

Clinical Pharmacology Review Amendment

BLA	125553
Submission Date:	May 8, 2014
Brand Name:	Zarxio
Proper Name:	To be determined
Formulation:	Intravenous and Subcutaneous solution
OCP Reviewer:	Sarah J. Schrieber, PharmD
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Sponsor:	Sandoz
Submission Type; Code:	BLA 351(k)

This review serves as an amendment to the original clinical pharmacology review for BLA 125553 submitted to DARRTS on January 27, 2015.

For studies EP06-109, EP06-101, EP06-103, and EP06-105, the statistical analyses results using the 90% CI, 80-125% limits for the single dose absolute neutrophil counts (ANC) and multiple dose CD34⁺ cell counts AUEC and Emax parameters are presented in the table below. The 90% CI for AUEC and ANC_{max} for ANC after single dose were within the limits of 80-125%. The 90% CI for AUEC and CD34_{max} for CD34⁺ cell counts after multiple doses (7 daily doses) were within the limits of 80-125%.

Study	Dose (mcg/kg)	<u>ANC</u> Geometric Mean Ratio (90% CI)	<u>CD34⁺</u> Geometric Mean Ratio (90% CI)
US-licensed Neupogen study			
EP06-109	10	AUEC _{0-120h} : 104 (101, 106) ANC _{max} : 101 (97, 104)	Multiple dose CD34 ⁺ not evaluated.
EU-approved Neupogen studies			
EP06-105	1	AUEC _{last} : 102 (98, 107) ANC _{max} : 100 (95, 106)	Multiple dose CD34 ⁺ not evaluated.
EP06-103	2.5	AUEC _{0-24h} : 105 (100, 109) ANC _{max} : 104 (98, 110)	AUEC _{0-216h} : 104 (98, 112) CD34 _{max} : 106 (98, 114)
	5	AUEC _{0-24h} : 101 (96, 105) ANC _{max} : 100 (95, 104)	AUEC _{0-216h} : 99 (89, 110) CD34 _{max} : 99 (86, 114)
EP06-101	10	Single dose ANC not reported	AUEC _{0-216h} : 110 (102, 118) CD34 _{max} : 113 (103, 123)

Ratio (%): EP2006/US- or EU-Neupogen

The data presented in this amendment do not alter the recommendation of the original clinical pharmacology review of BLA 125553, which was submitted to DARRTS on January 27, 2015.

Signatures:

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Attachment 1. The sponsor's November 5, 2014 response to FDA's October 31, 2014 information request.

1 Request for information 1

For studies EP06-109, EP06-101, EP06-103, and EP06-105, complete statistical analyses using the 90% CI, 80-125% limits for the single dose ANC and multiple dose CD34⁺ PD AUEC and E_{max} parameters.

Sandoz response

Table 1-1 provides the results for the following pharmacodynamic (PD) parameters: AUEC_{0-last} and E_{max}, for the absolute neutrophil count (ANC) and for the CD34⁺ cell profiles. The ANC parameters are reported following a single dose administration of investigational medicinal product (IMP), and the CD34⁺ cell parameters are reported following a multiple dose administration of IMP, except for study EP06-109 which was a single-dose study only. A point estimate and the corresponding 90% CI for the difference between EP2006 and Neupogen were calculated and were anti-logged to obtain the point estimate and the 90% CI for the ratio of the geometric means on the untransformed scale. The PD results for the comparisons show that the point estimate and all 90% CI are within the standard equivalence criteria of 80% to 125%.

Table 1-1 Summary of pharmacodynamic results

Study	Dose ^a [mcg/kg]	PD Parameter	Geometric Ratio ^b	Lower 90% CI	Upper 90% CI
EP06-101	10	Single Dose: AUEC - ANC	99.65	92.96	106.82
	10	Single Dose: E _{max} - ANC	102.26	95.67	109.30
	10	Multiple Dose: AUEC - CD34 ⁺	109.77	102.05	118.07
	10	Multiple Dose: E _{max} - CD34 ⁺	112.54	103.33	122.58
EP06-103	2.5	Single Dose: AUEC - ANC	104.47	99.85	109.32
	5	Single Dose: AUEC - ANC	100.68	96.18	105.40
	2.5	Single Dose: E _{max} - ANC	103.70	98.08	109.64
	5	Single Dose: E _{max} - ANC	99.83	95.47	104.39
	2.5	Multiple Dose: AUEC - CD34 ⁺	104.49	97.82	111.62
	5	Multiple Dose: AUEC - CD34 ⁺	98.98	88.75	110.39
	2.5	Multiple Dose: E _{max} - CD34 ⁺	105.71	98.19	113.81
	5	Multiple Dose: E _{max} - CD34 ⁺	99.24	86.32	114.10
EP06-105	1	Single Dose: AUEC - ANC	102.29	98.02	106.75
	1	Single Dose: E _{max} - ANC	100.38	95.30	105.72
EP06-109	10	Single Dose: AUEC - ANC	103.54	101.45	105.67
	10	Single Dose: E _{max} - ANC	100.71	97.45	104.08
	10	Single Dose: AUEC - CD34 ⁺	102.56	95.48	110.16
	10	Single Dose: E _{max} - CD34 ⁺	104.65	93.72	116.86

^a Study EP06-103 was the only study including more than 1 dose group.

^b Geometric ratio is the ratio of means for EP2006/Neupogen.

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/s/

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