

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
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Statistical Review Addendum

Clinical Studies

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1 Introduction

The purpose of this document is to clarify reasons for differences between the applicant's imputation based results and those of the Agency in discussing Study GLUSCC09-01 at the Oncologic Drug Advisory Committee (ODAC) meeting held on 24 May 2017.

Full details of study GLUSCC09-01 may be found in the ODAC the clinical review of the NDA.

2 Overview of Study GLUSCC09-01

Study GLUSCC09-01 (09-01) was the primary source of clinical evidence used to support NDA 208587 for L-glutamine, a treatment purported to improve sickle cell (b) (4)

The study was a randomized, placebo controlled, double-blind, multi center, trial comparing the efficacy L-glutamine to that of placebo in patients with sickle cell anemia or sickle beta thalassemia. A total of 230 patients were randomized in a 2:1 ratio to L-glutamine (n = 152) or placebo (n = 78). The primary endpoint was patients' number of sickle cell crises at week 48. The primary analysis was based on the Cochran Mantel Haenszel test using modified ridit scores.

The results of study GLUSCC09-01, as presented by the sponsor showed the median count of sickle cell crises in the placebo arm to be 4 and that of the L-glutamine arm to be 3 for the study period of 48 weeks. Patients' crises counts ranged from zero to 15 crises. It is noted that 3 and 4 are the mean number of crises for study completers in the L-glutamine and control arms respectively.

The study results could be biased for the following reasons:

- High early dropout rate and differential dropout rates between treatment arms. Figure 2 describes the dropout patterns by treatment arm. (Note: this observation is in conflict with MCAR and/or MAR assumptions)
- Imputation of incomplete sickle cell crisis event counts appeared to be inadequate. (Imputed data had an observably different distribution shape compared to recorded data)
- Interpretation of efficacy results based on data impacted by dropouts (application of CMH test did not take into account differential study times between patients)

3 Discussion of Imputation

Likely causes for disparity between results based on FDA's imputation of data for the L-glutamine 09-01 study and those of the sponsor are the differences in the amount of information imputed, the amount of information used in creating the imputation models and random variation in the imputation process.

1. The sponsor used only data from study completers (rows 1 and 2 of table 3) as the basis of imputation ($\frac{156}{230} = 67.8\%$ of patients). The Agency used all information available (rows 1, 2 and 3 of table 3) as the basis for imputation ($\frac{206}{230} = 89.6\%$ of patients).



Figure 1: Histograms of data as collected and the sponsor’s imputation

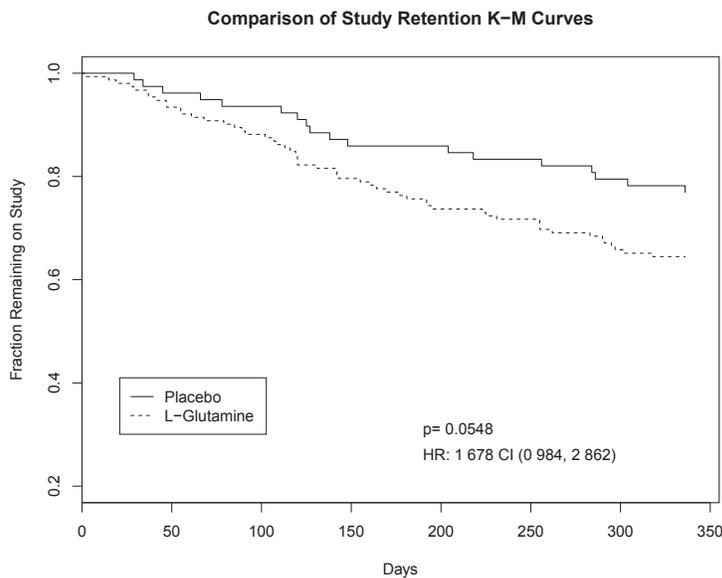


Figure 2: The K-M curves indicate a strong trend toward treatment dependent dropouts.

- Agency imputations were done in ways that tended to minimize the amount of information imputed. The sponsor’s method imputed the data to completely “fill out” the study. This is explained in more detail below.

Consider for illustrative purposes that the intended duration of the study was 336 days (7 weeks). We can think of the study as containing $230 \times 7 \times 48 = 77280$ patient-days. The Agency’s analysis imputed data only for patient with records of the type in the fourth row of figure 3. Using the reported days on study, we can estimate that amount of data to be 2507 patient-days or about 3.5% of the possible patient-days. The sponsor imputed data to fill all patient-days in the study. In other words, the sponsor did imputation to fill in the patient-days left empty in both rows three and four of figure 3, corresponding to 13447 of the 77280 total patient-days (patient-days) or 17.4%. The sponsor imputed approximately 5 times as much data as

Subset	L-glutamine N = 152	Placebo N = 78
48 week completers; at least one SCC	82 (53.9%)	55 (70.5%)
48 week completers; no recorded SCC	15 (9.9%)	4 (5.1%)
Dropped out; at least one SCC	35 (23.0%)	15 (19.2%)
Dropped out; no recorded SCC	20 (13.2%)	4 (5.1%)
Total	152	78

SOURCE: FDA Reviewer analysis

Figure 3: Patients' data were subsetted into different missingness classifications.

the Agency did. This is probably a major factor in the differences in modeling results on the various data sets used. Please note that several methods were used to calculate days on study for different purposes in the submission and these analyses are rough estimates. With that said, we expect the results to be reasonably good estimates.

3.1 Sponsor's Imputation Methods

3.1.1 Pooled Single Imputation

1. From patients with "complete data", determine pooled rate of crises per 100 days (0.986)
2. For each patient with incomplete data, find the residual number of days (*resid.days* = 336-days on study)
3. Estimate residual crises/(100 days) for each patient from *resid.days* and the pooled crisis rate.
4. For each patient, combine their recorded crises and their estimated residual crises
 - "For instance, a patient with 1 observed crisis during 100 days of exposure would have 236 days of residual time. Then, for this patient, there would be $236 \times 0.986/100 = 2.33$ expected residual crises. We add this expected number of residual crises to the observed number of crises to obtain 3.33, and then round to the nearest integer to obtain a final imputed value of 3 crises." [Source: Applicant's submitted analysis document]

With this imputation method, "using the stratified CMH test with modified ridit scores, the p-value is 0.048".[Source: Applicant's submitted analysis document]

3.1.2 Treatment Specific Event Rate Imputation

A process similar to the pooled event rate imputation described above was used, but stratified by treatment.

- "Note that the event rate for the treatment group was 0.917 per 100 patient days and 1.098 per 100 patient days for the placebo group." [Source: Applicant's submitted analysis document]

With this imputation method, "the resulting p-value is 0.021". [Source: Applicant's submitted analysis document]

3.2 Agency Analyses Presented at ODAC

The Agency presented three imputation results at ODAC. The analysis in the first row of figure 4 is an example of case deletion. The 24 cases in question are dropped from the data set before the analysis. Case deletion is discouraged, especially in situations where missingness is disproportionate across study arms. The analysis in the second row of figure 4 replaces missing data for the 24 patients in row three of figure 3 with zeros. Assuming that all 24 subjects had no crises for the study period may be overly optimistic, but one might try to justify the assumption by claiming that the patients reported no crises. Both of these methods are likely to result in biased results. Imputing with zeros is subjective and dropping cases will be impacted by the differential patient (informative) drop-out. The last Agency analysis is a fully conditional multiple imputation (FCS) in which the multiple imputation approach is adjusted for treatment group, study site, baseline hydroxyurea use, age, baseline crisis count, and time spent on study.

FDA strategy for handling incomplete crisis counts	Rate of crises/48 weeks L-glutamine vs Placebo	Rate Ratio [95% CI] Based on Negative Binomial model
FDA sensitivity analysis population N=206	3.3 v 4.1	0.80 [0.64, 1.01]
ITT population, assuming incomplete crisis counts for 24 patients are "0", N=230	3.3 v 4.2	0.77 [0.61, 0.99]
Multiple Imputation (FCS)* for 24 patients with incomplete crisis counts, N=230	3.9 v 4.3	0.91 [0.73, 1.12]

SOURCE: FDA Reviewer analysis
 All analyses adjusted for region and baseline hydroxyurea use; using time on study as offset
 *FCS = fully conditional specification;
 The multiple imputation approach adjusts for treatment group study site, baseline hydroxyurea use, age, baseline crisis count, and time spent on study to impute crisis counts for 24 patients.

Figure 4: Analysis results vary depending on the imputation approach used.

The Agency's imputation method imputed those missing count data for the 24 patients in row three of figure 3 by drawing a random sample from the posterior conditional distribution of the imputation model. The Agency's imputation method did not fill in the partially incomplete data rows, as those were adequately addressed by the analysis method. The analysis done using data imputed under this scheme, as well as the first two sets described, was a negative binomial regression adjusted for region and baseline hydroxyurea use and using time on study as offset.

4 Summary

The differences between imputation based analyses results presented by the Applicant and the Agency at the 24 May 2017 ODAC meeting are likely due to differences in the amount of data imputed and the amount of information used as a basis for imputation between the Applicant's and the Agency's approaches.

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/s/

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07/05/2017

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07/06/2017