Addendum

NDA/Serial Number:	20-592
Drug Name:	Olanzapine
Indication(s):	Schizophrenia for Adolescents
Applicant:	Eli Lilly and Company
Date(s):	December 29, 2006
Review Priority:	Priority
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1. BACKGROUND

Reference is made to Statistical Review of NDA 20592 submitted to DFS on April 6, 2007.

In this NDA submission, the sponsor conducted 2 pivotal short-term olanzapine studies HGIN and HGIU on adolescent patients, one (HGIU) for the treatment of Mania in Bipolar I Disorder and the other (HGIN) is for the treatment of schizophrenia. These studies were reviewed in the Statistical Review. The primary efficacy endpoint for Study HGIN was the change from baseline to Endpoint of BRPS-C total score and the primary statistical analysis was the ANCOVA procedure using LOCF for missing data. The sponsor provided the efficacy analysis results for LOCF, along with that of OC and MMRM.

In the statistical review that I submitted, with the data sets provided by the sponsor, the corresponding analysis results were also given. They are given in Table 1.

Table 1.1: Treatment Effects on the Change from Baseline of Primary Efficacy Measures at the Endpoint in Studies HGIN --- ITT Population

	Placebo	Olanzapine
Study HGIN	(N=35)	(N=72)
N (Analysis population)	35	72
N (BPRS-C Total Score)	35	72
Baseline Mean	50.1	50.3
Median change from baseline	-9.3	-19.4
ANCOVA Analysis (LOCF)		
LS Mean change from baseline (SE) [a]	-9.1 (2.73)	-19.3 (1.91)
Difference between LS Means and C.I.[a]	-10.1 (-16.7, -3.5)	
P-value [a]	0.003	
MMRM Analysis		
LS Mean change from baseline (SE) [b]	-23.5 (3.06)	-24.7 (1.70)
Difference between LS Means and C.I.[b]	-1.25 (-8.11, 5.61)	
P-value [b]	0.72	
OC Analysis		
N (BPRS-C Total Score)	15	50
LS Mean change from baseline (SE) [c]	-24.1 (3.35)	-24.4 (1.82)
Difference between LS Means and C.I.[c]	-0.25 (-7.9, 7.4)	
P-value [b]	0.95	

a: Test for no difference between treatments at the endpoint from ANCOVA model with treatment and country as factors and baseline efficacy measure as covariate.
b: Test for no difference between treatments at the endpoint from MMRM model with treatment, country, visit and the interaction of treatment and visit as factors and baseline efficacy measure as covariate.
c: Test for no difference between treatments at the endpoint from OC model with treatment and country as factors and baseline efficacy measure as covariate.
Note: Negative change in score indicates improvement.

Source: Table 3.7 in Statistical Review

Due to the contradictory results between LOCF, MMRM and OC, I suggested that this study did not support the claim of the effectiveness of Olanzapine on the adolescents with schizophrenia.

2. CORRECTIONS

The MMRM analysis was conducted based on the default variance-covariance structure of Variance Components in SAS software package, which requires the independence between the repeated observations for any subject. In fact, the choice of the variance-covariance structure affects the estimate of treatment effect as well as its significance levels dramatically. Usually, the Unstructured variance-covariance matrix is used for MMRM analysis. In order to see which variance-covariance structure gives a better fit for the data, I applied the MMRM procedure using several different variance-covariance structures and gave the corresponding results along with the AIC values. The AIC values are generally used as a goodness-of-fit criterion of the model. The smaller the AIC value is, the better the model seems to fit the data. These results are depicted in Table 2.1

Table 2.1 MMRM Analysis Results Using Different Variance-Covariance Structure in Study HGIN

Variance-covariance Structure	Placebo	Olanzapine	AIC
Variance Components			
LS Mean change from baseline (SE)	-24.1 (3.13)	-24.5 (1.73)	
Difference between LS Means and C.I.	-0.43 (-6.6,7.5)		
P-value	0.90		4691
Unstructured			
LS Mean change from baseline (SE)	-12.6 (2.99)	-21.5 (1.97)	
Difference between LS Means and C.I.	-8.9 (-16.0, -1.9)		
P-value	0.015		4055.2
Compound Symmetry			
LS Mean change from baseline (SE)	-17.8 (2.61)	-22.9 (1.60)	
Difference between LS Means and C.I.	-5.1 (-11.1, 0.9)		
P-value	0.10		4353.0
Toeplitz			
LS Mean change from baseline (SE)	-14.3 (2.68)	-21.9 (1.65)	
Difference between LS Means and C.I.	-7.67 (-13.8, -1.5)		
P-value	0.015		4129.0
Toeplitz with Two Bands			
LS Mean change from baseline (SE)	-21.7 (2.70)	-24.4 (1.53)	
Difference between LS Means and C.I.	-2.68 (-8.8, 3.4)		
P-value	0.39		4356.0
First Order Auto-regression			
LS Mean change from baseline (SE)	-15.4 (2.71)	-22.3 (1.64)	
Difference between LS Means and C.I.	-7.0 (-13.8, -0.8)		
P-value	0.029		4129.0

Note: Test for no difference between treatments at the endpoint from MMRM model with treatment, visit and the interaction of treatment and visit as factors and baseline efficacy measure as covariate.

Source: Reviewer

In this analysis, country is not used as a factor in the statistical models since it was not prespecified in the protocol. These results indicate that the Unstructured variance-covariance structure in the statistical model seems to give a better fitting. The significance results derived seem to support the claim that Olanzapine improves placebo in treating the adolescents with schizophrenia. Another important observation is that treatment effect estimates and the corresponding p-values are dramatically different for different choices of variance-covariance structure of the repeated observations. This suggests that the efficacy results derived from this model may not be as stable as we expect. Extra care should be exercised in doing such analyses.

Efficacy analysis for each country. The subgroup analysis with respect to country is considered as exploratory. In Table 2.2, the nominal p-values for the treatment effects at Endpoint using MMRM procedure are provided for each country using the Unstructured variance-covariance structure model.

Table 2.2 Treatment Effect by Country by MMRM Analysis

Country	Placebo	Olanzapine
Russia		
N (Number of patients)	16	34
LS Mean change from baseline (SE)	-5.3 (4.46)	-19.0 (2.73)
Difference between LS Means and C.I.	-13.7 (-23.9,3.3)	
P-value	0.012	
US		
N (Number of patients)	19	35
LS Mean change from baseline (SE)	-18.7 (4.13)	-23.5 (2.89)
Difference between LS Means and C.I.	-4.8 (-14.7, -5.1)	
P-value	0.35	

Recourse: Reviewer

Based on the above results, treatment effects seem to be more evident in Russia than in US. Given similar number of subjects in these two countries, the estimated treatment effect in Russia is 13.7 US while that of US is only 4.8. The data suggests that the there was a very small placebo effect in Russia while there was a certain placebo effect in US. Careful investigations might be needed to find why this is the case.

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