Statistical Review Addendum #1

Medical Division: Oncology Drug Products (HFD-150)
Biometrics Division: Division of Biometrics I (HFD-710)

NDA NUMBER: NDA 21-677 / N000

DRUG NAME: Alimta (Pemetrexed, LY231514)

INDICATION: Locally advanced or metastatic non-small cell lung cancer

SPONSOR: Eli Lilly and Company

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This addendum is to address some of the concerns raised by the sponsor at FDA-Industry statistical meeting on 07/06/2004.

1. After further review of the NDA submission and the IND reviews, this statistical reviewer concludes that the superiority hypothesis and the fixed margin (1.11) non-inferiority hypothesis were defined in the original protocol. However, the 50% retention hypothesis was a post-hoc addition to the study objectives. This post hoc addition may necessitate multiplicity adjustment for testing the non-inferiority objective multiple times. It is unclear how to properly adjust for such a post-hoc addition.

2. This statistical reviewer clarifies that the sponsor used 0.555 as the estimate of the control (docetaxel) effect and the log-estimate of the control (docetaxel) versus BSC was 0.59 (as reported in statistical section of the briefing document dated 29 June 2004) in their 50% retention non-inferiority hypothesis testing (please also refer to the updated Tables below).

3. Based on our internal discussion, we have determined that the lower limit of the 95% confidence interval is probably too conservative for estimating the control treatment (docetaxel) effect; thus, the resulting statistical test used in the statistical review dated 6/29/04 is also probably too conservative. However, it is well-known and needs to be emphasized that the validity of the sponsor's testing 50% retention using the method of Rothmann *et al* (2003) heavily relies on the assumption that docetaxel's effect has not changed from that one small historical trial (TAX317) to the current non-inferiority trial (JMEI). Given the most ideal situation that this assumption holds and there is no other problem with the current non-inferiority trial, the data appeared to barely suggest that alimta may preserve 50% of the docetaxel effect (p-value $\approx$ 0.05) using the point estimate of docetaxel effect. However, if the effect of docetaxel under the current non-inferiority trial setting is smaller than that in that TAX317 trial, then the method of Rothmann *et al* is no longer applicable and 50% retention cannot be concluded. Because of these concerns, for an alternative non-inferiority analysis, this reviewer applied the CBER/FDA method, that uses the lower confidence limit (LCL) of at least 90% confidence interval for the hazard ratio of placebo versus the control treatment from the historical trials, to define a fixed non-inferiority margin. The fixed margin is defined as $1+(1-\delta_0)\bullet$(90% LCL of HR(placebo/control)-1). If the non-inferiority margin lies in the 95% confidence interval of hazard ratio of new treatment (alimta) versus active control (docetaxel) in the current trial, the fraction retention cannot be concluded. Because of these changes, Table 2 and Table 14 in the statistical review dated 29 June 2004 should be replaced by the following table.

Updated Table 2 & Table 14. Exploratory Analyses[a] of Primary Endpoint: Overall Survival – ITT Population

	Sponsor Analysis		*FDA Analysis*	
	Alimta (N = 283)	Docetaxel (N = 288)	Alimta (N = 283)	Docetaxel (N = 288)
Events	206	203	206	203
50% retention non-inferiority test based on point estimate of control effect (HR(docetaxel/BSC) = 0.56)				
Estimate of control effect	0.555[d]		0.56[e]	
NI p-value for testing 50% retention[b]	0.047		0.0525	
95% Feiller CI of estimated percent of efficacy retained by alimta[c]	(52%, 157%)		(48.56%, 158.97%)	
50% non-inferiority test based on the method of 90% LCL of control effect (HR(docetaxel/BSC) = 0.88)				
NI margin for testing 50% retention[f]	Not reported		1.1073	

[a] Fraction retention non-inferiority analyses which were not pre-specified in the protocol.
[b] P-value is based on the test results for the two treatment groups by Rothmann's method for a 50% retention.
[c] 95% CI is based on Feiller approach where δ is regarded as the proportion retained by alimta of an average control effect.
[d] The sponsor's estimate based on middle point of 95% CI of log-HR (BSC vs. docetaxel) from historical trial for ITT population.
[e] Point estimate of HR in the historical trial for ITT population, published in docetaxel (taxotere) label.
[f] If non-inferiority margin lies in the 95% CI of HR(alimta/docetaxel), the 50% retention cannot be concluded. This margin is generated based on the CBER/FDA method using the lower limit of the 90% confidence interval for the hazard ratio of placebo versus the docetaxtel from the TAX317 trial.

Table 20 in the statistical review dated 29 June 2004 should be replaced by the following table.

Updated Table 20. Exploratory Analyses[a] of Primary Endpoint: Overall Survival – RT Population

	Sponsor Analysis		*FDA Analysis*	
	Alimta (N = 265)	Docetaxel (N = 276)	Alimta (N = 265)	Docetaxel (N = 276)
Events	192	198	192	198
50% retention non-inferiority test based on point estimate of control effect (HR(docetaxel/BSC) = 0.56)				
Estimate of control effect	0.555[d]		0.56[e]	
NI p-value for testing 50% retention[b]	0.036		0.0399	
95% Feiller CI of estimated percent of efficacy retained by alimta[c]	(58%, 168%)		(56.12%, 171.48%)	
50% non-inferiority test based on the method of 90% LCL of control effect (HR(docetaxel/BSC) = 0.88)				
NI margin for testing 50% retention[f]	Not reported		1.1073	

[a] Fraction retention non-inferiority analyses which were not pre-specified in the protocol.
[b] P-value is based on the test results for the two treatment groups by Rothmann's method for a 50% retention.
[c] 95% conditional CI is based on the fixed control effect as the estimate by the historical data.
[d] The sponsor's estimate based on middle point of 95% CI of log-HR (BSC vs. docetaxel) from historical trial for ITT population. Point estimate of control effect for RT population by the historical trial was not available.
[e] Point estimate of HR in the historical trial for ITT population, published in docetaxel (taxotere) label. Point estimate of control effect for RT population by the historical trial was not available.
[f] If non-inferiority margin lies in the 95% CI of HR(alimta/docetaxel), the 50% retention cannot be concluded. This margin is generated based on the CBER/FDA method using the lower limit of the 90% confidence interval for the hazard ratio of placebo versus the docetaxtel from the TAX317 trial.

Since in the current trial HR(alimta/docetaxel)=0.992, 95% CI of HR(alimta/docetaxel)=(0.817, 1.204), and 1.1073 lies within this CI, the non-inferiority

hypothesis in terms of retention of 50% of the docetaxel effect cannot be concluded, i.e., we cannot conclude that alimta is non-inferior to docetaxel (retaining at least 50% of the docetaxel effect), based on the CBER/FDA method.

4. In Appendix 3 of the statistical review dated 29 June 2004, the expressions for δ and Z^* should be replaced by the following.

$$\delta = \frac{\log(HR(P'/C')) - \log(HR(T/C))}{\log(HR(P'/C'))},$$

$$Z^* = \frac{\log(\hat{HR}(T/C)) - (1-\delta_0)\log(\hat{HR}(P'/C'))}{\sqrt{s.e.^2[\log(\hat{HR}(T/C))] + (1-\delta_0)^2 s.e.^2[\log(\hat{HR}(P'/C'))]}},$$

where δ_0 is the desired level of the fraction retention.

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This review consists of 4 pages of text
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