CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020772

MEDICAL REVIEW(S)

Pages: 76 through 91

2) Overall Computation of AEs

Events	
Total No. of Patients Experiencing AEs	26/34 = 76.5%
Total No. of AEs in the Safety Population	95
Attribution to Test Medication	
- Not Related (Due to Concurrent Illness)	49/95 = 52%
- Possibly Related	21/95 = 22%
- Not Indicated (in CRF)	25/95 = 26%
Resolution of AE	
Not Indicated (in CRF)	54/95 = 57%
Resolution NI + Relationship to Test Medication NI	20/95 = 21%

3) Nature of AEs Possibly Related to Test Medication

- 11 of 26 patients experienced one or more AEs that were considered by the Investigator to be possibly related to test medication (sucrase). Included among these events were abdominal pain, N&V, constipation, diarrhea, dehydration, headache, insomnia and nervousness.
- Additional events assessed as possibly related to test medication were facial edema, shock and asthma. Although these are not g.i. symptoms, they may occur in CSID patients.
- Included among the AEs considered not related to test medication and due to concurrent illness were: vomit, flu syndrome, diaper rash, decrease in weight, diarrhea, pharyngitis, ear infection, fever, rhinitis, increase of cough, increase frequency of urinary output, viral infection and abdominal pain.

4) Serious AEs/Withdrawals Due to AEs

- There were no deaths reported in this trial.
- 4/34 patients (#6, #23, #24 and #27) experienced serious AEs.[41] Details of these 4 SAEs are given in Table 24.

[41] The events in these 4 patients were classified as serious because they resulted in hospitalization or required an emergency room visit, even if the patient was not admitted to the hospital.

TABLE 24
Study S-2 (OMC-SUC-2)

Serious AEs

Patient ID Demograph.	Previous History (In addition to CSID)	Serious Event, Evaluation	W/D Due to Event	Relationship to Sucrase/Comments
#6	Had asthma and had been treated with steroids (not confirmed), at 5 mg b.i.d., tapered to 5 mg/day prior to first dose of YS.	First treated with single sucrase dose on 6/16/93; 7 days later, at the second BHT, the patient started **wheezing** 90 min. after receiving the YS+milk treatment. He was taken to the emergency room, admitted into ICU and discharged from the hospital the following day. Severity of the event was not recorded. The YS was D/C and the pt. was W/D from the trial for this event.	**YES**	In the investigator's opinion, the wheezing was **POSSIBLY** related to test medication. The pt. was subsequently **rechallenged** by skin testing with the sucrase solution. The allergist reported that the skin test was positive. This case of wheezing appears to be **ALMOST CERTAINLY** related to test medication and should be included in the labeling.
#23	Had pre-existing colostomy and stoma	First treated with YS on 3/21/94/; 17 days later, the pt. underwent elective surgery for closure of the colostomy, performed between the BHT and dose-response phases of the trial. Severity of the event was not recorded.	**NO**	Events not related to YS. The pt. recovered from surgery, completed the trial, and then continued on open-label YS with meals and snacks.
#24	Not relevant	First treated with sucrase on 9/7/94; 11 days later she started on Septra® for otitis media on the L ear and 2 days after that she vomited immediately after her Septra® dose following dinner; on the same day she was treated with YS (1:1000 dilution). On the subsequent day she experienced "projectile vomiting + shock". The patient was admitted to the ER for these symptoms the same day, vomited mucus, recovered fully in a short period and was not admitted to the hospital. The severity of the event was not recorded. Tx with YS was interrupted for these events on 9/22/94 but restored ca. 20 days later.	**NO**	In the opinion of the investigator, the vomiting that followed Septra® Tx was not related to YS. But the investigator considered the other symptoms to be **POSSIBLY** related to YS.

TABLE 24 (Con't)

#27	Not relevant	First treated with YS on 11/15/94; 4½ weeks later, the pt. became dehydrated. He was admitted to the hospital for re-hydration. On 12/02/95 he experienced N&V and diarrhea; 1½ mo. later, the pt. underwent same-day surgery for removal of a benign mass in his R breast. After discharge, the pt. became dehydrated and was re-admitted to the hospital for re-hydration, with an "apparently satisfactory" outcome. YS Tx was restarted on 3/16/96 to begin the dose-response phase of the trial. He completed the controlled trial and was continued on L-T open-label YS with meals and snacks. The severity of each event was not recorded.	NO	In the opinion of the investigator the first episode of dehydration was considered to be possibly related to YS. All other signs and symptoms, including the second episode of dehydration (following surgery) were assessed as unrelated to YS.
Reviewer's Table				

E. Results: Other

- As shown below, both sucrose and carbohydrate consumption (g/Kg/day) in the diet during the dose-response phase, were numerically higher for full-strength enzyme than for any other dosage treatment group.

Study S-2 (OMC-SUC-2)

Dose-Response Phase: Sucrose and Carbohydrate Consumption

Sucrose Treatment/ Dilution	Sucrose Composition (g/Kg/day)	Carbohydrate Consumption (g/Kg/day)
Full-Strength Enzyme	2.42 ± 0.34	5.82 ± 0.51
1:10	1.83 ± 0.27	5.20 ± 0.44
1:100	1.76 ± 0.23	5.20 ± 0.43
1:1000	1.85 ± 0.25	5.32 ± 0.50
Depicted are the mean ± S.E.M.		

- None of the pairwise comparisons between any treatment groups yielded significant p-values for sucrose or carbohydrate consumption.

12. Sponsor's Conclusions

"The results of this trial indicate convincingly that liquid yeast sucrase (sacrosidase) is an effective, well-tolerated, and well-accepted treatment for the major gastrointestinal symptoms of CSID. Furthermore, this effect is directly related to the dose of yeast sucrase, as increasing concentrations of the enzyme are associated with a decrease in total stools and fewer gastrointestinal symptoms. Treatment with yeast sucrase was very safe, with only one patient discontinuing due to a possible adverse event. Thus, yeast sucrase appears to be efficacious and safe in treating patients with congenital sucrase-isomaltase deficiency."

13. Reviewer's Additional Comments

Data from Study S-2 (OMC-SUC-2) were submitted by the sponsor as one of the two adequate and well-controlled main trials in support of the approval of SUCRAID™ (sacrosidase) for the treatment of congenital sucrase isomaltase deficiency.

Study S-2 was well-designed. Although information - sometimes critical - is missing for some patients it is important to consider the study population (infants, children and adolescent) in whom it is not easy to experiment. Taking these constraints into consideration, the trial was apparently well-executed. The Principal Investigator was Dr. William R. Treem, from the Hartford Hospital, Hartford, CT is a world renown specialist who later moved to the Duke University Medical Center in Durham, NC. A total of 26 Co-Investigators, from across the U.S., participated in this clinical trial. Study S-2 was a randomized, multi-site, double-blind, crossover trial which consisted of two phases: the breath hydrogen test (BHT) and the dose-response test. The BHT consisted of three single-dose treatments: placebo, yeast sucrase and yeast sucrase + milk, given in random order. The dose-response phase consisted of four multi-dose treatment groups: full-strength yeast sucrase (YS) **[A]** and the following three enzyme dilutions: 1:10 **[B]**, 1:100 **[C]** and 1:1000 **]D]**. These different strengths of the enzyme were administered in a randomized crossover design.

The study population was adequate for the proposed study and indication being sought. However, because of its importance in determining what information may be incorporated in the labeling, it is important to clarify matters related to the **study population**. When considering its clinical presentation, CSID is a very variable disease. In essence, CSID represents symptoms due to deficiency of not only sucrase (the main enzyme missing) but also (although not always and certainly not to the same degree and extent) deficiency of isomaltase. Although the patients in Study S-2 (as well as those in S-1) are being challenged with sucrose (to evaluate sucrase effects) they are not being challenged with starch (to evaluate isomaltase effects). But, as discussed in detail in sections I. (Background) and II. (Rationale) of this review most patients with sucrase deficiency also have a relative or absolute isomaltase deficiency. The g.i. symptoms elicited by sucrose challenge are always of greater frequency and severity than those elicited by starch challenge. In summary, CSID study population consists of patients with more deficiencies in enzymes than are being assessed in the present Study. But these important clinical considerations can be properly addressed in the labeling (see Recommendations for Regulatory Action).

In all of the children randomized into Study S-2 (as well as in S-1) the diagnosis of sucrase deficiency was **confirmed** either by disaccharide enzyme activity (DEA) in duodenal biopsy samples collected upon upper g.i. endoscopy or by breath hydrogen test (BHT) or by the combination of DEA + BHT. All patients (except #33) had normal levels of lactase. Therefore the study population met the protocol-stipulated disaccharidase-level criteria [Sucrase activity of <10% of controls with normal lactase levels and normal or decreased maltase activity]. The patients in Study S-2 did not have **suspected** sucrase deficiency (an additional inaccuracy incorporated in the sponsor's proposed labeling). The BHT with both sucrose and lactose challenges further confirmed that while negative with respect to lactase deficiency the patients were positive with respect to sucrase deficiency. Of a total of 40 patients screened, 32 entered and completed the BH phase of the trial while 28 entered the dose-response phase of the trial. Of these, 26 completed the dose-response phase, having received all 4 treatments.

The methodological approach used in Study S-2 can be briefly summarized as follows. Patients in confirmed CSID were evaluated for trial eligibility prior to commencement of the first phase (breath hydrogen phase tests - BH phase). During this BH phase the patients underwent three BHTs. These tests required ingesting sucrose (2 g/Kg) followed by either placebo, yeast-sucrase, or milk/yeast sucrase. During each 3-h BT, and for up to 24 h thereafter, gastrointestinal symptoms were recorded on a symptom dairy. Each BT was separated by one week during which the patient was expected to maintain a sucrose-free low starch diet. The second was a dose-response phase, during which patients were instructed to maintain a normal sucrose-containing diet while receiving each of four concentrations of yeast sucrase. These consisted of full-strength [A]; 1:10 dilution [B]; 1:100 dilution [C]; and 1:1000 dilution [D] in random order, for a period of 10 days each. Stool frequency and consistency measures, as well as gastrointestinal symptoms and dietary data, were recorded on a daily basis and AEs were collected throughout the trial.

In Study S-2, the criteria for evaluation of efficacy were adequate. As in Study S-1, these consisted of both primary and secondary efficacy parameters. The primary efficacy variables included total stools and the total symptoms score, collected during the dose-response phase. The secondary efficacy variables included peak, peak minus baseline and total BH output (area under the BH curve), in addition to individual and total symptoms scores (from the BH phase); as well as total watery, soft, formed and hard stools, average daily stools, average and total individual symptom scores and average total symptoms scores. Also included was a comparison of asymptomatics, defined post-hoc (from the dose-response phase).

The results of Study S-2 demonstrated that liquid yeast sucrase (sacrosidase) is an effective treatment for the major g.i. symptoms of CSID. With regard to the primary efficacy parameters, assessed during the dose-response phase of the trial, a dose-response relationship was shown for both parameters of evaluation. On the one hand, higher concentration of YS (A and B) were associated with significantly fewer total stools. On the other, higher concentrations of YS were also associated with a higher proportion of patients having a total symptom score of 7 or less.

In Study S-2, the efficacy demonstrated on the basis of analysis of the primary efficacy parameter was supported by the analyses of secondary efficacy parameters. It was shown that higher concentrations of YS were associated with a greater number of hard and formed stools as well as a fewer number of watery and soft stools. In addition, BH output decreased markedly when patients received YS, either alone or with milk, as compared to when they received no sucrase (placebo) in conjunction with the sucrose loading dose. The results of this study were very similar to those seen in Study S-1. In Study S-2, although the use of milk together with the YS enhanced the suppression of hydrogen excretion as compared to the YS sucrase given alone, this quantitative difference did not reach statistical significance [the display in graph form suggested, but did not prove, an additive effect of milk over YS sucrase alone].

The AE safety information suggests that - as in Study S-1 - liquid YS was well tolerated by the CSID patients in Study 2. Most of the reported AEs could be attributed to concurrent illnesses common in childhood and were not considered by the investigator (or the Medical Reviewer) to be related to YS. Many of the AEs that were considered by the investigator to be possibly related to test medication (YS) are also symptoms of sucrose (disaccharide) malabsorption. Therefore, these events were not unusual of the patient population assessed in Study S-2 (the same can be said about Study S-1) and most of these patients completed not only the BHT phase but also the dose-response phase of the trial. Nonetheless, four of the patients in this trial experienced AEs categorized as serious. In three of these (#23: colostomy closure; #24: projectile vomiting, gray skin, white lips; #27: dehydration and surgery for benign mass in R breast) the events did not appear to be related to YS. In addition, these three patients completed the trial and then continued to open-label YS replacement therapy. The fourth patient (#6, a 4 y old M) had pre-existing asthma and was being treated with concomitant steroids for this condition. He experienced wheezing 90 min. after receiving the YS+milk treatment. The patient was taken to the emergency room, admitted into the ICU and was discharged from the hospital the following day. The patient was subsequently **rechallenged** by skin testing with sucrase solution. The allergist reported that the skin test was positive. The YS was discontinued. But a direct consequence of the wheezing was the withdrawal of this patient from the trial. The Medical Officer concludes that this case of wheezing appears to be **almost certainly** related to YS and should be included in the labeling (see Recommendations for Regulatory Action).

In summary, in Study S-2, the protocol-stipulated specific aims were met. Yeast-derived liquid sucrase was shown to be efficacious in treating patients with CSID that were challenged with a normal sucrose-containing diet. Specifically, **YS** (1) completely prevented or blunted the expected rise in BH excretion when the CSID patient ingested a large sucrose load and (2) prevented the expected gastrointestinal symptoms of cramps, excessive gas, and diarrhea when the patient with CSID ingested a diet containing normal amounts of the disaccharide (sucrose).

IX. SUMMARY REVIEW OF ADDITIONAL STUDIES

Under this heading, the MO makes brief references to results of Studies S-3, S-4, S-5 and S-6, with emphasis on clinical information that may be useful to include in the labeling. Aspects of the studies, not germaine to the approval process, will not be commented upon. A brief description of studies S-3, S-4, S-5 and S-6 was given in Section V. Clinical Trials in NDA 20-772.

A. Study S-3 (OMC-SUC-3)

This was an open-label, long-term sucrase trial also carried out by Dr. William R. Treem, the principal investigators of studies S-1 and S-2, the two pivotal trials in NDA 20-772. The sponsor did not conduct controlled long-term trials. Dr. Treem cited a number of reasons to do S-3. These include to

continue to provide additional enzyme to those patients that in Studies S-1 and S-2 had experienced a salutary response. The parents were interested in continuing administering a regular, normal diet to their very young children and it did not seem ethical to revert to a restricted diet. Another reason was that having been accustomed to the need of restricting sucrose in their diet, these patients were initially timid about their new situation. It took them a while to overcome this timidity. So, Dr. Treem wanted to gather data from observations where the enzyme was given under normal conditions, which are more meaningful to the consumer. In addition (another reason to do Study S-3), he attempted to answer an important question often asked: after 12 months of this treatment, how is the life of these patients different, quantitatively? How had this change in their kind of diet affected their caloric intake? Growth? etc.?

Thus, S-3 included 34 CSID patients from Studies S-1 and S-2 who took sucrase for periods of from 2 up to 54 months. The dosage given was 1 or 2 ml of the full-strength enzyme with meals or snacks. According to the Clinical Report, these patients experienced few or no g.i. symptoms while consuming a normal diet. No evidence was reported of a loss of effectiveness upon L-T therapy that would be indicative of the development of pharmacologic tolerance (anyhow, this would, theoretically, be very unlikely).

B. Study S-4 (OMC-SUC-4)

This study's main objective was to provide an answer to the question (asked at the pre-NDA meeting) of whether sucrase therapy was better than the existing therapy (dietary restriction).

Thus, S-4 consisted of a survey of physicians and parents and relatives who participated in clinical trials of 32 CSID patients. An standardized questionnaire was completed post-hoc. The essential question was: what was your life like when you were on this restricted diet? Compared to now? The evaluation included QOL appraisal (emotional health) together with a symptomatic assessment. It was concluded from this study that compliance and effectiveness of sucrase enzyme therapy was superior to a sucrose-free/low starch diet.

Although Study S-4 does provide some information suggesting that dietary liberalization is better than dietary restriction, the design of this study (crossover, no placebo comparator) was not ideal to provide a conclusive answer to the proposed question. The ideal design should be two groups of patients, where the efficacy and safety of the two treatments are tested side by side, with a negative comparator (placebo) under randomized, controlled conditions [although admittedly, the use of a placebo group may be unethical].

C. Study S-5 (OMC-SUC-5)

This study, published by Harms et al. [NEJM 316:306-309 (1987)] used a lyophilized fresh baker's yeast preparation and is not really germaine to SUCRAID™'s approval process.

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D. Study S-6 (OMC-SUC-6)

This pilot study tested the preventive effects of liquid yeast-derived sucrase in the sucrose intolerance induced by SO-48334, an anti-HIV drug. This drug induces a secondary sucrase deficiency (and the expected symptoms of such a condition) in AIDS patients. But, once again, although these provided safety information, these data are not germaine to the approval process because secondary sucrase deficiency is a different indication than that being requested in NDA 20,772 (CSID).

X. RECOMMENDATIONS FOR REGULATORY ACTION

A review of the evidence presented in NDA 20,772 demonstrates that SUCRAID™ (sacrosidase) oral solution is an effective replacement therapy in patients with confirmed CSID. Therefore, approval of SUCRAID™ for the prevention of symptoms associated with sucrose malabsorption is recommended. This recommendation is primarily based on the results of Study S-2 (OMC-SUC-2), a double-blind, randomized, placebo-controlled, dose-response trial. This study showed effectiveness in a dose-response fashion, using primary efficacy parameters. Higher concentrations of the enzyme (especially the full strength, nondiluted preparation) were associated with significantly a) fewer total stools and b) higher proportion of patients having a total symptoms score of 7 or less. In this study, analyses of the secondary efficacy parameters supported the conclusions drawn from the primary efficacy parameters. Again, higher concentrations of YS (especially the full strength, nondiluted preparation) were associated with a significantly greater number of hard and formed stools as well as a significant fewer number of watery and soft stools. All of these represented very meaningful therapeutic gains, which were highly significant in statistical comparisons. In addition, BH output decreased markedly when patients received YS, either alone or with milk, as compared to when patients received no sucrase (placebo) in conjunction with the sucrose loading dose (challenge). Although the use of milk together with the YS enhanced the suppression of hydrogen excretion as compared to the YS sucrase given alone, this quantitative difference did not reach statistical significance.

Also recommended are the below listed changes to the labeling proposed by the sponsor. In its present form, the proposed labeling contains a number of inaccurate or promotional (not based on the scientific facts) statements.

6 Page(s) Redacted

DRAFT LABELING

14, 1997

/S/

Hugo E. Gallo-Torres, M.D., Ph.D.

cc:
NDA 20-772
HFD-180
HFD-180/LTalarico
HFD-180/HGallo-Torres
HFD-181/CSO
HFD-180/JChoudary
HFD-180/EDuffy
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