CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761104Orig1s000

PRODUCT QUALITY REVIEW(S)

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Biotechnology Products

LABELS AND LABELING REVIEW

Date of review:	September 12, 2018
Reviewer:	Vicky Borders-Hemphill, PharmD Labeling Review Specialist Office of Biotechnology Products (OBP)
Through:	Sang Bong Lee, PhD, Product Quality Reviewer OBP/Division of Biotechnology Review and Research IV
Application:	BLA 761104
Applicant:	AstraZeneca AB
Submission Date:	November 30, 2017
Product:	moxetumomab pasudotox-tdfk
Dosage form(s):	for injection
Strength and Container-Closure:	1 mg/vial single-dose vial
Indication, dose, route, and frequency of administration:	is a CD22-directed immunotoxin indicated for the treatment of adult patients with relapsed or refractory hairy cell leukemia who received at least two prior systemic therapies
Background and Summary Description:	The Applicant submitted a biologics license application for Agency review
Recommendations:	The container labels and carton labeling (submitted on August 22, 2018), the IVSS carton labeling (submitted on September 11, 2018), and the Prescribing Information/Medication Guide/Healthcare Provider IFU (submitted on September 11, 2018) are acceptable (see Appendix D) from an OBP labeling perspective.

Materials Considered for this Label and Labeling Review	
Materials Reviewed	**Appendix Section**
Proposed Labels and Labeling	A
Other	B (n/a)
Evaluation Tables	C
Acceptable Labels and Labeling	D

n/a = not applicable for this review

DISCUSSION and CONCLUSION

We evaluated the proposed labels and labeling for compliance to the applicable requirements in the Code of Federal Regulations, FDA Guidance, and United States Pharmacopeia (USP) standards (see Appendix C).

The prescribing information, medication guide, instructions for use, container labels, and carton labeling were reviewed and found to comply with relevant regulations (21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57; 21 CFR 201.100), and USP standards.

The container labels and carton labeling (submitted on August 22, 2018), the IVSS carton labeling (submitted on September 11, 2018), and the Prescribing Information/Medication Guide/Healthcare Provider IFU (submitted on September 11, 2018) are acceptable (see Appendix D) from an OBP labeling perspective.

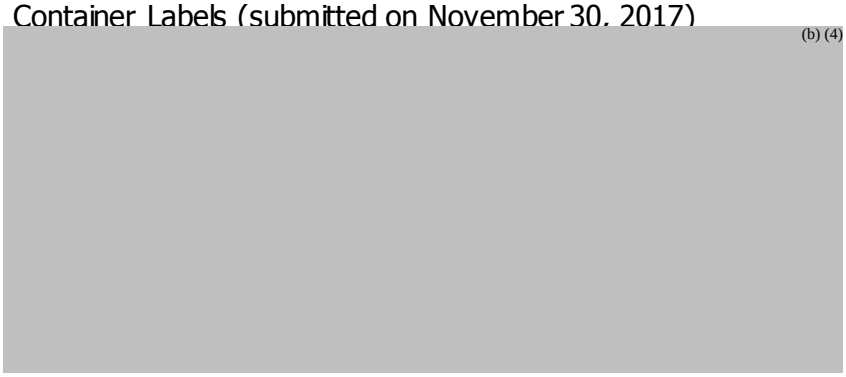
APPENDICES

Appendix A: Proposed Labeling
Prescribing Information/Medication Guide (submitted on November 30, 2017
\\cdsesub1\evsprod\bla761104\0001\m1\us\draft-labeling-text-clean.docx)

Healthcare provider Instructions for Use (submitted July 10, 2018
\\cdsesub1\evsprod\bla761104\0031\m1\us\draft-hcp-ifu-2018-07-10.pdf)

Container Labels (submitted on November 30, 2017)

(b) (4)



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Appendix B: Other (n/a)
Appendix C: Evaluation Tables (Label[1,2] and Labeling[3] Standards)

Container[4] Label Evaluation

Vial Label

Regulations, Guidance and CDER Best Labeling Practices	Conforms
Proper Name (21 CFR 610.60, 21 CFR 201.50, 21 CFR 201.10) *for container of a product capable of bearing a full label* **Comment/Recommendation:** *partial label*	☐ No ☐ Yes ☒ N/A
Manufacturer name, address, and license number (21 CFR 610.60) *for container of a product capable of bearing a full label* **Comment/Recommendation:** *partial label*	☐ No ☐ Yes ☒ N/A
Lot number or other lot identification (21 CFR 610.60, 21 CFR 201.18, 21 CFR 201.100) **Comment/Recommendation:** *partial label*	☐ No ☐ Yes ☒ N/A
Expiration date (21 CFR 610.60, 21 CFR 201.17) **Comment/Recommendation:** *partial label*	☐ No ☐ Yes ☒ N/A
Multiple dose containers (recommended individual dose) 21 CFR 610.60	☐ No ☐ Yes ☒ N/A
Statement: "Rx only" 21 CFR 610.60 21 CFR 201.100	☐ No ☒ Yes ☐ N/A
Medication Guide 21 CFR 610.60 21 CFR 208.24 **Comment/Recommendation:** *partial label*	☐ No ☐ Yes ☒ N/A
No Package for container 21 CFR 610.60	☐ No ☐ Yes ☒ N/A
Partial label 21 CFR 610.60 21 CFR 201.10	☒ No ☐ Yes ☐ N/A

[1] Per 21 CFR 1.3(b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.
[2] Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.
[3] Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.
[4] Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

Comment/Recommendation:
To comply with 21 CFR 610.60(c), add the name of the Manufacturer as follows: AstraZeneca AB U.S. Lic No 2059. To accomplish this, you may remove the NDC number as this is not required information for a partial label.
The applicant revised as requested

Revise the strength presentation from "1 mg" to read "1 mg/vial". see USP General Chapters <7> Labeling.
The applicant revised as requested

No container label 21 CFR 610.60	☐ No ☐ Yes ☒ N/A
Ferrule and cap overseal	☒ No ☐ Yes ☐ N/A

Comment/Recommendation:
FOR VIALS: Confirm there is no text on the ferrule and cap overseal of the vials to comply with a revised United States Pharmacopeia (USP), General Chapters: <7> Labeling (Ferrules and Cap Overseals).

Applicant's response: This is to confirm that there is no text on ferrule and cap overseal and it complies with USP guidance referred. Only lot identity code is printed on the side of Aluminum skirt which is also in conformance with this guidance.

OBP labeling response: acceptable

Visual inspection 21 CFR 610.60	☒ No ☐ Yes ☐ N/A

Comment/Recommendation:
FOR VIALS: Confirm there is sufficient area on the container to allow for visual inspection when the label is affixed to the vial and indicate where the visual area of inspection is located per 21 CFR 610.60(e).

Applicant's response: When affixed, the vial label partially wraps around the vial leaving a 5mm gap through which the product may be visually inspected.

OBP labeling response: acceptable

NDC numbers 21 CFR 201.2 21 CFR 207.35	☐ No ☒ Yes ☐ N/A

Comment/Recommendation: *Not required for partial labels per 21 CFR 610.60(c). See recommendation above to remove to permit addition of manufacturer name.*

Route of administration 21 CFR 201.5 21 CFR 201.100	☐ No ☒ Yes ☐ N/A

Preparation instructions 21 CFR 201.5	☐ No ☒ Yes ☐ N/A
Package type term 21 CFR 201.5 **Comment/Recommendation:** *partial label*	☐ No ☐ Yes ☒ N/A
Drugs **Misleading statements** 21 CFR 201.6	☐ No ☐ Yes ☒ N/A
Strength 21 CFR 201.10 21CFR 201.100 **Comment/Recommendation:** see comment above to revise strength statement to read as 1 mg/vial *The applicant revised as requested*	☒ No ☐ Yes ☐ N/A
Drugs **Prominence of required label statements** 21 CFR 201.15	☐ No ☒ Yes ☐ N/A
Spanish-language (Drugs) 21 CFR 201.16	☐ No ☐ Yes ☒ N/A
FD&C Yellow No. 5 and/or FD&C Yellow No. 6 21 CFR 201.20	☐ No ☐ Yes ☒ N/A
Phenylalanine as a component of aspartame 21 CFR 201.21	☐ No ☐ Yes ☒ N/A
Sulfites; required warning statements 21 CFR 201.22	☐ No ☐ Yes ☒ N/A
Bar code label requirements 21 CFR 201.25 21CFR 610.67	☐ No ☒ Yes ☐ N/A
Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) 21 CFR 610.68 21 CFR 201.26	☐ No ☐ Yes ☒ N/A
Net quantity 21 CFR 201.51	☐ No ☒ Yes ☐ N/A
Usual dosage statement 21 CFR 201.55 21 CFR 201.100 **Comment/Recommendation:** *partial label*	☐ No ☐ Yes ☒ N/A

Inactive ingredients 21 CFR 201.100 **Comment/Recommendation:** *partial label*	☐ No ☐ Yes ☒ N/A
Storage requirements **Comment/Recommendation:** *partial label*	☐ No ☐ Yes ☒ N/A
Dispensing container 21 CFR 201.100	☐ No ☐ Yes ☒ N/A
IV Solution Stabilizer Vial Label **Comment/Recommendation:** Ensure that the manufacturer name accompanies the US license number. Add the name of the Manufacturer (license holder) as follows: AstraZeneca AB U.S. Lic No 2059. *The applicant revised as requested*	☒ No ☐ Yes ☐ N/A

Package Label[5] Evaluation

Moxetumomab pasudotox carton labeling

Regulations, Guidance, and USP	Conforms
Proper name (21 CFR 610.61, 21 CFR 201.50, 21 CFR 201.10)	☐ No ☒ Yes ☐ N/A
Manufacturer name, address, and license number 21 CFR 610.61	☐ No ☒ Yes ☐ N/A
Lot number or other lot identification 21 CFR 610.61	☐ No ☒ Yes ☐ N/A
Expiration date 21 CFR 610.61 21 CFR 201.17	☐ No ☒ Yes ☐ N/A
Preservative 21 CFR 610.61	☐ No ☒ Yes ☐ N/A

[5] Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus, this includes the carton, prescribing information, and patient labeling.

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IV Solution Stabilizer Carton labeling

Regulations, Guidance, and USP	Conforms
Proper name (21 CFR 610.61, 21 CFR 201.50, 21 CFR 201.10)	☐ No ☒ Yes ☐ N/A
Manufacturer name, address, and license number 21 CFR 610.61 *For Drugs: see 21 CFR 201.1(a), 21 CFR 201.1(h)(5), 21 CFR 201.1(h)(6), 21 CFR 201.100(e)*	☐ No ☒ Yes ☐ N/A
Lot number or other lot identification 21 CFR 201.18	☐ No ☒ Yes ☐ N/A
Expiration date 21 CFR 610.61 21 CFR 201.17	☐ No ☒ Yes ☐ N/A
Strength/volume 21 CFR 610.61 21 CFR 201.10 21 CFR 201.100	☐ No ☒ Yes ☐ N/A
Storage temperature/requirements	☐ No ☒ Yes ☐ N/A
(b) (4)	
Route of administration 21 CFR 610.61 21 CFR 201.5 21 CFR 201.100	☐ No ☐ Yes ☒ N/A
(b) (4)	

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21 CFR 201.16	☐ Yes ☒ N/A
FD&C Yellow No. 5 and/or FD&C Yellow No. 6 21 CFR 201.20	☐ No ☐ Yes ☒ N/A
Phenylalanine as a component of aspartame 21 CFR 201.21	☐ No ☐ Yes ☒ N/A
Sulfites; required warning statements 21 CFR 201.22	☐ No ☐ Yes ☒ N/A
Net quantity 21 CFR 201.51	☐ No ☒ Yes ☐ N/A
Usual dosage statement 21 CFR 201.55 21 CFR 201.100	☒ No ☐ Yes ☐ N/A
Comment/Recommendation: see above comment in route of administration section	
Dispensing container 21 CFR 201.100	☐ No ☐ Yes ☒ N/A

Prescribing Information Evaluation

Regulations	**Conforms**
PRESCRIBING INFORMATION	
Highlights of prescribing information	
PRODUCT TITLE 21 CFR 201.57(a)(2)	☐ No ☒ Yes ☐ N/A
DOSAGE AND ADMINISTRATION 21 CFR 201.57(a)(7)	☐ No ☒ Yes ☐ N/A
DOSAGE FORMS AND STRENGTHS 21 CFR 201.57(a)(8)	☒ No ☐ Yes ☐ N/A
Comment/Recommendation: Revise the strength presentation from (b) (4) to read "1 mg" *The applicant revised as requested*	
Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION 21 CFR 201.57(c)(3)	☒ No ☐ Yes ☐ N/A
Comment/Recommendation: Delete the statement (b) (4) (b) (4) here and throughout	

the PI.
The applicant revised as requested

Revise section 2.4 step to include important information to the healthcare provider to reflect the accurate strength of the product per vial, the final concentration after reconstitution, the amount of diluent used to reconstitute, and the minimum deliverable volume after reconstitution.
The applicant revised as requested

We added "Only one vial of IV Solution Stabilizer should be used per administration of TRADENAME"
The applicant revised as requested

Revise the term "Sterile Water for Injection" to read "Sterile Water for Injection, USP" per USP nomenclature
The applicant revised as requested

The Agency proposes to add a table for the storage times and conditions for reconstitution, dilution and administration. *The applicant accepted the addition of the table but removed the statement* (b) (4) *from the reconstituted solution. OBP labeling finds this acceptable*
Table xx. show the storage times and conditions for reconstitution, dilution, and administration of TRADENAME.

Table xx. Storage Times and Conditions for Reconstituted and Diluted TRADENAME solution.

	Diluted Solution	
Reconstituted Solution	**After** (b) (4) **Dilution**	**Administration**
TRADENAME (b) (4) bacteriostatic preservatives. Use reconstituted solution immediately. **DO NOT STORE** reconstituted TRADENAME vials. (b) (4)	Use diluted solution immediately or after storage at room temperature (20°C to 25°C; 68°F to 77°F) for up to 4 hours or store refrigerated at 2°C to 8°C (36°F to 46°F) for up to 24 hours. **PROTECT FROM LIGHT. DO NOT FREEZE.**	If the diluted solution is refrigerated (2°C to 8°C; 36°F to 46°F), allow it to equilibrate at room temperature (20°C to 25°C; 68°F to 77°F) for no more than 4 hours prior to administration. Administer diluted solution within 24 hours of reconstitution as a 30-minute infusion. **PROTECT FROM LIGHT.**

3 DOSAGE FORMS AND STRENGTHS
21 CFR 201.57(c)(4)

☒ No
☐ Yes
☐ N/A

Comment/Recommendation: We added the identifying characteristics of the dosage form per 21 CFR 201.57(c)(4).
The applicant revised as requested
We revised the description of the drug product to "cake or powder".
The applicant revised as requested

11 DESCRIPTION
(21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q))

☒ No ☐ Yes ☐ N/A

Comment/Recommendation:
We deleted the [redacted] (b) (4)

The applicant revised as requested

We added "During the moxetumomab pasudotox-tdfk manufacturing process, fermentation is carried out in nutrient medium containing the antibiotic kanamycin. However, kanamycin is cleared in the manufacturing process and is not detectable in the final product"
The applicant revised as requested

In the second paragraph, revised to the appropriate dosage form "for injection", the inactive ingredients to appear in alphabetical order (see USP General Chapters <1091> labeling of inactive ingredients) and add the deliverable volume after reconstitution.
The applicant revised as requested

We revised the description of the drug product to "cake or powder".
The applicant revised as requested

Revise the term "Sterile Water for Injection" to read "Sterile Water for Injection, USP" per USP nomenclature
The applicant revised as requested

16 HOW SUPPLIED/ STORAGE AND HANDLING
21 CFR 201.57(c)(17)

☒ No ☐ Yes ☐ N/A

Comment/Recommendation:
We added the identifying characteristics per 21 CFR 201.57(c)(17).
The applicant revised as requested

We revised from "[redacted] (b) (4)" to read "The IV Solution Stabilizer is packaged separately from Tradename. Each carton (NDC -xxx-xxxx-xx) contains one single-dose vials" for clarity.
The applicant revised as requested

We added "Only one vial of IV Solution Stabilizer should be used per administration of TRADENAME"
The applicant revised as requested

MANUFACTURER INFORMATION
21 CFR 610.61, 21 CFR 610.64

☐ No ☒ Yes ☐ N/A

MEDICATION GUIDE and Instructions for Use

TITLE (NAMES AND DOSAGE FORM)

☒ No ☐ Yes ☐ N/A

Comment/Recommendation: For the medication guide and the IFU: We revised to the correct dosage form "for injection"

The applicant revised as requested	
STORAGE AND HANDLING **For the IFU**	☐ No ☒ Yes ☐ N/A
INGREDIENTS	☒ No ☐ Yes ☐ N/A
Comment/Recommendation: For the medication guide: Revise the inactive ingredients to appear in alphabetical order (see USP General Chapters <1091> labeling of inactive ingredients). *The applicant revised as requested* **For the medication guide:** Revise the term "Sterile Water for Injection" to read "Sterile Water for Injection, USP" per USP nomenclature *The applicant revised as requested*	
MANUFACTURER INFORMATION 21 CFR 610.61, 21 CFR 610.64	☐ No ☒ Yes ☐ N/A

APPENDIX D. Acceptable Labels and Labeling

Prescribing Information/Medication Guide/Healthcare provider Instructions for Use (submitted on September 11, 2018 **\\cdsesub1\evsprod\bla761104\0055\m1\us\clean-draft-label.pdf**)

Container Labels (submitted on August 22, 2018)

(b) (4)

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Vicky Borders-Hemphill

Digitally signed by Vicky Borders-Hemphill
Date: 9/12/2018 11:44:33AM
GUID: 50814c7000007a3d59329f660d8ddf02

Sang Bong Lee

Digitally signed by Sang Bong Lee
Date: 9/12/2018 11:59:35AM
GUID: 508da6d8000263e5e470ed27b1bd5a9b
Comments: Hi Vicky,
I want to let you know that I just signed.
Thanks,

Recommendation: Approval

BLA 761104
Review

Date: September 3, 2018

From: Chana Fuchs, Ph.D.
Team Leader, DBRRIV/OBP/OPQ

Through: Joel Welch, Ph.D.
Review Chief, DBRRIV/OBP/OPQ

Drug Name/Dosage	**LUMOXITI (Moxetumomab Pasudotox-dtfk)/for injection,**
Strength/Potency	**1 mg/vial**
Route of Administration	**Intravenous infusion**
Rx/OTC Dispensed	**Rx**
Indication	**Treatment of adult patients with relapsed or refractory hairy cell leukemia who received at least two prior systemic therapies, including treatment with a purine nucleoside analog**
Applicant/Sponsor	**AstraZeneca AB**
US Agent, if applicable	**AstraZeneca Pharmaceuticals LP**

Product Overview

LUMOXITI (Moxetumomab Pasudotox-dtfk) is a cytotoxin composed of an immunoglobulin light chain variable domain (VL) and a heavy chain variable domain (VH) genetically fused to a truncated form of *Pseudomonas* exotoxin (PE38). The cytotoxin is produced in E. coli cells. The PE38 toxin domain contains the translocation domain (Domain II), ADP ribosyl transferase enzyme domain (Domain III), and a portion of the expression improvement domain (Domain Ib) of *Pseudomonas* exotoxin. Moxetumomab Pasudotox targets CD22 expressed on B cells, and when bound to CD22 on the surface of these cells, Moxetumomab Pasudotox is internalized by endocytosis and processed to release the endotoxin. The truncated PE38 protein lacks the cell binding domain (Domain Ia) to reduce nonspecific cellular toxicity, but retains the sequences to allow for translocation to the cytosol and catalysis of ADP ribosylation of elongation factor 2, thereby inhibiting protein synthesis which results in cell apoptosis.
Moxetumomab Pasudotox drug product is supplied at 1mg/vial as a sterile, single dose, lyophilized powder for intravenous infusion. LUMOXITI is proposed as treatment for treatment of adult patients with relapsed or refractory hairy cell leukemia who received at least two prior systemic therapies, including treatment with a purine nucleoside analog.

The IV solution stabilizer (IVSS) manufactured under this BLA to be administered with LUMOXITI, is used as a stabilizer in the IV bag into which moxetumomab pasudotox is going to be diluted and (b) (4) The IVSS is supplied at 1mg/mL as a sterile, single dose liquid for intravenous infusion in conjunction with LUMOXITI. the IVSS is not co-packaged with LUMOXITI, but it is licensed within this BLA to be used with LUMOXITI as described in the package insert. (b) (4)

Quality Review Team

Discipline	Reviewer	Branch/Division
Drug Substance	Sang Bong Lee	DBRRIV/OBP/OPQ
Drug Product	Li Lu	DBRRIV/OBP/OPQ
Immunogenicity	Haoheng Yan	DBRRIV/OBP/OPQ
Labeling	Vicky Borders-Hemphill	OBP/OPQ
OBP Tertiary Reviewer	Joel Welch	DBRRIV/OBP/OPQ
Facility	Thuy Thanh Nguyen	DIA/OPF/OPQ
Facility Team Lead	Zhihao Qiu	DIA/OPF/OPQ
Microbiology (DS)	Diane Raccasi	OPF/DMA
Microbiology (DP)	Virginia Carroll	OPF/DMA
Microbiology Team Lead	Maria Jose Lopez-Barragan	OPF/DMA
CMC RPM	Andrew Shiber	RBPMBI/ OPRO/OPQ
Application Team Lead	Chana Fuchs	OBP/DBRR4

Multidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Wanda Nguyen, Quyen Tran	DHP/OHOP/OND
Cross-disciplinary Team Lead	Nicole Gormley	DHP/OHOP/OND
Medical Officer	Bindu Kanapuru	DHP/OHOP/OND
Pharm/Tox	Matthew Thompson	DHP/OHOP/OND
Clinical Pharmacology	Guoxiang Shen	DHP/OHOP/OND

a. Names:

i. Proprietary Name: Lumoxiti
ii. Trade Name: Lumoxiti
iii. Non-Proprietary/USAN: Moxetumomab pasudotox-tdfk
iv. CAS name: 1020748-57-5
v. INN Name: Moxetumomab pasudotox
vi. OBP systematic name: : FUS: MABFRAG MURINE (SCFV) ANTI P20273 (CD22_HUMAN); RPROTFRAG P11439 (TOXA_PSEAE) [CAT8015]

b. Pharmacologic category: Therapeutic recombinant CD22-directed cytotoxin.

Quality Review Team – Signature Block

DISCIPLINE	REVIEWER	SIGNATURE
Microbiology Branch Chief	Patricia Hughes	See Panorama
Facilities Branch Chief	Zhihao Peter Qiu	See Panorama
OBP Branch Chief	Joel Welch	See Panorama
OBP Team Lead BLA ATL	Chana Fuchs	See Panorama

Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 351(a)

2. RELATED/SUPPORTING DOCUMENTS:

1. A. Submissions Reviewed

Submission(s) Reviewed	Document Date
0001 (1)	11/30/2017
0004 (4)	12/21/2017
0005 (6)	1/5/2018
0007 (8) (Original BLA)	1/29/2018
0008 (9)	3/23/2018
0010(11)	4/9/2018
0016 (17)	5/15/2018
0019 (20)	5/22/2018
0024 (24)	6/5/2018
0025 (27)	6/11/2018
0029 (29)	6/21/2018
0028 (30)	6/26/2018
0031 (32)	7/10/2018
0034 (35)	7/16/2018
0035 (36)	7/16/2018
0037 (38)	8/1/2018
0038 (39)	8/6/2018
0039 (40)	8/14/2018
0040 (43)	8/22/2018
0041 (42)	8/22/2018
0043 (44)	8/28/2018
0044 (45)	8/28/2018
0046 (47)	8/31/2018
0047 (48)	9/4/2018
0048(49)	9/4/2018

B. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code[1]	Status[2]	Comments
(b) (4)	V	(b) (4)		3	N/A	Sufficient information was provided in the BLA for its intended use.
	III			3	N/A	Sufficient information was provided in the BLA for its intended use.

			surface, RB2 coating)			
(b) (4)	III		(b) (4)	3	N/A	Sufficient information was provided in the BLA for its intended use.
	III			3	N/A	Sufficient information was provided in the BLA for its intended use.
	III			3	N/A	Sufficient information was provided in the BLA for its intended use.
	III			3	N/A	Sufficient information was provided in the BLA for its intended use.

1. Action codes for DMF Table: 1- DMF Reviewed; Other codes indicate why the DMF was not reviewed, as follows: 2- Reviewed previously and no revision since last review; 3- Sufficient information in application; 4- Authority to reference not granted; 5- DMF not available; 6- Other (explain under "comments")

2. Adequate, Adequate with Information Request, Deficient, or N/A (There is not enough data in the application; therefore, the DMF did not need to be reviewed.

A. Other documents: IND, Referenced Listed Drug (RLD), or sister application:
IND 115709, IND 100372

3. Consults: NONE

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

The Office of Pharmaceutical Quality, CDER, recommends approval of STN 761104 for LUMOXITI (moxetumomab pasudotox-tdfk), manufactured by AstraZeneca AB. The data submitted in this application are adequate to support the conclusion that the manufacture of moxetumomab pasudotox-tdfk is well-controlled and leads to a product that is pure and potent. It is recommended that moxetumomab pasudotox-tdfk be approved for human use under conditions specified in the package insert.

B. Approval Action Letter Language:

Manufacturing location:

- Drug Substance: (b) (4)
- Drug Product: manufacturing and fill, labeling and packaging are all conducted at (b) (4)

- Fill size and dosage form: 1mg/vial injection, for infusion, in single-dose vials
- Dating period:
  - Drug Product: 48 months: 2-8°C
  - Drug Substance: (b) (4) months: (b) (4) °C
  - (b) (4)
  - IV Solution Stabilizer (IVSS) 48 months: 2-8°C

  Results of ongoing stability studies should be submitted in the annual reports.

  - Stability Option (select one below):
    - Limited stability data [less than 3 full scale lots (and the applicant is committed to continue stability testing)]:
      Results of ongoing stability studies should be submitted in the annual reports
    - For stability protocols:
      - We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating of your drug substance, drug product and IV Solution Stabilizer under 21 CFR 601.12.
- Exempt from lot release
  - Yes. Moxetumomab pasudotox –tdfk is a specified product exempted in accordance with 21 CFR 601.2a.

C. Benefit/Risk Considerations:

- **Description**

Moxetumomab Pasudotox-dtfk is indicated for the treatment of patients with relapsed or refractory hairy cell leukemia who received at least two prior systemic therapies, including treatment with a

purine nucleoside analog. Moxetumomab Pasudotox-dtfk received Orphan drug designation on 11/15/2007 and the BLA was granted a priority review, with a rolling BLA.
Primary support for the efficacy and safety of moxetumomab pasudotox for the treatment of HCL is provided by studies CD-ON-CAT-8015-1053 (CAT-1053) and CAT-8015-1001 (CAT-1001) in adults with relapsed/refractory HCL. In the pivotal phase 3 study, durable CR rate was 30%, and in the phase 1 supportive study, PFS at 1 year was 88%. The pivotal clinical studies supporting the BLA identified some serious adverse reactions, including hemolytic uremic syndrome, capillary leak syndrome, renal toxicity, infusion reactions, electrolyte abnormalities, and liver enzyme abnormalities. These are described in the package insert.

The immunogenicity assays identified a high percentage of immunogenicity to moxetumomab pasudotox, with Patients who tested positive for ADA having decreased systemic moxetumomab pasudotox-tdfk concentrations. In Study 1053, 59% (45/76) of patients tested positive for ADA prior to any treatment. Seventy out of 80 subjects tested ADA positive at any point during the study and were subsequently tested for nAb. The results showed that 67 of 70 subjects were nAb-positive. Among these 67 patients who tested nAb-positive, 99% (66/67) had ADA specific to the PE38 binding domain, and 54% (36/67) also had ADA specific to the CD22 binding domain. The high levels of ADA and NAb rates do not preclude the approval of the BLA as the overall treatment benefits outweigh the risk.

The OPQ review of manufacturing has identified that the methodologies and processes used for drug substance and drug product manufacturing, release and stability testing are robust and sufficiently controlled to result in a consistent and safe product. The overall control strategy for LUMOXITI manufacture incorporates control over raw materials, facilities and equipment, the manufacturing process, release of Drug Substance (DS) and Drug Product (DP), and stability of these materials There were a number issues with the DS and DP control strategy that were resolved during the review cycle through communication with the applicant and updates to the BLA. The BLA is also recommended for approval from a sterility assurance and microbiology product quality perspective. The technical assessments for OBP drug substance and drug product quality and immunogenicity assay, DMA microbiological drug substance and drug product, DIA facility, and OBP labeling are located as separate documents in Panorama (see list in the end of this review).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable:

1. Conduct a low endotoxin recovery study to determine the ability of the kinetic chromogenic test to detect bacterial endotoxin spiked in the undiluted moxetumomab pasudotox drug product (b) (4) for up to (b) (4).
2. Develop an alternative method for endotoxin release testing of the IVSS which can overcome the low endotoxin recovery (LER) phenomenon. Demasking buffers may be used in combination with the LAL bacterial endotoxin test to mitigate LER.
3. Submit updated limits for long term stability timepoints up to the 24 month timepoint for DS stored at (b) (4) °C. The limits will be established using the stability data from 5 DS. A maximum of two lots in the years when manufacturing occurs will be placed on stability at (b) (4) °C. A justification for the limits will be provided.

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA (type)	Risk	Origin	Control Strategy	Other notes
Cell based apoptosis assay (potency)	Efficacy	Intrinsic to molecule	(b) (4)	
(b) (4) Product related impurities	Efficacy	(b) (4): Introduced during (b) (4) process steps		(b) (4) of the protein PE domain reducing bioactivity
Fragments Product related impurities	Efficacy	Introduced during (b) (4) process steps, and storage (temperature, pH)		Fragment due to partial reduction of VL form aggregates, and those formed by peptide bond cleavage lose biological activity.
High molecular weight species (Aggregates) Product related impurities	Efficacy and Immunogenicity	Improper disulfide bond formation: Introduced during (b) (4) process step		Aggregates may be more immunogenic and may cause lower bioavailability and faster clearance due to immunogenicity.
Disulfide bond modifications	Efficacy	Introduced during (b) (4) process steps		improper disulfide bond formation will cause formation of aggregates
Higher order structures	Efficacy	Introduced during (b) (4) process steps		Change of higher order structure of PE38 can lead to loss of biological activity
CDR oxidation (VL His-56 and VH Trp107)	Efficacy	During manufacturing or storage		CDR oxidation under extreme light exposure reduced CD22 binding and biological activity

B. Drug Substance [moxetumomab pasudotox] Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

Table 2: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management.

Table 2 below is a summary of the identification, risk, and lifecycle knowledge management for drug substance CQAs that are derived from the drug substance manufacturing process and general drug substance attributes.

CQA (type)	Risk	Origin	Control Strategy	Other
Bacterial Endotoxins	Safety, Purity and	Endotoxin can be	(b) (4)	

Contaminants or Process related impurities	immunogenic response	introduced through raw materials and through the manufacturing process	(b) (4)	
Bioburden	Safety, Purity and Efficacy (degradation or modification of the product by contaminating microorganisms)	Bioburden can be introduced through Raw materials and manufacturing process		
Host Cell Proteins Process related impurities	Immunogenic response and Efficacy (degradation of the product by HCP-derived protease)	Introduced by production cell line and during DS manufacturing process		Bacterial protease has had an impact on product quality through fragmentation prior to changes made in manufacturing.
Host cell DNA Process related impurities	Safety	Introduced by production cell line and during DS manufacturing process		
Residual Kanamycin (process related impurity	Safety, Immunogenicity	(b) (4)		Also evaluated by pharm/tox reviewer
Residual (b) (4) and other (b) (4) (process related impurity)	Safety, Immunogenicity	(b) (4)		
Bacteriophage	Safety, production capability (drug shortage)	Cell line or other contaminating bacterial cells		See more extensive description of the bacteriophage issue in the text below
Mycoplasma (contaminant)	Safety	Mycoplasma would most likely be		

		introduced during [redacted] (b) (4)	
Leachables (Process-related impurity)	Safety	Manufacturing components and the DS container closure system	
Protein Concentration	Efficacy	[redacted] could be changed during storage (b) (4)	
[redacted] (b) (4)			(b) (4)
Appearance (with visible particles)	Safety and Immunogenic response	In-process and stability	
Color	Efficacy	In-process and stability	Change in color may indicate Product oxidation
Clarity	Safety and Immunogenic response	In-process and stability	
Osmolality	Safety (injection site reaction) and Stability	In-process	(b) (4)
pH	Efficacy and Stability	In-process and stability	

			(b) (4)

a. Description:

Moxetumomab pasudotox is a recombinant immunotoxin fusion protein targeting the B cell-specific surface antigen CD22, and consists of an immunoglobulin Fv fragment (light chain variable domain (VL) and a heavy chain variable domain (VH)) with the VH domain genetically fused to a truncated form of Pseudomonas exotoxin, PE38 (VH-PE38). (b) (4) . This change resulted in increased affinity (K_D of 6 nM versus 85 nM) and cytotoxic activity (5- to 10-fold in CD22-positive cell lines and up to 50-fold in cells from chronic lymphocytic leukemia and hairy-cell leukemia patients) compared to CAT-3888, a first generation molecule.

(b) (4) the VL and VH-PE38 are connected by a disulfide-bond engineered at position G100C in the VL subunit and at position R44C in the VH subunit. The PE38 contains the translocation domain (Domain II), ADP ribosyl transferase enzyme domain (Domain III), and a portion of the expression improvement domain (Domain Ib) of Pseudomonas exotoxin, but not the cell-binding region (Domain Ia).

b. Mechanism of Action (MoA):

After binding to target CD22 receptors on the membrane of B cells, the C-term K in the VH-PE38 is removed by plasma carboxypeptidase (ending in REDL). Moxetumomab pasudotox is internalized through clathrin-coated pits into the endocytic compartment where reduction of disulfide bond in domain II of PE38 occurs. Furin-catalyzed cleavage in domain II resulting in separation of the Fv from a 37 kDa C-term toxin fragment *(Furin cleavage site is specific to PE)*. The toxin fragment (ending in REDL) is transported via the KDEL recycling receptor from the Golgi to the ER and to the cytosol where ADP-ribosylation of EF-2 by the toxin leads to a rapid decreased level of anti-apoptotic protein Mcl-1 resulting in induction of apoptosis and cell death

a. Potency Assay:

Potency is measured as the capability to induce apoptotic cell death of the Daudi human B (Burkitt's) lymphoma cell line expressing CD22 on the cell membrane. The signal is measured by a commercially available Caspase-Glo 3/7 Assay System. The amount of luminescence after reaction with a Caspase 3/7 luciferase substrate is proportional to the amount of apoptosis. The relative potency is determined by dividing the EC50 value of Reference Standard (RS) by the EC50 value of test sample and multiplying by 100. Samples and controls are diluted to 10 concentrations. IN addition to the reference standard, a control sample which could be the RS or another DS positive control, is included in the assay. Placebo samples are used to rule out any measurable biological activity.

b. Reference Materials:

(b) (4)

(b) (4)

.

c. Critical starting materials or intermediates:

(b) (4)

d. Manufacturing process summary:

(b) (4)

The moxetumomab pasudotox drug substance process was developed using a Quality by Design (QbD) approach with risk assessment tools to define critical quality attribute acceptance criteria, critical process parameters (CPPs) and non-CPPs, and the final manufacturing control strategy. No design space is claimed for the manufacturing process.

The current control strategies for DS and DP include control and monitoring of critical and noncritical operating process parameters, in-process testing for microbial control and assessment of other outputs that ensure product quality and allow for monitoring of performance attributes, and release and stability testing of DS and DP. Critical parameters selected for routine monitoring relate to (b) (4) , assurance of acceptable levels of critical quality attributes (CQAs), including potency and strength, and assurance of correct formulation

e. **Container closure:**

The primary container for moxetumomab pasudotox drug substance is (b) (4) The container closure system is suitable for moxetumomab pasudotox-tdfk based on stability data and maintenance of closure integrity.

f. Dating period and storage conditions:

The dating period for the DS will be (b) (4) months when stored at (b) (4) °C.

A stability protocol for extension of expiration dating of the DS up to (b) (4) months is included in the BLA submission.

C. Drug Product [Lumoxiti] Quality Summary:

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes.

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Management

CQA (type)	Risk	Origin	Control Strategy (b) (4)	Other
Sterility (contaminant)	Safety, Purity and Efficacy (degradation or modification of the product by contaminating microorganisms)	Contamination may be introduced throughout the DP manufacturing process or through a container closure integrity failure.		
Endotoxin (contaminant)	Safety, Purity and Immunogenicity	Materials used in manufacturing. contamination may be introduced throughout the DP manufacturing process or through a container closure integrity failure.		A low endotoxin recovery (LER) study performed (b) (4) for up to (b) (4) is a PMC.
Container closure integrity (maintenance of sterility during shelf-life)	Safety, efficacy. (failure in closure integrity may lead to contamination through a loss of sterility or increasing humidity entering the vial and impacting product stability.	Container closure breaches during storage		CCIT performed using a validated dye ingress test
Protein concentration *(general)*	Efficacy and safety	Formulation		Product is a potent cytotoxin. Too low concentration would impact efficacy and too high concentration may impact safety. Critical for accurate dose delivery.
Appearance, Color,	Safety	Formulation		Appearance may

Clarity (*general*)			(b) (4)	impact stability of lyophilized products.
Appearance – Cake or powder (*general*)	Efficacy	Formulation and lyophilization process		For release, specification is for cake as any other form would signal some issue. for stability, cake or powder is acceptable.
Subvisible particles (*product and/or process related impurities*)	Immunogenicity, safety	Manufacturing process and container closure system (CCS)		There is less of a chance of CCS impact since this is a lyophilized product.
Fragmentation (by (b) (4))	Efficacy	Manufacturing process, time, and temperature.		
Leachables/extractables (*process related impurities*)	Safety	Manufacturing equipment		Low risk of leachables from CCS since this is a lyophilized product. (b) (4) have short contact time.
pH *(general)*	Safety	Formulation		
Osmolality *(general)*	Safety, efficacy	Formulation		Osmolality supports appropriate formulation. It is not critical for impact on injection site as the product is significantly diluted in 0.9% Saline for infusion.
Moisture Content	Efficacy	lyophilization process, container closure system integrity		Critical for product stability
Reconstitution time	Product quality as related to safety and efficacy	Excipient quality, (b) (4), Lyophilization process		Reconstitution time points to product quality.

Polysorbate-80	Product quality as related to Safety and efficacy	[redacted]	[redacted]	
Extractable volume *(general)*	Efficacy/Dosing	Manufacturing process	[redacted]	Critical for accurate dose delivery.
Apoptosis bioassay	Efficacy	Manufacturing process	[redacted]	
Identity (ELISA) *(general)*	Safety, Efficacy	Intrinsic to molecule	[redacted]	

- **Potency and Strength:** 1mg/vial

- **Summary of Product Design:**
A sterile, White to off-white lyophilized cake; for reconstitution with WFI and dilution into IV solution for infusion. Single use vials, contains no preservatives. Product is dosed by mg/Kg so multiple vials of LUMOXITI are needed per dose.

  The lyophilized product was designed to have appearance of cake. [redacted] some vials may have the form of Powder.

- **List of Excipients:** The excipients [redacted] contain [redacted] sodium phosphate monobasic monohydrate; 4% (w/v) sucrose; 8% (w/v) glycine ; 0.02% (w/v) polysorbate 80.

- **Reference Materials:** Same as the moxetumomab pasudotox drug substance reference materials.

- **Manufacturing process summary:** The Lumoxiti drug product manufacturing includes the following steps: [redacted] Vials are 100% visually inspected, labeled, packaged, and stored at 2-8°C.

  [redacted]

(b) (4)

Bioburden and endotoxin are tested during manufacture, and sterility and endotoxin are tested at release. Container closure integrity testing using a validated method is included in the stability program.

(b) (4)

A post approval protocol for verification of long term stability of the powder form is included in the BLA.

Endotoxin: No low endotoxin recovery (LER) effect was observed with drug product stored at 2-8°C for duration of 48 hours. (b) (4)

A PMC was included as part of approval to provide data from a study conducted at (b) (4)

- **Container closure:** the CCS is made up of a 3cc clear (b) (4) glass vial with a 13mm (b) (4) rubber, (b) (4) stopper and a flip off, (b) (4) seal
- **Dating period and storage conditions:**
  The dating period for Lumoxiti™ shall be 48 months from the date of manufacture when stored at 2-8 °C.
- **List of co-package components, if applicable**: see IVSS quality summary below. the IVSS is not co-packaged with LUMOXITI, but it is licensed within this BLA to be used with LUMOXITI as described in the package insert. (b) (4)

D. Drug Product [IVSS] Quality Summary:
The IVSS is used as a stabilizer in the IV bag into which moxetumomab pasudotox is going to be diluted.

Table 4 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes.

Table 4: Drug Product CQA Identification, Risk, and Lifecycle Management

CQA (type)	Risk	Origin	Control Strategy (b) (4)	Other
Pyrogens (contaminant)	Safety, Purity and Immunogenicity	Raw materials, contamination may be introduced throughout the DP manufacturing		Development of an alternative method for endotoxin release testing which can

		process	(b) (4)	overcome the low endotoxin recovery (LER) phenomenon is a PMC.
Sterility (contaminant)	Safety, Purity and Efficacy (degradation or modification of the product by contaminating microorganisms	Contamination may be introduced throughout the DP manufacturing process		
Container closure integrity (maintenance of sterility during shelf-life)	Safety (failure in closure integrity may lead to contamination through a loss of sterility or evaporation/leakage impacting concentration or content)	Container closure breaches during storage		
Polysorbate 80 concentration	Efficacy	Formulation during manufacturing		Polysorbate 80 in the IVSS (b) (4)
Particles (subvisible and visible)	Safety	Raw material quality and polysorbate 80 stability		Measurement for polysorbate 80 was implemented to the stability protocol during BLA review.
Extractable volume	Efficacy	Manufacturing process		Insufficient IVSS can result in loss of drug (b) (4)
Total protein (identity)	safety			
Osmolality	Safety	Formulation during manufacturing		Osmolality is a measure (b) (4)
pH	Efficacy	Formulation during manufacturing		As pH is a CQA for the DP, IVSS pH is also considered a CQA.
Clarity	Safety	Formulation during manufacturing		Changes in clarity suggest a change in excipients
color	Safety	Formulation during manufacturing. Quality of the polysorbate 80		Changes in color suggest a change in excipients or degradation of the polysorbate 80 during stability.

- **Potency and Strength:** 1ml/vial. No active ingredient/protein.

- **Summary of Product Design:** A sterile, colorless to slightly yellow solution for injection into the IV bag system (b) (4)
  Contains no preservatives. Presented in single-dose vials.

- **List of Excipients:** (b) (4), 0.65% (w/v) polysorbate 80, pH 6.0

- **Reference Materials:** no reference standard. This is a formulation (b) (4)

- **Manufacturing process summary:**
The manufacturing process of IVSS involves (b) (4)
100% visually inspected, labeled, packaged, and stored at 2-8°C.

(b) (4)
(b) (4) An *in vitro* bacterial endotoxin test is the preferred method for release testing if the low endotoxin recovery (LER) phenomenon can be mitigated. A PMC to develop an alternative method for endotoxin release of the IVSS which can overcome the LER phenomenon is included as part of approval of this BLA.

- **Container closure:**
  The primary packaging components consist of a vial and a stopper. The secondary packaging components consist of a seal, a vial label, (b) (4) carton. The vialed IVSS is packaged as a single vial per carton.

- **Dating period and storage conditions:**
  The dating period for IV Solution Stabilizer for Lumoxiti™ shall be 48 months from the date of manufacture when stored at 2-8°C.

- **List of co-package components, if applicable.**
  There are no co-packaged components. IVSS and LUMOXITI are packaged separately for shipping to the distributor.

E. Novel Approaches/Precedents: none

F. Any Special Product Quality Labeling Recommendations:

- Single-Dose Vial.
- Discard Unused Portion.
- Storage: Refrigerate LUMOXITI and IV Solution Stabilizer at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. Do not shake.
- Reconstitute LUMOXITI with 1.1 mL Sterile Water for Injection, USP. Use reconstituted solution immediately.
- Add the IV Solution Stabilizer to the infusion bag containing 50 mL 0.9% Sodium Chloride Injection, USP.
- After dilution of reconstituted DP in 0.9% Sodium Chloride Injection with IVSS, the infusion solution may be stored at room temperature (20-25°C) for up to 4 hours or stored refrigerated (2-8°C) for up to 24 hours prior to use. Protect from light. Do not freeze. Do not shake. The intravenous infusion will be completed over 30 minutes, according to the label.
- Protect from light (DP, (b) (4) and DP in the IV bag)

G. Establishment Information:

Overall Recommendation:					
DRUG SUBSTANCE					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Manufacturing DS, release and stability testing	(b) (4)		Inspection required.	A three item 483 included observations on (b) (4)	Acceptable
Bioassay testing for Drug Substance release and stability testing			No inspection required. Has long inspectional history with good compliance record.		Acceptable
Manufacture of Master and Working Cell Banks			No inspection needed. Has long inspectional history.		No Further Evaluation
DRUG PRODUCT					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation

Manufacturing DP and IVSS. release and stability testing	(b) (4)	Acceptable. Inspection waived. See waiver memo for more information		Acceptable.
DP release and stability testing		Inspection required.	A three item 483 included observations on (b) (4)	Acceptable
Bioassay testing for Drug Product release and stability testing		No inspection required. Has long inspectional history with good compliance record.		Acceptable
Container closure testing for DS and IVSS on stability		No inspection required.		No Further Evaluation needed
Pyrogen testing for IVSS release		No inspection required. Has acceptable inspectional history		Acceptable

H. Facilities:

A pre-license inspection at the moxetumomab pasudotox drug substance (DS) manufacturing facility, (b) (4) was conducted between (b) (4) by OPQ/OPF/DMA and OPQ/OBP in support of this BLA. This multiproduct manufacturing facility manufactured multiple licensed as well as investigational drugs and is responsible for the manufacturing of moxetumomab pasudotox (b) (4),

for the QC testing of DS, including release and stability testing, and for QC release and stability testing of moxetumomab pasudotox drug product (DP). The inspection covered drug substance manufacturing, the testing laboratories and support facilities.
A three item 483 was issued at the end of inspection which included an observation on (b) (4) The sponsor responded to these observations. The facility was found to be adequate for licensure of this BLA. The initial recommendation for this inspection is VAI. The final facility recommendation is for approval.

A pre-license inspection of the drug product manufacturing facility, (b) (4) was waived. This site manufactures the moxetumomab pasudotox drug product and the Intravenous Solution Stabilizer (IVSS) finished product. The assessment that lead to a waiver included assessment of the manufacturing processes conducted for the DP and IVSS. The moxetumomab pasudotox manufacturing process entails (b) (4) All these activities are highly similar to other licensed immunotoxins manufactured at the site (b) (4). The QC release testing done at this site for the DP and IVSS are also of the general and compendial assays that are common for other approved products manufactured and tested at the facility. Review of recent FDA inspections coverage at this site as well as the firm's compliance history and current acceptable GMP status were also considered in the final decision to waive the inspection at this facility.

The compliance recommendations for the other facilities described in section G, above, which are not inspected within scope of this BLA, are for approval.

I. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:

1. Stability of the MCB and WCB
2. (b) (4) stability protocols
3. Post-Approval Annual Stability Protocols for (b) (4)
3. Cycle Lifetime Verification of the (b) (4)
4. (b) (4) lifetime Validation
5. Stability protocol at (b) (4) C for all DS lots for (b) (4).
6. Stability Studies for the Primary and Working Reference Materials
7. Ongoing Primary drug substance Stability Study
8. Post-Approval Annual Stability Protocols (at recommended storage condition of (b) (4) C and accelerated condition of (b) (4) C)

ii. Outstanding review issues/residual risk:

See Post Marketing Commitments #3 in section I D.

iii. Future inspection points to consider: None

b. Drug Product

i. **Protocols approved:**
1. Ongoing Stability Studies of Primary Batches (Validation lots) and supporting batch
2. Post-Approval Annual Stability Protocols
3. Protocol for stability study verifying long term stability of powder form.

ii. **Outstanding review issues/residual risk:**
See Post Marketing Commitments #1 in section I D.

iii. **Future inspection points to consider:** None

c. IVSS

i. **Protocols approved:**
1. Ongoing Stability Studies of Primary Batches (Validation lots) and supporting batches
2. Post-Approval Annual Stability Protocols

ii. **Outstanding review issues/residual risk:**
See Post Marketing Commitments #2 in section I D.

iii. **Future inspection points to consider:** None

Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

#	Checklist		Yes	No	N/A
	Product Type				
1.	Recombinant Product		x		
2.	Naturally Derived Product			x	
3.	Botanical			x	
4.	Human Cell Substrate/source material			x	
5.	Non-Human Primate Cell Substrate/Source Material			x	
6.	Non-Primate Mammalian Cell Substrate/source material			x	
7.	Non-Mammalian Cell Substrate/Source Material			x	
8.	Transgenic Animal source			x	
9.	Transgenic Plant source			x	
10.	New Molecular Entity		x		
11.	PEPFAR drug			x	
12.	PET drug			x	
13.	Sterile Drug Product		x		
14.	Other: [immuno-cytotoxin]		x		
	Regulatory Considerations				
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application [fill in number]			x	
16.	Comparability Protocol(s)			x	
17.	End of Phase II/Pre-NDA Agreements tem			x	
18.	SPOTS (special products on-line tracking system)			x	
19.	USAN assigned name		x		
20.	Other [orphan designation, priority review, rolling BLA]		x		
	Quality Considerations				
21.	Drug Substance Overage			x	
22.	Design Space	Formulation		x	
23.		Process		x	
24.		Analytical Methods		x	
25.		Other		x	
26.	Other QbD Elements		x		
27.	Real Time release testing (RTRT)			x	
28.	Parametric release in lieu of Sterility testing			x	
29.	Alternative Microbiological test methods			x	
30.	Process Analytical Technology in Commercial Production			x	
31.	Non-compendial analytical procedures	Drug Product	x		
32.		Excipients		x	
33.		Drug Substance	x		
34.	Excipients	Human or Animal Origin		x	
35.		Novel		x	
36.	Nanomaterials			x	
37.	Genotoxic Impurities or Structural Alerts			x	
38.	Continuous Manufacturing			x	
39.	Use of Models for Release			x	
40.	Other [fill in]				

Review documents related to this Executive Summary are in Panorama

- Drug substance quality technical assessment by Sang Bong Lee, PhD (OPQ/OBP/DBRRIV)

- Drug product quality technical assessment by Li Lu, PhD(OPQ/OBP/DBRRIV)
- Drug substance microbiology technical assessment by Diane Raccasi (OPQ/OPF/DMA IV)
- Drug product microbiology technical assessment by Virginia Carroll, PhD (OPQ/OPF/DMA IV)
- Facility assessment by Thuy Thanh Nguyen, CSO (OPQ/OPF/DIA)
- Immunogenicity assay review by Haoheng Yan, MD, PhD (OPQ/OBP/DBRRIV)
- OBP Labeling review by Vicky Borders-Hemphill, PharmD (OPQ/OBP)

Joel Welch

Digitally signed by Joel Welch
Date: 9/06/2018 01:51:37PM
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Patricia Hughes Troost

Digitally signed by Patricia Hughes Troost
Date: 9/06/2018 01:16:34PM
GUID: 508da717000297bcbfce0919f8c09594

Zhihao Peter Qiu

Digitally signed by Zhihao Peter Qiu
Date: 9/06/2018 01:16:48PM
GUID: 508da7480002bfb5825e149b2b4eb91d

Chana Fuchs

Digitally signed by Chana Fuchs
Date: 9/06/2018 01:15:38PM
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Memorandum of Review

STN:	BLA761104
Subject:	**Immunogenicity Assay Review**
Submission Date:	January 29, 2018
Review/Revision Date:	June 18, 2018
Primary Reviewer:	Haoheng Yan, MD, PhD (Immunogenicity assays) Product Quality Reviewer, OPQ/OBP/DBRR IV
Secondary Reviewer:	Chana Fuchs, PhD Team Leader, OPQ/OBP/DBRR IV
Tertiary Reviewer:	Joel Welch, PhD Review Chief, OPQ/OBP/DBRR IV
Applicant:	AstraZeneca AB
Product:	Moxetumomab pasudotox
Indications:	Treatment of adult patients with relapsed or refractory hairy cell leukemia who received at least two prior systemic therapies, including treatment with a purine nucleoside analog
Action Due Date:	September 29, 2018

Summary

Moxetumomab pasudotox (CAT-8015) is a recombinant, immunotoxin composed of a murine anti-CD22 immunoglobulin light chain variable domain and an anti-CD22 heavy chain variable domain genetically fused to a truncated form of Pseudomonas exotoxin (PE38). CAT-8015 binds to CD22 on the surface of B cells and the complex is rapidly endocytosed and then processed to release the exotoxin which inhibit cellular protein synthesis. To evaluate the immunogenicity of CAT-8015, the sponsor developed an anti-drug antibody (ADA) screening assay, an ADA titer assay and an ADA domain specificity assay and a neutralizing antibody (NAb) assay. The ADA assays (screening, titer and domain specificity) use electrochemiluminescence (ECL) based bridging format. The NAb assay measures neutralization effect of CAT-8015 induced cytotoxicity in Raji cells. Assay sensitivities are 42ng/mL and 165ng/mL for the ADA and NAb assay respectively, measured by a surrogate positive control of anti-CD22 binding domain antibody. The ADA screening assay sensitivity is between 40-104ng/mL, measured by a surrogate positive control of anti-PE38 antibody. The sponsor also provided supporting data demonstrating the NAb assays can detect neutralizing anti-PE38 antibody. The drug tolerance aspect of the immunogenicity assays is not a concern, because at the time of the ADA sampling,

the level of the on-board drug were at baseline. Overall, the immunogenicity assays are adequate to evaluate the immunogenicity of CAT-8015.

Review

- Unless otherwise noted, figures and tables in this review are copied directly from the submission.
- The review sequence of the individual aspect of the assay validation may not follow the exact sequence in the submission.
- The "guidance" cited in the review refers to the "FDA Draft Guidance to Industry: Assay Development for Immunogenicity Testing of Therapeutic Proteins, April 2016" http://www.fda.gov/downloads/Drugs/.../Guidances/UCM192750.pdf

Testing Strategy

Immunogenicity results of moxetumomab pasudotox are reported for Study CD-ON-CAT-8015-1053 (pivotal trial) and Study CAT-8015-1001(phase 1 dose finding study). Four immunogenicity assays were used to test patient plasma samples from the pivotal trial, including an ADA screening assay, a NAb assay, an ADA titer assay and an ADA domain specific assay. Screened positive samples were tested in the NAb assay. NAb positive samples were tested further for ADA titer and ADA domain specificity (anti CD22 binding domain or anti PE38 toxin).

Reviewer's Comment: *Clinical impact of immunogenicity was assessed using data from the pivotal trial, therefore the review of the immunogenicity assays focuses on the assays used for testing samples from the pivotal trial, including the following validation reports and addenda. The addenda are method transfer reports.*

- 5.3.1.4 v-im-0039 Validation of Luminescent Cell-Based Assay for Detection of Neutralizing Antibodies Against CAT-8015 Immunotoxin in Sodium Heparin Plasma (Report and Cross Validation Addendum)
- 5.3.1.4 v-im-0040 Validation of Electrochemiluminescence Method for Screening Detection of Antibodies Against CAT-8015 in Human Heparin Plasma (Report and Cross Validation Addendum)
- 5.3.1.4 v-im-0061 Validation of Electrochemiluminescence Method for Determination of Titer of Anti-CAT-8015 Antibodies in Human Heparin Plasma
- 5.3.1.4 v-im-0068 Validation of Electrochemiluminescence Method for Determination of Domain-Specificity of Anti-CAT-8015 Antibodies in Human Heparin Plasma (Report and Cross Validation Addendum)

The sponsor did not use a confirmatory ADA assay for which they reasoned that "due to the immunogenic nature of the PE38, most patients were expected to develop anti-moxetumomab pasudotox antibodies; therefore, the confirmatory assays were not deemed necessary".

Reviewer's Comment:

The recommended tiered immunogenicity testing includes an ADA screening assay, a confirmatory assay and a NAb assay. Screened positive sample are tested in the confirmatory assay. Confirmed positive samples are further tested for titer and NAb. In the current case, the

sponsor skipped the confirmatory assay, and titer are only tested in NAb positive samples. I found such testing strategy is acceptable in this case, based on the following rationale:

It is expected that both the murine anti-CD22 and PE38 moieties of CAT-8015 are immunogenic. The sponsor reported ADA prevalence rate to be 87.5% (70/80) among the 80 patients enrolled in the pivotal trial. Sixty seven patients (67/70) were tested NAb positive. In addition, ADA titers increased with dose, and the median titers in Cycles 2, 3 and 5 were 320, 2400, and 19200, respectively (Figure 11.4.4.3-1). Considering the immunogenic nature of the product as well as the reported high ADA/NAb results, the immunogenicity assessment of CAT-8015 is more likely to use ADA/NAb titer rather than ADA positivity status. Therefore, a confirmatory assay is not essential. Considering the high prevalence of NAb positive subjects, testing titer for NAb positive samples, instead of ADA positive samples, are acceptable too.

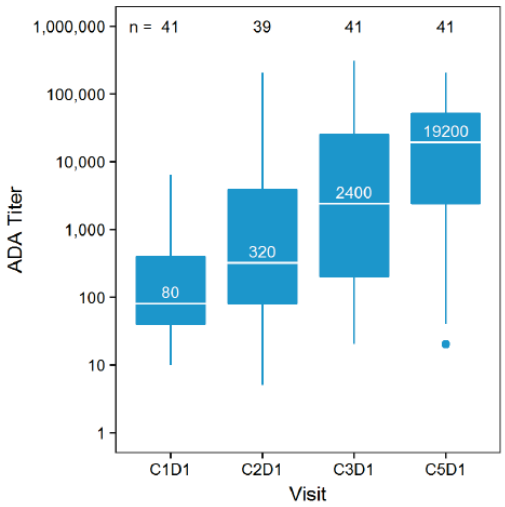

Figure 11.4.4.3-1 ADA Titers in HCL Subjects with Positive Neutralizing ADA Results

Anti-drug Antibody Screening Assay:

The assay validation is provided in Report No. V-IM-0040 and addendum.

Method

The ADA screening assay is an electrochemiluminescence (ECL) based bridging assay. In brief, human plasma samples are incubated in a mixture of biotinylated and ruthenylated labeled CAT-8015 and the formed complex were captured on the streptavidin MSD plates. After washing, the bound immune complexes are detected by using the MSD Imager. Plasma samples were all tested at 10% concentration.

Essential Reagents and Concentrations

Positive Control (PC):	G09.4, anti-idiotypic antibody against anti-CD22 moiety of CAT-8015.
PC1:	40ng/mL of PC
PC2:	60ng/mL of PC

Negative Control (NC): Pooled human plasma with undetectable ADA (pooled pre-screened individual samples whose assay signal <2 x NSB)

Nonspecific binding control (NSB): I-block (casein-based block reagent by ThermoFisher)

Negative Control for the immuno-depleted condition (NCDR): NC in the presence of CAT-8015.

Reviewer's Comments:

PC against toxin moiety (PE38) of the drug was not included in the assay validation. An information request (IR) was sent to the sponsor on May 28, 2018 requesting data to demonstrate the performance of the immunogenicity assays, including ADA screening, titer and NAb assays, against the PE38 domain. The sponsor submitted the response on June 6, 2018. In the response, the sponsor states that during assay development, a non-neutralizing anti-PE38 monoclonal antibody, IP-49, was used as PC in the ADA screening assay, and a goat anti-PE38 serum was used as PC in the NAb assay. G09.4 (antibody against the anti-CD22 binding domain) was chosen to serve as PC in the validation and sample runs. The sponsor provided data and dosing curves of the anti-PE38 PCs to support the assay sensitivity in detecting anti-PE38 antibodies. These data are reviewed in the assay sensitivity sections. The response is found acceptable.

The validation study consisted of 18 acceptable assay runs performed by 2 analysts over 4 testing days. Each assay plate included two PC levels (PC1 and PC2), Negative Controls in the absence and presence of CAT-8015 (NC and NCDR), and NSB. Each of the controls was examined in quadruplicate. %CV for all controls were less than 13%.

Screening Cut Point Determination

Screening cut points were determined from a population of healthy volunteers. Individual human plasma of 60 healthy volunteers was assayed in the presence of 0.8 µg/mL CAT-8015 ("plasma samples + CAT-8015" was referred as immunodepleted plasma samples). All samples were analyzed in duplicate by two analysts over 2 days. The rationale to include 0.8 µg/mL of CAT-8015 in the assay (for cut point determination) was "to create negative population" considering the prevalence of "pre-existing ADA in plasma of healthy individuals and disease patients".

The ECL units of the individual immunodepleted plasma samples were log transformed and evaluated for outliers using a boxplot analysis. Outliers were defined as ECL <Q1-1.5*IQR or > Q3+1.5*IQR. Q1 and Q3 were defined as the ECLs at which 25% of the population had lower or higher ECLs, respectively. IQR were defined as Q3-Q1.

Statistical analysis of ECL values identified 6 analytical outliers, which were excluded from the cut point analysis. Shapiro-Wilk test revealed that the data did not follow normal distribution after outlier exclusion. Therefore, the screening cut point was established non-parametrically at 95th percentile of the ECL value (referred by the sponsor as CPDR), which was 387 ECL units.

The average of ECL values of all negative control in the presence of CAT-8015 in all accepted runs (referred as NCDR) = 166. The cut point factor (CPF) was determined as follows:

CPF = CPDR/NCDR = 387/166 =2.33

The assay floating cut point, F-CP, (which is the cut point used to score plasma samples in validation and clinical testing) = CPF x NC = 2.33 x NC

Samples with ECL above or equal to the F-CP are considered positive, otherwise are considered negative.

Addendum

The assay was originally validated at MedImmune Hayward Site (V-IM-0040), but later transferred to MedImmune Mountain View (MV) Site. Method transfer consisted of 19 individual assays performed by 2 analysts over 5 days. The sponsor states that statistical fit of MV and Hayward data sets showed that they were outside of the 90% confidence interval, CPF was re-determined using 82 individual samples (60 normal, 10 NHL, 10 CLL and 2 HCL) tested at MV. New CPF=3.94 (assay LOD≈42ng/mL)

F-CP = CPF x NC = 3.94 x NC, this was used in the testing clinical samples from the pivotal study.

Reviewer's Comment:

Due to the prevalence of pre-existing antibody, the sponsor took an unusual approach to create a pseudo-negative sample population by including drug in the assay reaction during cut point determination. A pre-selected low signal plasma pool was created to serve as NC to mitigate the impact of pre-existing ADA on the assay. It is worth noting that while the drug was included in the assay reaction during cut point determination, it is not included in assay reaction for clinical sample testing. While the experimental design for cut point determination is debatable, I conclude the cut point is acceptable based on the ADA testing results: the high pre-existing ADA rate (59%) and high overall ADA prevalence rate (87.5%) fit the general immunogenic expectation of the drug. The sponsor has determined that titer of ADA showed correlation with clinical events (impact on PK and efficacy). In other words, the current cutpoint seems fit the purpose to allow for a meaningful immunogenicity assessment of the drug.

Sensitivity

Addendum

Assay sensitivity was determined from G09.4 (PC) standard curve generated from all acceptable runs. The assay sensitivity is approximately 42ng/mL. In the IR response received on 6/8/2018, the sponsor also provided standard curve using IP-49 (PC for anti-PE38). The two dosing curves are shown in Figure 1 below. The prozone/hook effect was observed at high concentration of PC.

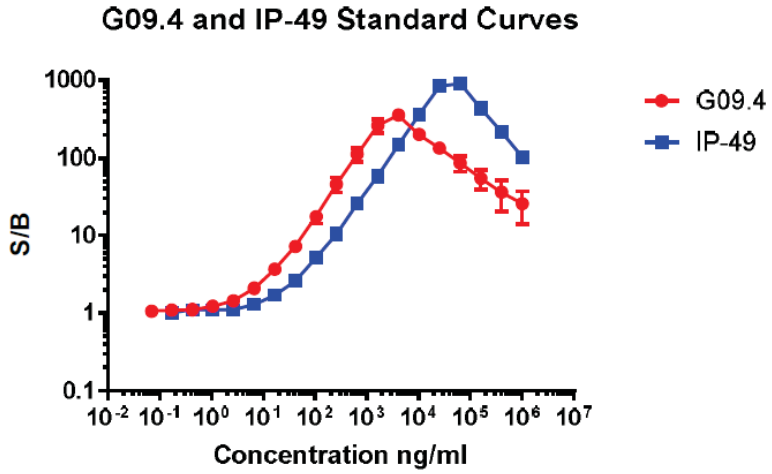

Figure 1 **Standard curves of G09.4 and IP-49 antibodies in 100% human plasma tested in the ADA screen assay**

Reviewer's Comment:

Assay sensitivity of 42ng/mL, measure by PC of G09.4, is acceptable per current draft guidance recommendation (at least 100ng/mL). Assay sensitivity measured by IP-49 is between 41.94 and 104.86ng/mL (based on the data in Table 3 of the IR response).

Drug Tolerance

The sponsor evaluated the ability of the assay to detect ADA(PC G09.4) in the presence of drug using different concentrations of CAT-8015 (0-500,000ng/mL) in the assay (data provided in Table A6). The assay can detect at least 655ng/mL of PC in the presence of 500ng/mL CAT-8015 in plasma.

Reviewer's Comment:

Half life of the drug is $t_{1/2}$≈1.2hrs, (5.3.3.5 Population Pharmacokinetic and Exposure-Response Analysis Report). See Figure 6.6.2-1. At the time of the ADA sampling (dosing day), the level of the on-board drug are at baseline. Therefore, the assay is not required to be drug tolerant.

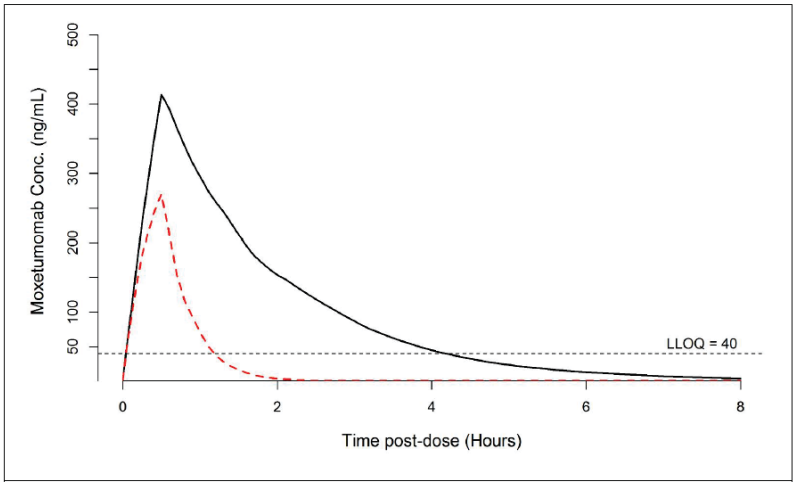

Figure 6.6.2-1 Impact of high ADA titer (> 10240) on moxetumomab pasudotox PK Exposure (Cycle 5 Day 1)

ADA = antidrug antibody; LLOQ = lower limit of quantification; PK = pharmacokinetic.
Black solid line presents the simulated moxetumomab pasudotox PK profile with low ADA titer (<= 10240).
Red dashed line represents the simulated moxetumomab pasudotox PK profile with high ADA titer (>10240).
The black dashed line represents the LLOQ of the assay (40 ng/mL).

Assay Precision

Inter and intra assay precision for PC1, PC2, NC, NSB, and NCDR are all below 18% and 25% in the original validation and addendum, respectively.

Reviewer's Comment: *Assay precision is acceptable.*

Assay Acceptance Criteria

Reviewer's Comments: *The sponsor did not include assay acceptance criteria determination in the validation report. In the ADA screening assay study report (clinical sample testing) G-IM-0142, all assay runs are valid with maximum %CV of NC, NSB observed at 21.8%, maximum %CV of PC observed at 19.6%, all PC were scored positive. Therefore, all assay runs were appropriately controlled.*

Titer Assay

The assay validation is provided in Report No.V-IM-0061.

Samples were titrated in a series of step-wise (1:2) dilutions before subjecting to the ADA screening assay. The highest dilution with detectable ADA was used to calculate sample titer. Sample titer = MRD x dilution =10 x dilution. In the validation exercise, titers of PC samples (G09.4, TS1=500 and TS2=20,000ng/mL) were tested by two analysts over three days. Titer of TS1=320-640, and TS2=20480

Reviewer's Comments:

Titer determination is appropriate. Titer assay precision is acceptable. In the ADA titer assay study report (clinical sample testing) G-IM-0144, maximum %CV of PC were observed at 20.4%, all PC were scored positive. All assay runs seem appropriately controlled.

Domain Specificity

The assay validation is provided in Report No.V-IM-0068 and addendum.

Method

CAT-8015 is a recombinant immunotoxin comprised of a CD22-binding (referred as ADA1) and a PE38 (referred as ADA2) domain. In the domain specificity assay, samples were pre-incubated in the presence and/or absence of ADA subtype inhibitors before subjecting to the screening assay. Specifically, the presence of ADA1 or ADA2 subtype is determined based on percent inhibition of ADA associated signals by their respective inhibitors, D1 (CAT-8015 IgG) or D2 (LMB-9). To eliminate the effect of a dominating ADA subtype in the ADA1/ADA2 mixed samples, an inhibitory effect of each of ADA-subtype specific inhibitors, D1 or D2, were assessed under the conditions where signals of the counterpart ADA were suppressed, e.g. to determine signal inhibition by D1, each sample was tested in parallel in the presence of D2-only (D2) and a mixture of D1 and D2 (D1/D2). This allowed determination of signal inhibition in D1/D2 relative to D2, which was attributed to D1 inhibitory effect on ADA1-associated signals (D1 %Inhibition). In the assay run, each sample was tested using three assay configurations: 1) D1, 2) D2, 3) D1/D2, which allowed determination of both D1% and D2 % inhibition values (see calculation formula below). D1% and D2% inhibition were used to identify domain specificity.

$$\text{D1 \% } Inhibition = \left(1 - \frac{\text{ECL of D1/D2}}{\text{ECL of D2}}\right) \text{ x } 100$$

$$\text{D2 \% } Inhibition = \left(1 - \frac{\text{ECL of D1/D2}}{\text{ECL of D1}}\right) \text{ x } 100$$

The validation consisted of 14 valid runs conducted by 2 analysts over 3 testing days.

Essential Reagents and Concentrations

NC: pooled ADA-negative human heparin plasma

PC1 (ADA1): G09.4; PC1A=400ng/mL, PC1B=1000ng/mL

PC2 (ADA2): IP-49 a mouse monoclonal antibody directed against PE38 domain of CAT-8015; PC2A=1000ng/mL, PC2B=2500ng/mL

D1: CAT-8015 IgG, a monoclonal anti-CD22 antibody

D2: LMB-9, an immunotoxin containing PE38 domain

Cut point determination

Spec-CP1:

A cutpoint for detection of ADA1 specificity (Spec-CP1) was determined using 60 individual plasma samples (52 healthy subjects and 8 leukemia subjects). Each of the samples was tested in D2 and D1/D2 configurations. D1 %Inhibition for ea***ch sample was calculated.***

The Spec-CP1 was determined by statistical analysis of the percentages of D1 %inhibition. Using a false positive rate of 0.1%, Spec-CP1 was determined to be 19.8%. During the method transfer to MV, the new (MV) set of data fell outside of the 90% confidence interval of the data set obtained at the Hayward site, therefore a new Spec-CP of 19.78% was established for use at the Mountain View site (clinical sample testing site) using 82 individual samples.

Spec-CP2:

Due to the presence of pre-existing anti-PE antibodies in plasma of drug naïve individuals, availability of ADA2-negative samples are limited. Spec-CP2 was established based on the assumption of its equality to Spec-CP1. The sponsor verified CP2 using combination of PC1 and PC2 spike in samples. Results are shown in Table 2 (copied below) and 3.

Table 2. Detection of ADA subtypes by Analyst 1

Analyst 1											
		ADA1 Detection					ADA2 Detection				
Sample Name	ADA1/ADA2 ng/ml	F-CP D2	Mean ECL D2	Mean ECL D1/D2	D1%Inhibition	Pos/Neg	F-CP D1	Mean ECL D1	Mean ECL D1/D2	D2%Inhibition	Pos/Neg
MS1	2000/10000	658	61353	351	99.4	Pos	855	170529	351	99.8	Pos
MS2	4000/20000		107228	844	99.2	Pos		289577	844	99.7	Pos
MS3	40/20000		1458	305	79.1	Pos		251280	305	99.9	Pos
MS4	4000/80		133348	299	99.8	Pos		3070	299	90.3	Pos
MS5	40/100000		3374	797	76.4	Pos		110310	797	99.3	Pos
MS6	20000/80		131434	323	99.8	Pos		1008	323	67.9	Pos
MS7	40/0		1708	311	81.8	Pos		312	311	0.3	Neg
MS8	0/80		283	314	-11.0	Neg		882	314	64.5	Pos
IHP4-100	ADA1-100	640	3910	356	90.9	Pos	863	1070	356	66.7	Pos
IHP5-100	ADA1-100		3373	287	91.5	Pos		5297	287	94.6	Pos
IHP6-100	ADA1-100		3468	216	93.8	Pos		59152	216	99.6	Pos
IHP4-20000	ADA1-20000		138460	295	99.8	Pos		1144	295	74.2	Pos
IHP5-20000	ADA1-20000		143270	334	99.8	Pos		4697	334	92.9	Pos
IHP6-20000	ADA1-20000		130222	261	99.8	Pos		56627	261	99.5	Pos

Table 3. Detection of ADA subtypes by Analyst 2

Analyst 2											
		ADA1 Detection					ADA2 Detection				
Sample Name	ADA1/ADA2 ng/ml	F-CP D2	Mean ECL D2	Mean ECL D1/D2	D1%Inhibition	Pos/Neg	F-CP D1	Mean ECL D1	Mean ECL D1/D2	D2%Inhibition	Pos/Neg
MS1	2000/10000	677	63878	303	99.5	Pos	741	156845	303	99.8	Pos
MS2	4000/20000		124621	340	99.7	Pos		305861	340	99.9	Pos
MS3	40/20000		1995	338	83.1	Pos		286041	338	99.9	Pos
MS4	4000/80		132717	312	99.8	Pos		1478	312	78.9	Pos
MS5	40/100000		1872	634	66.2	Pos		128679	634	99.5	Pos
MS6	20000/80		145199	281	99.8	Pos		1454	281	80.7	Pos
MS7	40/0		1533	301	80.4	Pos	→	375	301	19.9	Neg
MS8	0/80		308	289	6.3	Neg		1342	289	78.5	Pos
IHP4-100	ADA1-100	737	4138	331	92.0	Pos	819	1087	331	69.6	Pos
IHP5-100	ADA1-100		3526	305	91.3	Pos		5296	305	94.2	Pos
IHP6-100	ADA1-100		3465	231	93.3	Pos		64523	231	99.6	Pos
IHP4-20000	ADA1-20000		139915	346	99.8	Pos		1111	346	68.9	Pos
IHP5-20000	ADA1-20000		133896	293	99.8	Pos		5214	293	94.4	Pos
IHP6-20000	ADA1-20000		138011	220	99.8	Pos		59438	220	99.6	Pos

Reviewer's Comments:

The assay sensitivity and specificity were verified by MS7 and MS8 samples (red frame added by the reviewer), therefore both the Spec cut points are acceptable.

Note: the sponsor determined floating cut points for D1, D2 and D1/D2 settings, using the same data set, cut points = 2.33xNC, these cut points were used to sample positivity (for ADA1 or ADA2). To be scored positive, sample should be positive by both the floating cut point and %inhibition (see red arrow added by the reviewer).

Assay precision

Intra-assay precision for NC and PCs (PC1A/PC2A, PC1B and PC2B) for all three runs was calculated. All results %CV are less than 24.8% and 23.4% in the original validation and the addendum, respectively.

Reviewer's Comment: *Assay precision is acceptable.*

Neutralizing Antibody Assay:

The validation of this assay is provided in Report No. V-IM-0039 and addendum.

Method

The NAb assay is a cell-based luminescent method that utilizes the B-cell lymphoma line Raji. Samples are pre-incubated with CAT-8015, followed by addition of Raji cells for 48hrs incubation. After the incubation, cell viability was measured by adding CellTiter Glo reagent to the mixture. Assay signal was measured by a luminometer. Results obtained for each test sample in the presence of CAT-8015 are normalized to results for each test sample in the absence of CAT-8015 (%viability), where results in the absence of CAT-8015 represent 100% viability.

Reviewer's Comments:

Raji cells are human lymphoblast cells that express CD22 on cell surface. The NAb assay measures neutralization effect of CAT-8015 induced cytotoxicity, which reflects the proposed mechanism of action. The NAb assay format is acceptable.

Essential Reagents and Concentrations

- PC: G09.4, anti-idiotypic antibody against anti-CD22 moiety of CAT-8015.
- PC1: 600ng/mL of PC (15ng/mL in 2.5% plasma)
- PC2: 3000ng/mL of PC (75ng/mL in 2.5% plasma)
- NPC: Negative Plasma Control, pooled human sodium heparin plasma from six individual donors determined to be 'negative' for anti-CAT-8015 neutralizing antibodies during pre-validation experiments.
- MRD: 1:40, 2.5% plasma
- CAT-8015 concentration: 1.6ng/mL CAT-8015-PM2 was used in the assay during original validation. After the method transfer, 1.1ng/mL CAT-8015-PM3 was used to adjust for the difference due to high potency of the PM3 reagent.

Cut Point Determination

The sponsor tested a panel of 60 samples, including normal (34/60) and Non-Hodgkin's Lymphoma (NHL, 14/60), and Chronic Lymphocytic Leukemia (CLL, 12/60) plasma samples PL01 – PL60, to establish an assay cut point. The entire panel of 60 samples was assayed in six independent runs of the method by two separate analysts over a three day period. Due to the pre-existing neutralizing antibody to PE38 in normal human plasma, plasma samples were pre-treated with another PE38 containing immunotoxin, CAT-5001 (1μg/mL), to inhibit pre-existing anti-CAT-8015 activity.

The statistical analysis of cut point determination was conducted using %viability. No outlier was identified using box-plot analysis. Because neither the %viability and log transformed %viability fit normal distribution, assay cut point was established using non-parametric method at 1-sided 95th percentile which equals 49% cell viability. A normalization factor for floating assay cut point determinations was calculated by dividing the cut point value (49%) by the average cell viability of the NPC sample replicates (39%)→49%/39%=1.3

Assay cut point = Mean NPC of individual assay run x 1.3

Addendum:

During method transfer from Hayward to Mountain View, the cut point was recalculated using 81 individual samples (normal, CLL, NHL and HCL) over 5 days by 3 analysts. The same statistical method (as described above) was used. A new normalization factor of 1.18 was determined.

Assay cut point = Mean NPC of individual assay run x 1.18

Reviewer's Comments:

No significant difference was observed in %viability for normal and diseased sample, therefore, it is acceptable to pool normal and diseased sample for cut point determination. The cut points are appropriately determined.

Assay Sensitivity

Positive control antibody was serially diluted 1:3 in undiluted negative control plasma and tested for neutralizing activity. Six independent runs of positive antibody dilutions were performed by two separate analysts. The LOD is 5.2ng/mL in 2.5% plasma, corresponding to 280ng/mL in neat serum.

Addendum:

During method transfer from Hayward to Mountain View, the LOD was recalculated, using the new normalization factor of 1.18, to be 165ng/mL. Figure 4.3-1 showes the PC titration curve for LOD determination.

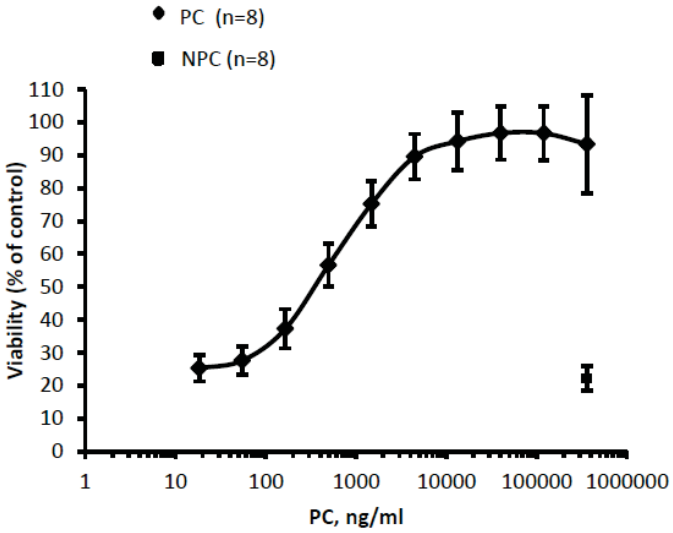

Figure 4.3-1 PC Titration Curve

In the IR response received on 6/8/2018, the sponsor provided a dosing curve using goat anti-PE38 serum.

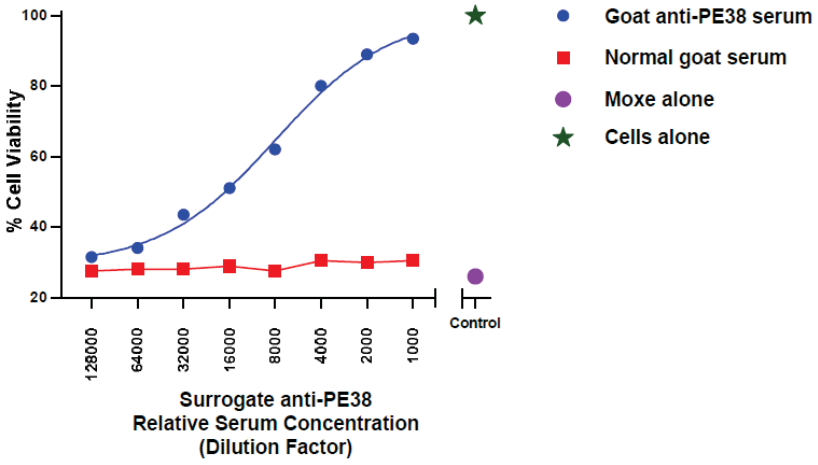

Figure 2 Neutralization of moxetumomab pasudotox mediated Raji cell killing by goat anti-PE38 serum

Moxe = moxetumomab pasudotox; NAb = neutralizing antibody

Reviewer's Comment: *The assay sensitivity, measured by G09.4(anti-CD22 binding domain) is acceptable. The dilution curve (figure 2 above) does not directly reports assay sensitivity in mass unit, however, the curve demonstrates the assay capacity in detecting NAb against PE38.*

Matrix Interference

PC1 and PC2 were spiked into normal, NHL, and CLL plasma samples (4 each). The assessment was conducted in 2 runs by 1 analyst. All spiked in samples showed positive results.

Reviewer's Comment:

No significant matrix interference/difference were observed in normal, NHL and CLL plasma.

Assay Precision

The sponsor evaluated inter- and intra-assay precision of control samples, including "Cell+Matrix Control", NPC, PC1, PC2, "Cells +Media Control" and "Negative Media Control", from one validation run and six independent validation runs by two analysts, respectively. Intra-assay precision %CV were between 1.3% and 4.7%. Inter-assay precision %CV were between 1.8%-22.1%.

Addendum:

During method transfer from Hayward to Mountain View, the inter- and intra-assay precision was re-evaluated. The same control samples were included in the evaluation. Intra-assay precision %CV were between 0.4% and 20.5%. Inter-assay precision %CV were between 1.7%-23.6%.

Reviewer's Comment: *The assay precision is acceptable.*

Robustness (days of cell harvest)

Assay results (% viability) were compared between cells harvested at 5 days (standard condition) or 7 days post vial thaw. The control samples included in the comparison are "Cells+Matrix Control", NPC, PC1 and PC2. All %CVs are below 11%.

Addendum

At Mountain View, the sponsor further evaluated the assay performance using cells up to 41 days post thaw.

Reviewer's Comment: *In the IR response received on 6/8/2018, the sponsor submitted data to support the claim that use of Raji cells was validated up to 41 days. The NC and PC1/NC ratio stayed comparable up to 41 days (passage 15, Table 1 and 2 in the IR response). The assay is robust for cells harvested up to 41 days (passage 15) post thaw.*

Drug Tolerance

Positive control antibody at final concentrations of 3000, 1000, 333.3, 111.1, 37.04, 12.35, 4.115 and 0 ng/ml were assessed for neutralizing activity in the presence of CAT-8015 concentrations 25.6, 12.8, 6.4, 3.2, 1.6 and 0 ng/ml in 2.5% plasma. The highest concentration of CAT-8015 that allowed detection of the positive control antibody was used to define the 'drug tolerance limit' of the assay for each neutralizing concentration of antibody. Titration curves were provided in Figure 5.2. Assay can detect 494ng/mL PC in the presence of 64ng/mL on board CAT-8015.

Reviewer's Comments:

As described in the section of ADA assay/Drug tolerance, at the time of the immunogenicity sampling (dosing day), the level of the on-board drug are at baseline. Therefore, the assay is not required to be drug tolerant.

Assay Acceptance Criteria

Reviewer's Comments: *The sponsor did not include assay acceptance criteria determination in the validation report. In the NAb assay study report (clinical sample testing) G-IM-0140, all assay runs are valid with %CV of NPC and PC (%cell viability) <25% all PC were scored positive. Therefore, all assay runs were appropriately controlled.*

Haoheng Yan

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Chana Fuchs

Digitally signed by Chana Fuchs
Date: 8/25/2018 03:49:54PM
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Joel Welch

Digitally signed by Joel Welch
Date: 8/26/2018 01:05:24PM
GUID: 508da6dc0002673d83d264d81364d6cf

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 51
10903 New Hampshire Ave.
Silver Spring, MD 20993

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

Reviewer: Diane Raccasi
Acting QAL: Maria Jose Lopez-Barragan, PhD
Branch Chief: Patricia Hughes, PhD

To:	Administrative File, STN 761104/0
Subject:	New Biologic License Application (BLA)
US License:	2059
Applicant:	AstraZeneca AB
Product:	**LUMOXITI (**Moxetumomab pasudotox)
Facility:	(b) (4) (Drug Substance manufacture)
Dosage:	Lyophilized powder (1 mg/vial) administered as an IV infusion and single-dose vial containing 1 mL IV solution stabilizer
Indication:	Adult patients with relapsed or refractory hairy cell leukemia (HCL)
Action date:	September 29, 2018

Recommendation for Approvability: The drug substance part of BLA 761104, as amended, is recommended for approval from a microbial control and microbiology product quality perspective.

Review Summary

AstraZeneca has submitted BLA 761104 to license moxetumomab pasudotox for the treatment of adult patients with relapsed or refractory hairy cell leukemia (HCL) who received at least two prior systemic therapies, including treatment with purine nucleoside analog. The drug substance (DS) is manufactured in (b) (4).

This review contains the assessment of the manufacturing process of moxetumomab pasudotox bulk drug substance from a microbiology product quality perspective.

BLA 761104 was submitted by AstraZeneca as a rolling BLA on November 30, 2017 in electronic format under sequence 0001. The last rolling BLA component was submitted on January 29, 2018.

Drug Product Quality Microbiology Information Reviewed

Description	eCTD	Date
Original BLA	0001	30 November 2017
Information request #1 part 1	0008	23 March 2018
Information request #1 part 2	0010	09 April 2018
Information request #2	0035	11 July 2018

S DRUG SUBSTANCE

S.1 General Information

Moxetumomab pasudotox (HA22) is a recombinant immunotoxin fusion protein that binds to B cells at the B-lymphocyte-specific adhesion receptor CD22. Moxetumomab pasudotox is produced in recombinant *E. coli*, (b) (4) VL (light chain variable domain) and VH-PE38 (heavy chain variable domain fused to *Pseudomonas* exotoxin 38).

The description is satisfactory

S.2 Manufacture

(b) (4)

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(b) (4)

S.7 Stability

S.7.1 Stability Summary and Conclusions

The proposed shelf life of Moxetumomab pasudotox DS is (b) (4) months at the recommended storage temperature (b) (4) based on data currently available for clinical batches manufactured under process 3.

S.7.3 Stability Data

Reviewer's comment: no microbial attributes (bioburden and endotoxin) were monitored during the stability studies. (b) (4)

Satisfactory

CGMP Status

Refer to Panorama for the CGMP status of the relevant facilities

Conclusion

I. The Drug Substance section of this BLA, as amended, was reviewed from a microbial control and microbiology product quality perspective and it is recommended for approval.

II. Information and data in this submission not related to microbial control of the drug substance should be reviewed by the appropriate division.

III. A pre-license inspection of (b) (4) is planed from (b) (4).

Diane Raccasi

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Maria Jose Lopez-Barragan

Digitally signed by Maria Jose Lopez-Barragan
Date: 8/17/2018 04:38:40PM
GUID: 5565e91d00144667b9fe95c7f98fbf85

U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment
WO Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

Reviewer: Virginia Carroll, PhD
Acting Quality Assessment Lead: Maria Jose Lopez-Barragan, PhD
Branch Chief: Patricia Hughes, PhD

BLA:	761104/0
Applicant:	AstraZeneca
US License Number:	2059
Submission Reviewed:	Original BLA
Product:	Lumoxiti (moxetumomab pasudotox)
Indication:	Adult patients with relapsed or refractory hairy cell leukemia who received at least two prior systemic therapies
Dosage Form:	Single-dose vial containing 1 mg sterile lyophilized powder for intravenous infusion and single-dose vial containing 1 mL IV solution stabilizer
Manufacturing Site (DS):	(b) (4)
Manufacturing Site (DP):	(b) (4)
FDA Receipt Date:	1/29/2018
Action Date:	9/29/2018

Conclusion and Approvability Recommendation

The drug product part of the BLA was reviewed from a sterility assurance and quality microbiology perspective and is recommended for approval. There are two post-marketing commitments (PMCs):

1. Conduct a low endotoxin recovery (LER) study to determine the (b) (4) bacterial endotoxin in moxetumomab pasudotox at (b) (4) for up to (b) (4)
2. Develop an alternative method for endotoxin release testing of the IVSS which can overcome the low endotoxin recovery (LER) phenomenon. Demasking buffers may be used in combination with the LAL bacterial endotoxin test to mitigate LER. (b) (4)

(b) (4)

Product Quality Microbiology Assessment: Drug Product

Drug Product Quality Microbiology Information Reviewed

Sequence number	Date	Description
0001	11/30/2017	Original BLA
0005	1/5/2018	IR Response
0008	3/23/2018	IR Response
0016	5/15/2018	IR Response
0024	6/5/2018	IR Response
0025	6/11/2018	IR Response
0029	6/21/2018	IR Response
0028	6/26/2018	IR Response
0035	7/16/2018	IR Response

Module 3.2 - Moxetumomab pasudotox

P.1 Description and Composition of the Drug Product

Moxetumomab pasudotox is a sterile lyophilized product for intravenous infusion packaged in a single-use 3 cc glass vial. It is reconstituted with 1.1 mL sterile water for injection (WFI). The volume of reconstituted product needed for each patient is calculated as follows: (dose of 0.040 mg/kg) x (patient weight in kg) / 1 mg/mL. For dilution, 1 mL of IV Solution Stabilizer (IVSS) is added to an infusion bag containing 50 mL of 0.9% w/v saline, then the required volume of moxetumomab pasudotox is injected into the bag for infusion. The composition of the drug product is copied below.

Table P.1-1 Composition of Moxetumomab Pasudotox Drug Product (1 mg/vial)

Component	Unit Formula	Purpose	Quality Standard	Concentration after Reconstitution
Active Ingredient				
Moxetumomab pasudotox	1.0 mg	Active	In-house Reference Standard	1.0 mg/mL
Excipients				
Sodium phosphate monobasic monohydrate [a]	3.4 mg	(b) (4)	USP	(b) (4)
Sucrose	40 mg		NF; Ph. Eur.	4% (w/v)
L-glycine	80 mg		USP; Ph. Eur.	8% (w/v)
Polysorbate 80	0.2 mg		USP; Ph. Eur.	0.02% (w/v)

NF = National Formulary; Ph. Eur. = European Pharmacopoeia; USP = United States Pharmacopeia

[a] (b) (4)

SATISFACTORY

P.2 Pharmaceutical Development

(b) (4)

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Reviewer's Comment: Real-time stability data for 60 months for three additional clinical lots manufactured at MedImmune, LLC were also included to support the shelf-life, and are deferred to OBP.

The stability protocol at the 2-8°C long term storage condition includes container closure integrity testing by dye ingress at 12, 24, 36, 48, and 60 months, performed at (b) (4). Sterility is tested at 0 and 60 months at (b) (4). The CCI results met the acceptance criteria for all lots tested.

SATISFACTORY

CGMP Status

The assessment of manufacturing facilities is documented in panorama.

Conclusion

I. The drug product part of the BLA was reviewed from a sterility assurance and product quality microbiology perspective and is recommended for approval. There are two post-marketing commitments (see first page of this review).

II. Product quality aspects other than microbiology should be reviewed by OBP.

III. No inspection follow-up items were identified.

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Virginia Carroll

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Maria Jose Lopez-Barragan

Digitally signed by Maria Jose Lopez-Barragan
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