ADDENDUM TO THE CLINICAL REVIEW OF OBILTOXAXIMAB (ANTHIM®)

Product:	**Obiltoxaximab (ETI-204)**
BLA:	**125509**
Brand name:	**Anthim®**
Applicant:	**Elusys Therapeutics Inc.**
Date of Addendum:	**March 15, 2016**
Clinical Reviewers:	**Elizabeth O'Shaughnessy, MD (efficacy)** **Ramya Gopinath, MD (safety)**
Cross Discipline Team Leader:	**John Alexander, MD, MPH**

Introduction

Anthim® is a chimeric, humanized monoclonal antibody against the protective antigen (PA) of *Bacillus anthracis*. It was developed under the Animal Rule by Elusys Therapeutics Inc. for treatment of inhalational anthrax due *B. anthracis* in combination with antibacterial drugs, and for prophylaxis of inhalational anthrax when alternative therapies are not available or not appropriate; it is to be administered as a single 16 mg/kg intravenous dose. Please see the Clinical Review dated 12/29/15 for a full review of the efficacy of Anthim® in animal models of inhalational anthrax and its safety in healthy human volunteers. Anthim® is recommended for approval for the indications listed above.

This Addendum to the Clinical Review contains:

a) the clinical and analytical inspection summary,
b) corrections to Tables 8.36 and 8.39 in the Clinical Review
c) final label

A) Inspections Summary

A pharmacology review of GLP EIR at [redacted] (b) (4)), the site of many of the animal efficacy studies, was also carried out by the Office of Study Integrity and

Surveillance-Division of New Drug Bioequivalence Evaluation (OSIS-DNDBE). No Form 483 was issued, and OSIS' final classification for this inspection was NAI. A few minor items were identified and discussed with Elusys' management, but since none were expected to impact the quality of the data, the audited studies were deemed acceptable for review by the Agency.

At the request of the review team, clinical inspections for five studies conducted at six clinical sites were conducted by OSIS-DNDBE, and a review of the Establishment Inspection Reports (EIRs) was provided. Following the inspections, 5 sites had a No Action Indicated (NAI) classification, but a Form 483 was issued to Quintiles Phase One Services, Overland Park, KS related to studies AH109 and AH110. Specifically, the inspectors found that some samples of blood from these two studies were not allowed to clot for 30 minutes prior to processing as specified in the protocol, and were centrifuged at 4°C, rather than the 24°C stated in the protocol. Elusys acknowledged the observations and responded with a list of planned corrective actions, which were acceptable to OSIS. The final classification of the inspection at that site was Voluntary Action Indicated (VAI). The clinical OSIS-DNDBE reviewer, Dr. Mohsen Rajabi, recommended that the clinical portion of the audited studies were acceptable for review by the Agency.

As part of FDA's Bioresearch Monitoring Program which monitors nonclinical laboratory studies of products regulated by FDA, an inspection was conducted at (b) (4) Drs. Denise Visco and Abhijit Raha found violations in the bioanalytical report pertaining to the finding of contamination of some assay blanks with varying quantities of ETI-204 > lower limit of quantitation (LLOQ). A Form 483 was issued, and Elusys responded with corrective actions, which the inspectors found to be adequate.

Drs. Kara Scheibner and Mohsen Rajabi from OSIS also audited the analytical portion of 12 nonclinical and clinical studies conducted by (b) (4) A five-item Form 483 was issued for the nonclinical studies and several issues were discussed with management; the final classification for this inspection was VAI. The final classification of the clinical studies was NAI, and the inspectors recommended that the analytical portion of the clinical and nonclinical studies be accepted for review with certain limitations.

Dr. Rashmi Rawat, the Application Technical Lead in The Office of Pharmaceutical Quality in CDER recommended approval of obiltoxaximab (ETI-204; Anthim). The microbiology product quality reviewer Dr. John Metcalfe, identified a drug substance (DS) and drug product (DP) endotoxin testing issue related to the endotoxin recovery assessment in the product formulation. The sponsor was asked to perform a study demonstrating that the DS and DP formulation does not affect the endotoxin recovery in the proposed LAL endotoxin test. Elusys' response was found to be adequate in addressing the issue of endotoxin recovery in the Limulus amebocyte lysate LAL assay. Additionally, some drug substance manufacturing facility

issues were identified in Form FDA 483 during pre-licensing inspection of the Lonza facility; these were also adequately addressed. Some minor product quality issues were identified during the BLA review which will be addressed as post marketing commitments.

B) Corrections to Tables 8.36 and 8.39 in the Clinical Review

1. Table 8.36 (p. 463)

FDA Analysis of Occurrence of TEAE's Correlated with Diphenhydramine Use in the FDA PSP

Number of subjects in FDA PSP N=370	**Obiltoxaximab, N=300**		**Placebo, N=70**	
	DPH+ (n=226) (75.3%)	DPH- (n=~~73~~74) (24.~~3~~7%)	DPH+ (n=48) (68.6%)	DPH- (n=22) (31.4%)
Number of subjects with TEAE's N=165 (44.5%)	**Obiltoxaximab, N=138**		**Placebo, N=27**	
	95 (95/226=42%)	43 (43/7~~3~~4=58.~~9~~1%)	18 (18/48=37.5%)	9 (9/22=40.9%)

The denominator in the obiltoxaximab arm who did not receive diphenhydramine premedication was changed from 73 to 74, based on the Applicant's inclusion of a subject who received Anthim but subsequently had a missing treatment record. The percentage of these subjects out of 300 was thus corrected to 24.7%, rather than 24.3% as in the original clinical review (12/29/15). The percentage of subjects with TEAEs in this arm also accordingly changed to 58.1%, rather than 58.9%.

2. Table 8.39 (p. 465-6)

The denominators have been changed to include all subjects who received diphenhydramine or not in the placebo and obiltoxaximab arms, and the percentages in each cell have accordingly been changed. The corrected table is presented below:

Table 8.39 (corrected): FDA Analysis of Diphenhydramine Premedication Correlated with Occurrence of TEAEs and Their Severity in the FDA PSP

Preferred Term	Severity	Placebo		Obiltoxaximab	
		DPH		DPH	
		No, n=22 N (%)	Yes, n=48 N (%)	No, n=74 N (%)	Yes, n=226 N (%)
General Disorders and Administration Site Conditions					
Application site erythema	MILD	0	0	1 (1.4%)	1 (0.4%)
Chills	MILD	1 (4.5%)	0	0	0
	MODERATE	0	0	1 (1.4%)	1 (0.4%)
Influenza like illness	MILD	0	0	0	1 (0.4%)
Infusion site discolouration	MILD	0	0	0	3 (1.3%)
Infusion site erythema	MILD	1	1 (2.1%)	3 (4.1%)	1 (0.4%)
Infusion site pain	MILD	0	0	2 (2.7%)	5 (2.2%)
Infusion site swelling	MILD	0	0	1 (1.4%)	7 (3.1%)
Pain	MILD	2 (9.1%)	0	1 (1.4%)	2 (0.9%)
Vessel puncture site bruise	MILD	0	1 (2.1%)	1 (1.4%)	7 (3.1%)
Vessel puncture site pain	MILD	0	0	1 (1.4%)	1 (0.4%)
Infections and Infestations					
Upper respiratory tract	MILD	0	1 (2.1%)	2 (2.7%)	9 (4%)
	MODERATE	1 (4.5%)	0	0	0
Urinary tract infection	MILD	1 (4.5%)	1 (2.1%)	0	0
Nervous System Disorders					
Dizziness	MILD	0	0	0	2 (0.9%)
	MODERATE	0	0	0	1 (0.4%)
Headache	MILD	3(13.6%)	1 (2.1%)	12(16.2%)	11 (4.9%)
	MODERATE	0	0	1 (1.4%)	0
Migraine with aura	MODERATE	0	0	1 (1.4%)	0
Somnolence	MILD	0	0	0	17 (7.5%)
Respiratory, Thoracic and Mediastinal Disorders					
Cough	MILD	0	0	6 (8.1%)	3 (1.3%)
Dry throat	MILD	0	0	2 (2.7%)	0
Dysphonia	MILD	0	0	1 (1.4%)	0
Dyspnoea	MODERATE	0	0	1 (1.4%)	0
Nasal congestion	MILD	0	1 (2.1%)	2 (2.7%)	3 (1.3%)
Oropharyngeal pain	MILD	0	0	0	3 (1.3%)
Rhinorrhoea	MILD	0	0	2 (2.7%)	0
Throat	MILD	0	1 (2.1%)	2 (2.7%)	0
Gastrointestinal Disorders					
Abdominal pain	MILD	1 (4.5%)	0	0	1 (0.4%)
Diarrhoea	MILD	1 (4.5%)	1 (2.1%)	0	0
Nausea	MILD	1 (4.5%)	1 (2.1%)	0	5 (2.2%)

Preferred Term	Severity	Placebo		Obiltoxaximab	
		DPH		DPH	
		No, n=22 N (%)	Yes, n=48 N (%)	No, n=74 N (%)	Yes, n=226
	MODERATE	0	0	0	1 (0.4%)
Vomiting	MILD	0	0	0	2 (0.9%)
	MODERATE	0	0	0	1 (0.4%)
Skin and Subcutaneous Tissue					
Dermatitis contact	MILD	0	1 (2.1%)	2 (2.7%)	4 (1.8%)
Papule	MILD	0	0	1 (1.4%)	0
Pruritus	MILD	0	1 (2.1%)	3 (4.1%)	7 (3.1%)
	MODERATE	0	0	1 (1.4%)	1 (0.4%)
	SEVERE	0	0	1 (1.4%)	0
Rash	MILD	0	2 (4.2%)	1 (1.4%)	2 (0.9%)
	MODERATE	0	0	2 (2.7%)	1 (0.4%)
Rash erythematous	MILD	0	0	0	1 (0.4%)
Rash generalised	MILD	0	0	1 (1.4%)	1 (0.4%)
Rash papular	MILD	0	0	1 (1.4%)	0
Skin exfoliation	MILD	0	0	0	1 (0.4%)
Skin irritation	MILD	0	0	0	1 (0.4%)
Urticaria	MILD	0	0	1 (1.4%)	2 (0.9%)
	MODERATE	0	0	1 (1.4%)	3 (1.3%)
	SEVERE	0	0	1 (1.4%)	0

DPH – diphenhydramine group

C) Label for Anthim

The prescribing information originally submitted by Elusys underwent extensive revisions and the final version is reproduced below:

18 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RAMYA GOPINATH
03/18/2016

JOHN J ALEXANDER
03/18/2016