CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

Biometrics Division: VI

NDA NO.:	207920
DATE RECEIVED BY THE CENTER:	March 26, 2015
DRUG NAME:	Esomeprazole
DOSAGE FORM:	(b) (4)
INDICATION:	Treatment of frequent heartburn
SPONSOR:	Pfizer
REVIEW FINISHED:	July 31, 2015
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1 EXECUTIVE SUMMARY

This review provides statistical evaluation on the bioequivalence between Nexium banded OTC capsule and Nexium (b) (4) tablet under both fasted and fed conditions. From the results of our independent analyses as shown in Table A, we conclude the followings.

- For the comparison between Nexium (b) (4) tablet and Nexium banded OTC capsule under the fasted condition:
    a. Statistical analysis of AUC_{inf} supports a demonstration of bioequivalence because the 90% confidence interval of the mean difference is (0.891,1.011) which is completely covered by the acceptance criteria of (0.80, 1.25);
    b. Statistical analysis of C_{max} supports a demonstration of bioequivalence because the 90% upper confidence limit -0.048 is less than the acceptance limit of 0 using the reference-scaled average bioequivalence test (RSAB);
- For the comparison between Nexium (b) (4) tablet and Nexium banded OTC capsule under the fed condition:
    a. Statistical analysis of AUC_{inf} supports a demonstration of bioequivalence because the 90% upper confidence limit of the mean difference is -0.056 which is less than the acceptance limit of 0 using RSAB;
    b. C_{max} does not establish bioequivalence because the point estimate of the Test/Reference geometric mean ratio is 1.27, which is outside (0.80, 1.25).
- Regarding the food effect, our analysis results are consistent with the sponsor's results. That is, for AUC_{inf} and C_{max}, their mean values under the fed condition are much smaller than their means under the fasted condition for both Nexium (b) (4) tablet and Nexium banded OTC capsule. Please refer to Table 2 for detailed results.

Table A: Summary of Bioequivalence Test from FDA CMC Stats Reviewer's Independent Analysis using All Available Data. (CI = Confidence Interval; CB = Confidence Bound)

Tablet vs Capsule	Parameter	Ratio(Test/ Reference)	90% CI or 95% CB	Acceptance Criteria	Method	Support Bioequivalence?
Fasted	AUC_{inf}	0.949	(0.891,1.011)	(0.80, 1.25)	Unscaled	Yes
	C_{max}	1.022	-0.048	< 0	Scaled	Yes
Fed	AUC_{inf}	0.983	-0.056	< 0	Scaled	Yes
	C_{max}	**1.270**	-0.197	< 0	Scaled	No

Please refer to Section 4 for the sponsor's analysis. Section 5 provides our detailed analysis of the PK data and our comments regarding the sponsor's study design and analysis.

2 INTRODUCTION

On March 26, 2015, FDA office of New Drug Products (ONDP) requested the division of biometrics VI, Office of Biostatistics consult on the analysis of the sponsor's submitted clinical data with SAS. The specific request is as follows:

1. Is the statistical analysis plan for Protocol B5141002 adequate to meet the primary and secondary objective?
2. Is it appropriate to conduct analyses on the fasted and fed data separately?

All statistical analysis by sponsor was performed using SAS, but the sponsor did not provide complete SAS code. In addition, in sponsor's data set, the sequence number is not correctly coded. These issues were conveyed to the sponsor in an Information Request (IR) dated June 18, 2015.

The EDR location of the data set for PK parameters is \\cdsesub1\evsprod\NDA207920\0006\m5\datasets\b5141002\analysis\adam\datasets\fda-adpp.xpt.

The EDR location of the SAS code for bioequivalence testing is \\cdsesub1\evsprod\NDA207920\0006\m5\datasets\b5141002\analysis\adam\programs\program.txt.

3 OVERVIEW OF PROTOCOL B5141002

3.1 Objectives of the study

The primary study objective is to access the bioequivalence between Nexium banded OTC capsule and Nexium (b) (4) tablet under both fasted and fed conditions. The secondary study objective is to conduct food-effect bioavailability for either Nexium banded OTC capsule or (b) (4) tablet.

3.2 Sample size determination

The sample size of 42 subjects was estimated to ensure at least 80% power, but in order to account for drop outs, approximately 54 subjects were to be enrolled.

Reviewer's comments: The sponsor's data set contains a total of 60 subjects (10 subjects randomly assigned to each of six sequences). However, in the sponsor's sample size determination, approximately 54 subjects were to be enrolled.

3.3 Study design

54 healthy subjects were enrolled in the randomized six-period, partial replicate crossover study, and 42 subjects completed this study. The subjects were randomly assigned to one of following six sequences:

1. B-A-C-D-A-C
2. A-D-B-C-C-A
3. D-C-A-A-B-C
4. C-A-D-C-A-B
5. A-C-C-B-D-A
6. C-B-A-A-C-D

where A is the treatment of Nexium banded OTC capsule in the fasted condition, B is the treatment of Nexium (b) (4) tablet in the fasted condition, C is the treatment of Nexium banded OTC capsule in the fed condition, and D is the treatment of Nexium (b) (4) tablet in the fed condition.

3.4 Pharmacokinetic Parameters

PK parameters for primary analyses are the area under the drug concentration-time curve from time zero to infinity (AUC_{inf}), and the maximum observed drug concentration (C_{max}).

4 SPONSOR'S ANALYSES

Due to potential high variability of the pharmacokinetics of esomeprazole, the sponsor conducted bioequivalence using the reference-scaled bioequivalence (RSAB) approach as described in the FDA February 2011 Draft Guidance on Progesterone. For AUC_{inf} and C_{max}, the within-subject standard deviations for the reference formulations (A and C) denoted by s_{wr} were calculated.

- If $s_{wr} \geq 0.294$, RSAB approach was used. Test and reference formulations are considered as bioequivalent if the 95% upper confidence bound for $(\mu_T - \mu_R)^2 - \theta s_{wr}^2$ is no greater than 0, and the point estimate of the Test/Reference geometric mean ratio is within (0.80, 1.25). Here, μ_T and μ_R are the population average response of log-

transformed measure for the test and the reference formulations, respectively, and $\theta \equiv \left(\frac{\ln 1.25}{0.25}\right)^2$.

- If $s_{wr} < 0.294$, the unscaled average bioequivalence approach was used. If 90% confidence interval of $\mu_T - \mu_R$ is within (0.80, 1.25), test and reference formulations are considered as bioequivalent.

Table 1 provides the sponsor's results of their statistical bioequivalence tests.

Table 1: Sponsor's summary of the statistical bioequivalence tests

Comparison	Parameter	s_{wr}	Ratio (Test/Reference)	90% CI	95% Upper Confidence Bound	Method
B vs A (fasted)	AUC_{inf}	0.202	0.948	(0.890,1.010)	-----	Unscaled
	C_{max}	0.304	1.009	-----	-0.050	Scaled
D vs C (fed)	AUC_{inf}	0.351	0.994	-----	-0.061	Scaled
	C_{max}	0.763	**1.341**	-----	-0.156	Scaled

Again, A is the treatment of Nexium banded OTC capsule in the fasted condition, B is the treatment of Nexium (b) (4) tablet in the fasted condition, C is the treatment of Nexium banded OTC capsule in the fed condition, and D is the treatment of Nexium (b) (4) tablet in the fed condition.

Sponsor's analyses demonstrate that the Nexium (b) (4) tablet is bioequivalent to the Nexium banded OTC capsule in terms of AUC_{inf} and C_{max} under fasted conditions. Under fed conditions, sponsor's analyses support bioequivalence of the two formulations in terms of AUC_{inf}. However, for C_{max}, the result shows that two formulations are not bioequivalent because the point estimates of the Test/Reference geometric mean ratio is outside (0.80, 1.25).

Sponsor's analysis for the secondary objective of food effect is assessed by computing the ratio of the geometric mean between the fed and the fasted conditions for each formulation. Their results in Table 2 suggest that co-administration with food affect the relative bioavailability of both the Nexium banded OTC capsule and Nexium (b) (4) tablet formulations.

Table 2: Sponsor's summary of the statistical comparisons for food effect

Comparison	Parameter	Ratio(Test/Reference)
fed vs fasted (Nexium OTC capsule)	AUC_{inf}	0.539
	C_{max}	0.255
fed vs fasted (Nexium (b) (4) tablet)	AUC_{inf}	0.563
	C_{max}	0.317

5 FDA REVIEWER'S ANALYSES

FDA CMC Stats reviewer evaluated the sponsor's analysis and conducted independent analyses to assess bioequivalence and food effect. The overall results from the reviewer's analyses are consistent with the sponsor's results.

5.1 Review of the Sponsor's Study Design

In response to the consulting request by FDA office of New Drug Products (ONDP), this review includes an evaluation of the sponsor's statistical analysis plan for Protocol B5141002. In general, the sponsor's crossover design is appropriate because this design allows unbiased estimate of formulation effects under both fasted and fed conditions.

As described in Section III, the sponsor proposed a six-period and six-sequence crossover design. With such a design, the response can be expressed by the following linear model.

$$Y_{ijk} = \mu + S_{ik} + P_j + F_{(j,k)} + C_{(j-1,k)} + e_{ijk}$$

where Y_{ijk} be the response observed on the i^{th} subject in period j of sequence group k. n_k is the number of subjects in k_{th} sequence, and

1) μ is the overall mean.
2) S_{ik} is the random effect of the i^{th} subject in the k^{th} sequence, where $k = 1,2,3,4,5,6$.
3) P_j is the fixed effect of the j^{th} period, where j = 1,2,3,4,5,6.
4) $F_{(j,k)}$ is the direct fixed effect of the formulation in the k^{th} sequence at the j^{th} period. For example, $F_{(1,1)} = F_B,\ F_{(2,1)} = F_A,\ F_{(3,1)} = F_C$, ...
5) $C_{(j-1,k)}$ is the fixed carryover effect of the formulation in the k^{th} sequence carried over from $(j-1)^{th}$ period. For example, $C_{(1,1)} = C_B,\ C_{(4,2)} = C_C$, ...

It is assumed that $S_{ik} \sim N(0, \sigma_s^2)$ and $e_{ijk} \sim N(0, \sigma_e^2)$. Under the fasted condition, the direct formulation effect is denoted by $F = F_B - F_A$. Without the carry-over effect, the unbiased estimator of the direct formulation effect is

$$\hat{F} = \frac{1}{6}\Big[\bar{y}_{.11} + \bar{y}_{.32} + \bar{y}_{.53} + \bar{y}_{.64} + \bar{y}_{.45} + \bar{y}_{.26} - \frac{1}{2}(\bar{y}_{.21} + \bar{y}_{.51} + \bar{y}_{.12} + \bar{y}_{.62} + \bar{y}_{.33} + \bar{y}_{.43} + \bar{y}_{.24} + \bar{y}_{.54} + \bar{y}_{.15} + \bar{y}_{.65} + \bar{y}_{.36} + \bar{y}_{.46})\Big]$$

i.e., $E(\hat{F}) = F_B - F_A$. Similarly, under the fed condition, $E(\hat{F}) = F_D - F_C$. Please note, if carryover effects are present in this crossover study, the estimate of the direct formulation effect is biased.

To estimate the within-subject variability of the reference treatment, each subject receives the reference product twice in each sequence. Denote the within-subject variance of the reference treatment (Treatment A) as σ_{WA}^2, and the unbiased estimator of σ_{WA}^2 is as follows:

$$\hat{\sigma}_{WA}^2 = \frac{1}{2(n_1+n_2+\cdots+n_6-6)} \sum_{k=1}^{6}\sum_{i=1}^{n_k}(D_{ik} - \bar{D}_{.k})^2$$

where

1) $D_{i1} = Y_{i21} - Y_{i51}$,
2) $D_{i2} = Y_{i12} - Y_{i62}$,
3) $D_{i3} = Y_{i33} - Y_{i43}$,
4) $D_{i4} = Y_{i24} - Y_{i54}$,
5) $D_{i5} = Y_{i15} - Y_{i65}$,
6) $D_{i6} = Y_{i36} - Y_{i46}$,
7) $\bar{D}_{.k} = \frac{1}{n_k}\sum_{i=1}^{n_k} D_{ik}$.

5.2 Bioequivalence Analysis for Primary Study Objective

In sponsor's analysis, only subjects with complete data for all sequences are included in the analysis. Table 3 lists those subjects excluded from the sponsor's analysis. To investigate possible effects of incomplete responses, we conducted additional statistical analyses using all the available data. Our analyses show the PK responses pass the statistical bioequivalence test. The results are summarized in Table 4.

Please note, treatment effect can be estimated from the difference between a subject's response value on test treatments and the average of the subject's two response values on reference treatments.

It is seen from Table 4 that the results from additional analyses for the possible effects of missing data do not affect the sponsor's statistical support for the equivalence of Nexium (b) (4) tablet and Nexium banded OTC capsule in terms of AUC_{inf} and C_{max} under fasted conditions. Under fed condition, two formulations are not bioequivalent in terms of C_{max} because the point estimates of the Test/Reference geometric mean ratio is still outside (0.80, 1.25).

Table 3: Subjects with missing responses in one of two response values of reference treatments (A or C)

	AUC_{inf}	C_{max}
B vs A	B5141002-1001-10011065 B5141002-1001-10011194 B5141002-1001-10011093	B5141002-1001-10011065 B5141002-1001-10011093
D vs C	B5141002-1001-10011201 B5141002-1001-10011168 B5141002-1001-10011080 B5141002-1001-10011118 B5141002-1001-10011105 B5141002-1001-10011017 B5141002-1001-10011178 B5141002-1001-10011143 B5141002-1001-10011084 B5141002-1001-10011205 B5141002-1001-10011113	B5141002-1001-10011084 B5141002-1001-10011205

Table 4: Summary of Bioequivalence Test from FDA CMC Reviewer's Independent Analysis using All Available Data

Comparison	Parameter	Ratio(Test/Reference)	90% CI	95% Upper Confidence Bound	Method
B vs A	AUC_{inf}	0.949	(0.891,1.011)	-----	Unscaled
	C_{max}	1.022	-----	-0.048	Scaled
D vs C	AUC_{inf}	0.983	-----	-0.056	Scaled
	C_{max}	1.270	-----	-0.197	Scaled

We also noticed that the within-subject standard deviations of A in the case of C_{max} and C in the case of AUC_{inf} are close to the cutoff value of 0.294 for applying RSAB. To confirm the sponsor's primary results, we conducted additional analyses based on the unscaled average bioequivalence approach. From Table 5, additional analyses results also support a demonstration of bioequivalence between Nexium (b) (4) tablet and Nexium banded OTC capsule in terms of C_{max} under the fasted condition and a demonstration of bioequivalence between Nexium (b) (4) tablet and Nexium banded OTC capsule in terms of AUC_{inf} under the fed condition.

Table 5: Unscaled average bioequivalence for B vs A(C_{max}) and D vs C(AUC_{inf})

Comparison	Parameter	Ratio(Test/Reference)	90% CI	Method
B vs A	C_{max}	1.03272	(0.92779, 1.14951)	Unscaled
D vs C	AUC_{inf}	0.99118	(0.86031, 1.14195)	Unscaled

5.3 Secondary study objective: Food effects

According to the sponsor's results for food effects in Table 2, the bioavailability of both Nexium (b) (4) tablet and Nexium banded OTC capsule was affected by co-administration with food. We focuses on the case of Nexium banded OTC capsule administered with food or without food (C vs A) in terms of AUC_{inf}. In the sponsor's analysis, the geometric mean ratio can be estimated based on the average of all treatments of Nexium banded OTC capsule. However, because subjects receive two treatments of Nexium banded OTC capsule in each sequence, we considered additional analyses based on replicated treatments of Nexium banded OTC capsule.

Table 6 summarizes our analysis results, which are consistent with the sponsor's results. That is, for AUC_{inf} and C_{max}, their mean values under the fed condition are much smaller than their means under the fasted condition for both Nexium (b) (4) tablet and Nexium banded OTC capsule.

Table 6: Summary of Test/Reference GMR based on replicated treatments of Nexium banded OTC capsule by this reviewer

Comparison	Parameter	Test/Reference GMR
C vs A	AUC_{inf}	0.29306

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/s/

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