CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

US Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

New Drug Application

Biometrics Division: VI

NDA NO.:	209604
DATE RECEIVED BY OB:	10/13/2016
DRUG NAME:	Gemcitabine Injection
INDICATION:	
SPONSOR:	Accord Healthcare Inc
REVIEW FINISHED:	06/08/2017
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1 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

1.1 Purpose of this review

On April 17, 2017, Office of New Drug (OND) requests CMC statistics team in the Office of Biostatistics (OB) to evaluate adequacy of the sponsor's sample size in pharmacokinetic Bioequivalence study 311-13.

1.2 Sponsor's study design

This was a multicentre, randomized, open label, two-period, two-treatment, two-way crossover, single dose bioequivalence study comparing Gemcitabine Injection 100 mg/mL (10 mL) (Manufactured by: Intas Pharmaceuticals Ltd.) to the reference listed drug Gemzar

1g/vial (Gemcitabine for Injection 1g/vial, Lilly USA, LLC, Indianapolis, IN 46285, USA) in patients with Pancreatic or Ovarian Cancer.

The study was planned to be conducted on 44 patients with pancreatic or ovarian cancer. However, due to the issue of the date of expiry of the reference medicinal product, and the subsequent advice received from the USFDA on the matter, the sponsor carried out equivalence evaluation using 30 patients.

1.3 Reduced sample size issue

Office of Clinical Pharmacology expressed the concern on the power reduction due to sample size reduced from 44 to 30 and further concern on validity of BE Study 311-13. In order to under the power and consumer's risk for a bioequivalence study, we first have to set up an appropriate hypothesis tests. Let μ_T be the population mean of AUC of Gemcitabine for patients treated with

Gemcitabine Injection 100 mg/mL (10 mL) (Manufactured by: Intas Pharmaceuticals Ltd.). Let μ_R be the population mean of AUC of Gemcitabine for patients treated with the reference listed drug Gemzar1g/vial. The sponsor proposed the following hypothesis for the bioequivalence study comparing ratio of two means.

$$H_0 : \mu_T / \mu_R \le \theta_1 \text{ or } \mu_T / \mu_R \ge \theta_2$$
$$H_a : \theta_1 < \mu_T / \mu_R < \theta_2 \quad . \qquad (1)$$

Here θ_1 and θ_2 are pre-specified constants, also called equivalence margins, and $\theta_1 < \theta_2$. Here $\theta_1 = 0.8$ and $\theta_2 = 1.25$.

The null hypothesis, H_0, states that μ_T and μ_R are not equivalent. The alternative hypothesis, H_a, states that they are equivalent. The alternative hypothesis representing equivalence, H_a, is the intersection of the two one-sided parameter regions, $\{ \theta_1 < \mu_T - \mu_R \}$ and $\{ \mu_T - \mu_R < \theta_2 \}$. We conclude the test product is bioequivalent to the reference product if H_0 is rejected.

We can calculate sample sizes provided that the ratio of means and variability are known from previous experience and the type I and type II error rates are specified assuming that log(AUC) is a normal variable.

For equivalence hypothesis tests in (1), the power to reject the H_0 (not equivalent) under H_a (equivalent) will decrease due to smaller number of subjects. The producer's risk (type II error rate) is 1-power. So the producer's risk will increase due to smaller number of subjects. On other hand, the type I error rate is the probability of rejecting H_0 under H_0 (not equivalent). Under the intersection-union hypothesis testing, the type I error rate is controlled at the significance level, α. The consumer's risk is type I error rate. Hence the consumer's risk of having not-equivalent

product is fixed at α. In other words, smaller number of subjects will not increase the consumer's risk.

1.4 Conclusion and recommendation

For equivalence hypothesis tests in (1), the power to reject the H_0 (not equivalent) under H_a (equivalent) will decrease due to smaller number of subjects. The producer's risk (type II error rate) is 1-power. So the producer's risk will increase due to smaller number of subjects. On other hand, the type I error rate is the probability of rejecting H_0 under H_0 (not equivalent). Under the intersection-union hypothesis testing, the type I error rate is controlled at the significance level, α. The consumer's risk is type I error rate. Hence the consumer's risk of having not-equivalent product is fixed at α. In other words, smaller number of subjects will not increase the consumer's risk.

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/s/

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06/08/2017

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