

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-667

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 21-667
Drug Name: Glutamine
Indication(s): Treatment of short bowel syndrome
Applicant: Nutritional Restart Pharmaceuticals
Date(s): Received 08/08/03; user fee (10 months) 06/11/04
Review Priority: Standard review
Biometrics Division: Division of Biometrics II
Statistical Reviewer: Dionne L. Price, Ph.D.
Concurring Reviewer: J. Todd Sahlroot, Ph.D.
Medical Division: Division of Gastrointestinal and Coagulation Drug Products
Clinical Team: Gary DellaZanna, M.D. (medical reviewer)
Project Manager: Tanya Clayton

Keywords: NDA review, clinical studies

Nutritional Restart Pharmaceuticals (NRP) submitted the current application (NDA 21-667) on 08 August 2003 to evaluate the safety and efficacy of oral glutamine as a cotherapy with recombinant human growth hormone (rhGH) for the treatment of short bowel syndrome. The submission consisted of a randomized, double-blind, controlled study.

Serono submitted NDA 21-597 for Zorbtive (rhGH) on 31 October 2002. Evidence of effectiveness for both applications was derived from the same study; therefore, the completed statistical review of NDA 21-597 will serve as a primary reference for the current NDA. A pre-NDA meeting occurred between the Division of Gastrointestinal and Coagulation Drug Products and NRP on 12 November 2002. Discussion focused on the appropriate analyses that would be required to demonstrate efficacy of oral glutamine. Specifically, the agency requested an additional analysis which will be the focal point of my current review.

Forty-one eligible patients with short bowel syndrome were randomized to a regime of Zorbtive alone, glutamine alone, or a cotherapy of Zorbtive and glutamine. The primary measure of efficacy was the change in total volume of intravenous parental nutrition (IPN) from Week 2 to Week 6. The primary efficacy endpoint was analyzed via an analysis of covariance (ANCOVA) model with baseline measurement as a covariate. Originally, primary analyses focused on assessing treatment group differences among Zorbtive (singly or as a cotherapy with glutamine) and glutamine alone. The agency requested the effect of glutamine be evaluated via the comparison between Zorbtive alone and the cotherapy of glutamine and Zorbtive.

Internally, substantial thought was given to the potential multiplicity issue created by the additional comparison not previously considered in the original protocol. The "case" was presented by Dr. J. Todd Sahlroot at the Office of Biostatistics Statistical Rounds on 05 March 2004 for further input and discussion. Attendees included, but were not limited to, Drs. Robert O'Neill, Charles Anello, and S. Edward Nevius. The consensus reached was that the additional pairwise comparison did not need to be adjusted in order to control the type I error. Numerous arguments were formulated to support the decision. In the evaluation of glutamine, there were only two pairwise treatment comparisons from which one could infer the efficacy of glutamine. These comparisons were between the cotherapy and Zorbtive and between glutamine and Zorbtive. The latter comparison was previously adjusted for via the two-sided test in the original analysis. Thus for the current regulatory decision, the former comparison is of primary interest and can be tested without adjustment and no inflation of the type I error.

There existed a decrease in IPN utilization over the treatment duration of 3.8L, 5.9L, and 7.7 L among the glutamine, Zorbtive, and cotherapy groups, respectively. The unadjusted analysis yielded a significant reduction in total IPN volume when comparing Zorbtive alone and the cotherapy of Zorbtive and glutamine. The p-value for this comparison was 0.023. The result suggested a glutamine effect. The evidence indicated statistical support favoring glutamine as an add-on therapy to Zorbtive for the treatment of short bowel syndrome.

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/s/

Dionne Price
4/21/04 02:43:14 PM
BIOMETRICS

Todd Sahlroot
4/26/04 12:54:17 PM
BIOMETRICS

S. Edward Nevius
5/6/04 09:32:36 AM
BIOMETRICS
Concur with review.

NDA 21-667

Statistical Review (Carcinogenicity)

This section is not applicable.

/S/

Tanya Clayton
Regulatory Project Manager

NDA 21-667

Statistical Review (Stability)

The review of stability data is included in the DMF review of the drug product.

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6/9/04

Tanya Clayton
Regulatory Project Manager