for standard or high risk subjects and 9 weeks for very high risk subjects); (d) CNS phase (3 weeks) (e) consolidation II phase (27 weeks), and (f) continuation phase (until 24 months from the date that complete remission was achieved).

This multicenter study was conducted across eight clinical study sites in the U.S., Puerto Rico, and Canada. The study was initiated on June 4, 2012. The last subject was dosed (calaspargase pegol or Oncaspar®) on February 18, 2016. Participation in the Continuation phase is ongoing. The total study duration was 4 years and 4 months until survival data cutoff date (October 5, 2016). Follow-up for survival outcome is ongoing. The Intent-to-treat (ITT) analysis set comprised 239 enrolled

and randomized subjects (119 calaspargase pegol and 120 Oncaspar®). The safety analysis set (SAS) consisted of 237 subjects (118 calaspargase pegol and 119 Oncaspar®) who received at least a single dose of study drug.

The primary safety endpoints involved an analysis of adverse events, including bacterial and invasive fungal infections, height and weight changes, and assessment of post-baseline positive anti-drug antibodies. Secondary endpoints, in part, included efficacy evaluation at Day 32 end-induction minimal residual disease (MRD) status; complete remission overall survival, event free survival, and disease free survival status.

3. RESULTS (by site):

Name of Clinical Investigator/Sponsor Address	**Protocol # DFCI 11-001/ Site #/# Subjects**	**Inspection Dates**	**Classification**
Lewis Silverman, M.D. Dana-Farber Cancer Institute 450 Brookline Ave. Boston, MA 02215	Site #1031 76 enrolled	March 28 to April 5, 2018	NAI
Uma Athale, M.D. McMaster Children's Hospital at Hamilton Health Sciences 1200 Main St. W. Hamilton, Ontario Canada	Site #1037 24 enrolled	April 18 to 20, 2018	NAI
Bruno Michon, M.D. CHU de Québec 2705 Laurier Boulevard Québec, Québec G1V 4G2, Canada	Site #1038 20 enrolled	April 23 to 27, 2018	NAI
Baxalta US, Inc (Shire, PLC) 650 East Kendall Street Cambridge, MA, 02142	Sponsor: Study DFCI 11-001 239 subjects	April 9, 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. Lewis Silverman, M.D.

Dr. Silverman is a sponsor-investigator of this Study DFCI 11-001.

A total of 76 subjects were screened and 76 subjects were enrolled. Eight patients discontinued from the study. Sixty-eight subjects completed the study.

The following reasons why these eight subjects discontinued from study and did not complete treatment were:

(i) Subject # (b) (6): Philadelphia chromosome positive
(ii) Subject #: Philadelphia chromosome positive
(iii) Subject #: subject moved out of state
(iv) Subject #: ineligible
(v) Subject #: treatment induction failure
(vi) Subject # Philadelphia chromosome positive
(vii) Subject #: treatment induction failure, and
(viii) Subject #: treatment induction failure.

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 25 enrolled subjects whose records were reviewed were verified against the case report forms and BLA subject line listings. Source documents for the raw data used to assess the primary 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. Uma Athale, M.D.

A total of 34 subjects were screened, and 24 subjects were enrolled. Four subjects discontinued during study: Twenty study subjects completed the study.

The four subjects who discontinued and reasons for discontinuation included the following:

(i) Subject (b) (6) – death
(ii) Subject – site withdrew the subject due to treatment non-compliance
(iii) Subject – family withdrew consent to pursue alternative treatment
(iv) Subject – induction failure

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 the 24 enrolled subjects whose records were reviewed were verified against the case report forms and BLA subject line listings. Source documents for the raw data used to assess the primary 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. No Form FDA 483 was issued.

3. Bruno Michon, M.D.

A total of 29 subjects were screened, and 20 subjects were enrolled. Subjects (b) (6) and (b) (6) were found to be Philadelphia chromosome-positive, were considered discontinuations, and taken off the study. Thus, eighteen patients 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 the 20 enrolled subjects, whose record were reviewed, were verified against the case report forms and BLA subject line listings. Source documents for the raw data used to assess the primary 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.

Sponsor

4. Baxalta US, Inc. (Shire, PLC)

The CDER assignment memorandum for this inspection issued to ORA was for Baxalta US, Inc. located at 650 Kendall St., Cambridge, MA 02142. The ORA field investigator verified that Shire, PLC had acquired Baxalta Inc., and the personnel and records needed to conduct this inspection were located at Shire, PLC in Lexington, MA.

Records reviewed included but were not limited to: organizational charts; vendor list; vendor oversight plans; transfer of obligations; investigator agreements; financial disclosures; monitoring plans; monitoring reports; safety reports; adverse events; protocol deviations; and standard operating procedures.

Monitoring reports indicated that the sites received adequate periodic monitoring. There was no under-reporting of serious adverse events by the sponsor.

In general, this sponsor 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}
Susan D. Thompson, M.D., GCPAB Team leader, for
Janice Pohlman, M.D., M.P.H.
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/s/

ANTHONY J ORENCIA
06/12/2018

SUSAN D THOMPSON
06/12/2018

U.S. FOOD & DRUG ADMINISTRATION

Consult Memorandum

Date:	May 25, 2018
To:	Donna Przepiorka (Cross-Discipline Team Leader) and Suria Yesmin (RPM); CDER/OND/OHOP/DHP
From:	Aaron Schetter; CDRH/OIR/DMGP/MGB
Through:	Donna Roscoe and Reena Philip
Subject:	BLA761102
Drug Name:	calaspargase pegol
Drug Sponsor	Baxalta US Inc.
Biomarker(s):	MRD as measured by (b) (4)
Device Name:	(b) (4) as performed by (b) (4) as performed by (b) (4)
Laboratory:	(b) (4)
CDRH Tracking Number:	ICC1800141

I. BACKGROUND and PURPOSE

Baxalta submitted a BLA for calaspargase for treatment of ALL, (b) (4) The assay information (Module 5 and attached) and proposed PI (Module 1 and attached) are at: \\CDSESUB1\evsprod\BLA761102\0001

CDER has asked for CDRH to review the analytical data for the MRD assay. Specifically:

(b) (4)

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(b) (4)

(b) (4) we recommend that the sponsor re-tests specimens with a test/lab that can provide appropriate analytical validation.

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/s/

SURIA YESMIN
05/25/2018
Signing on behalf of Aaron Schetter