CENTER FOR DRUG EVALUATION AND RESEARCH

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MEDICAL REVIEW(S)

Pages: 51 through 75

3. Randomization/Treatment Regimen/Compliance

As S-1, Study S-2 was divided into two phases: breath hydrogen and dose-response.

- The sponsor notes that with respect to the breath hydrogen phase, the treatment sequences in the database are based on documentation provided by the PI and did not always agree with the order of the dates of the BHTs recorded on the CRFs.[34]

The protocol stipulated that the BHT treatment sequence was to be randomized, but this procedure was not followed.

With respect to the dose-response phase, patients were randomly assigned to one of 24 possible treatment sequences. In five cases, however, the actual treatment sequence differed from the randomized sequence; and in one case, the actual treatment sequence could not be verified.[35]

- Following one week of a sucrose-free/starch restricted diet (baseline) and a 12-h fasting interval, each patient underwent three BHTs, each separated by one week of sucrose-free/starch restricted diet. The procedure for the three tests was, in summary, as follows:

  1) The patient was given 2 g/Kg Bwt of oral sucrose up to a maximum of 50 g as a 20% solution in water, followed immediately by yeast sucrase.

     If the sucrose load was less than 30 g, 1.0 mL YS was administered mixed with 29 mL of sterile water.

     If the sucrose load was between 30 and 50 g, 2.0 mL of YS was administered mixed with 28 mL of sterile water.

     The sponsor notes that these doses were selected based on the results of preliminary studies.

  2) The patient was given 2 g/Kg Bwt of oral sucrose followed immediately by 30 mL sterile water with no added yeast sucrase (placebo).

  3) The patient was given 4 mL/Kg Bwt of whole cow's milk (up to 8 ounces), followed by 2 g/Kg Bwt of oral sucrose and yeast sucrase.

- At the conclusion of the BHTs, each patient underwent another week of a sucrose-free/starch restricted diet. With this, the dose-response phase began. Each patient was then told to comply with a diet containing ca.

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[34] The actual order in which the BHTs were performed were found in sponsor's Appendix 18.3.

[35] A list of the randomized (planned) and actual treatment sequences was submitted in sponsor's Appendix 18.3.

2 g/Kg body weight of sucrose per day (a normal amount of dietary sucrose) for four 10-day periods. During this time, each patient administered four different yeast sucrase preparations (one preparation per period) marked in vials **A, B, C** and **D**. These were assigned in random sequence.

- Each vial contained one of the following concentrations of YS: full-strength enzyme **[A]**, 1:10 dilution **[B]**, 1:100 dilution **[C]** or 1:1000 dilution **[D]**.

- The solutions were distributed with calibrated droppers and the patients were asked to administer either 1.0 or 2.0 mL of the enzyme with each meal, in accordance with the previous dose administered during BH testing.

- The patient (or parent) was asked to draw up the yeast sucrase liquid into the dropper and mix it with 2 to 4 ounces of water, drinking this solution 5 min. after beginning each meal.

- The sponsor notes that to verify compliance with the normal sucrose-containing diet, sucrose intake during each 10-day period was assessed with two measures:

  1) a 48-h diet diary; and

  2) repeat 24-h diet recalls collected at two random timepoints by telephone.

4. Trial Design/Blinding

Study S-2 was a randomized, multi-site, double-blind, controlled, two-phase trial: breath hydrogen (Phase 1) and dose-response (Phase 2).

Phase 1

This was the breath hydrogen phase, where patients were asked to abstain from sucrose in their diet for at least 3 days and to fast totally for 12 h prior to each BHT. During this phase, patients received each of three treatments in random order: yeast sucrase (YS), placebo (water without YS), and YS+milk. The first two treatments were given immediately after ingesting 2 g/Kg Bwt of sucrose. The third treatment consisted of milk which was given immediately prior to the 2 g/Kg of sucrose followed by YS.

The THREE treatments were separated by one week of a sucrose-free diet.

Phase 2

Following the completion of Phase 1, patients entered into Phase 2, the dose-response phase. Patients were randomly assigned to one of 24 possible treatment sequences. Each treatment sequence consisted of four treatments

assigned in random order: A = full-strength enzyme, B = 1:10 dilution, C = 1:100 dilution, and D = 1:1000 dilution. Each patient administered each of the four treatments for a period of 10 days, while on a normal sucrose diet. As in Study S-1, **there was no wash-out period between treatments**.

> **[NOTE:** It is important to realize that the four random assignments in Study S-2, identified as A, B, C and D, do not correspond to the same random assignments (they represent different strengths of the enzyme) in Study S-1.

Blinding

Study S-2, just as S-1, qualifies as double-blind (although not in the usual sense) because both the patient and the patient's parent/guardian were blinded to the treatments given during the BH phase and the dose-response phase of the trial.

- The investigator, however, was unblinded with respect to the treatment sequences. The four different yeast sucrase preparations were marked in vials A, B, C and D, and recorded on the CRF by the patient as he/she administered each treatment.

- It is worth noting, however, that the two primary efficacy parameters and all secondary efficacy measures except the BH values were recorded on stooling and symptom diaries completed by the patients or the patients' parent or guardian. All of these participants were blinded with respect to the treatment conditions.

5. <u>Test Medications/Concomitant Medications</u>

- The source of the liquid sucrase product used in Study S-2 was the same as that used in Study S-1.

- With respect to concomitant medications, the sponsor notes that patients were told not to use antibiotics within one week of breath hydrogen testing. But any other concomitant medications taken during the trial were recorded on CRFs. Nonetheless, if a concomitant medication was collected during the period between the end of the BH phase and the beginning of the dose-response phase, and that time period was greater than 2 to 4 weeks, the concomitant medication was not included in the database. **[This is essentially the same approach as that used in Study S-1].**

- It is to be noted that the actual manner in which the trial was conducted differed somewhat from what was described in the protocol.

  - Firstly, random ordering of the BHTs was not conducted as described in the protocol. The yeast plus milk was always given as the final BT. However, since the half-life of the enzyme is rather short and there were ± 7 days in between the treatments no

carrying over effects, which could confound the results of Phase 1, are expected.

- Secondly, BHTs for some patients may have occurred more than one week apart. There were, however, justifications because these protocol violations could have been due to:

  1) the occurrence of an elevated BH baseline value as a consequence of inadequate dietary conditions. This resulted in the test being repeated

  2) the occurrence of an AE

  3) the use of previous diagnostic test results in place of placebo.

- Thirdly, GI symptoms (diarrhea, gas, bloating, and cramps) were recorded during each 3-h BHT, as well as for a period of 24 h following each BHT.

- Fourthly, only symptom severity was recorded.

- Lastly, stool consistency was not recorded during the BH phase.

- At the beginning of the dose-response phase, the patient was again instructed to adhere to a sucrose- and starch-free diet for one week. During this week, as specified in the protocol, the patient recorded stool frequency and consistency, in addition to severity of g.i. symptoms. The patient was then provided with a list of sucrose-containing foods, along with a description of the content of sucrose in each food, and directions for the correct number of grams of sucrose to ingest each day. This was based on the patient's weight in kilograms. Each patient was asked to consume approximately 2 g/Kg/day of sucrose, since the average American adult consumes approximately 100 g/day of this disaccharide. In this way, a child weighing 30 Kg would consume 60 g/day which would approximate the quantity in a normal diet.

- During the four 10-day periods of the dose-response phase, the patients ingested four liquid yeast solutions marked in vials A, B, C and D, and assigned (according to the protocol) in random order.

  - The solutions were distributed with calibrated droppers and the patients were instructed to mix either 1.0 or 2.0 mL (depending on the dose administered during the BH phase, which was 1.0 mL up to 15 Kg weight, and 2.0 mL for heavier patients), with 2 to 4 ounces of water, and ingest the solution 5 min. after beginning each meal.

  - During each of the four 10-day periods, patients completed daily stool and symptom diaries similar to those completed during the week prior to the dose-response phase.

- Any intercurrent illness, use of other medications, or deviations from the diet was recorded on the symptom diary and dietary record forms (CRFs).

- Snacks containing sucrose were prohibited between meals.

- Compliance with the sucrose-containing diet, dietary sucrose intake was assessed as above mentioned.

6. Study Execution

- Demographic information, disease history and symptom history were collected from patients that met the inclusion/exclusion criteria and signed an IC.

- The patients were then contacted by a trial dietitian who counseled them on a strict **sucrose-free diet,** necessary for accurate interpretation of the BT results.

    - For one week, the patient (or patient/guardian for patients under age 12) recorded his/her diet as well as stool and g.i. symptom pattern[36] on a daily basis. The record served as a baseline measurement prior to commencement of testing, and documented the degree of sucrose and starch restriction practiced by the patient prior to entry into the trial.[37]

- Following the baseline period, each patient underwent 3 randomized, blinded BHTs, each separated by one week of a sucrose and starch restricted diet.

    - Breath samples were obtained and analyzed immediately for hydrogen content using GC.

    - A baseline BH level of less than 10 ppm was required before the test could begin.

    - All BHTs were carried out for a period of 3h, immediately following ingestion of sucrose, and BH levels were obtained every 30 min.

    - Patients were required to be in the doctor's office for at least 3h after ingesting the sucrose.

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[36] This included symptoms of abdominal pain and cramping, gas, diarrhea, stool frequency and consistency.

[37] The actual symptoms recorded on the diaries (CRFs) included gas, bloating, nausea, vomiting, cramps, stool frequency and stool consistency (watery, soft, formed, hard). Total stool frequency and frequency of watery, soft, formed and hard stools were recorded, as was symptom severity (0=none, 1-mild, 2=moderate, 3=severe). For the purpose of this clinical trial, "Mild" was defined as lasting less than 5 min. and not interrupting normal activity; "Moderate" was defined as lasting 5-30 min. and interrupting activity but resolving rapidly; and "Severe" was defined as lasting more than 30 min. and causing a cessation of normal activity for a prolonged period of time.

- For 24 h after each BHT, patients were scheduled to record stool frequency and consistency, and frequency and severity of symptoms (gas, bloating, nausea, vomiting and cramps).

7. Efficacy Evaluations and Criteria for Efficacy

Primary Efficacy Assessments

As per Study S-1, these included total stools and the total symptoms score collected during the dose-response phase.

Secondary Efficacy Assessments

These were as in Study S-1.

Criteria for Efficacy

The criteria for efficacy during the BH phase (a) and the dose-response phase (b) were as per Study S-1.

In addition to the protocol-stipulated assessments, after the dose-response data were summarized, a post-hoc efficacy measurement, asymptomatic [YES/NO], was defined (as in Study S-1).

8. Safety Assessments

As in Study S-1, the gathering, handling and reporting of AEs occurring in Study S-2 were all adequate.

Removal of Patients From the Trial

Patients could withdraw from the trial at any time.

9. Data Handling Procedures/Validation of Data

Data handling procedures and validation of the gathered data were as described in detail for Study S-1.

10. Statistical Methodology

Except as noted, this was essentially as described in detail for Study S-1 under headings such as a. Generalities, b. Determination of sample size,[38]

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[38] **Determination of Sample Size**

The sponsor notes that data from preliminary studies provided the basis for estimating group sizes needed to detect differences between BHTs with placebo and yeast sucrase. The variable of comparison was area under the curve (AUC), calculated as the mean of 6 samples, obtained 30 min. apart for each patient. The cutoff point of age 14 ca. corresponded to a sucrose load of greater than 30 g.

Estimates of statistical power for the paired t-test were calculated, based on mean differences and standard deviations. For all ages combined, a sample of 12 patients was estimated to demonstrate the expected mean difference of 85.9 with 90% power at an alpha level of 0.010. It was

c. Patient populations analyzed (same definition for Efficacy Population and Safety Population), d. Patient Enrollment and Accountability, e. Demographic and Background Characteristics, f. Concomitant Medications and g. Analyses of Efficacy. For the latter, however, some of the methodology varied somewhat because S-2 had three treatments instead of two and additional statistical procedures were introduced. Thus, the analyses of efficacy for Study S-2 are described in detail below.

i) Breath Hydrogen Phase

- For continuous variables, BH output was summarized with descriptive statistics for each treatment (placebo, YS, YS+milk), at baseline (0 min.), and every 30 min. up to 3h. Peak BH, peak minus baseline, and total BH output were also summarized.

- For peak minus baseline and total BH output, negative values were converted to zero before descriptive statistics were calculated. Total BH output was calculated as the area under the curve (AUC) of BH output over time, using the trapezoidal rule.

- Treatments were compared for peak, peak minus baseline, and AUC using an analysis of variance (ANOVA) model with effects for treatment, Principal Investigator's location, and patient within Principal Investigator's location. (Co-investigator locations were too small to analyze for differences.) P-values for Principal Investigator's location were obtained by testing Principal Investigator's location against patient within Principal Investigator's location. Ninety-five percent confidence intervals and p-values for pairwise treatment comparisons were obtained based on the ANOVA least squares means.

- During each treatment period of the breath hydrogen phase, and for the following 24 h, severity of g.i. symptoms were recorded as none, mild, moderate and severe.

- For each symptom, the worst response recorded during or after the test was summarized for each treatment with frequencies and percentages.

- A total symptoms score, obtained by summing the most severe response across the four symptoms for each patient, was also summarized with frequencies and percentages.

- P-values for pairwise treatment comparisons of each symptom and the total symptoms score were obtained from a Wilcoxon signed-rank test of the difference in response between the two treatments.

    - The sponsor noted that the signed-rank test was performed in place of Friedman's test (specified in the protocol) because, although both are nonparametric rank-based techniques, the signed-rank test captures information about the magnitude of the difference in response between treatments for a patient, whereas Friedman's test does not.

ii) Dose-Response Phase

- For each patient, period totals for each efficacy measurement (number of stools, stool consistency measures, g.i. symptoms) were calculated at baseline and for each treatment by summing over the 7-day period for baseline, and over the 10-day period for each treatment.

- A total symptoms score was obtained for each patient by summing the total responses of all five symptoms across each period.

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deduced that if the sample were to include only patients above the age of 14, ca. 26 patients would be needed for similar statistical power, given no change in the dose of YS per gram of sucrose. It was expected that the increase in dose of YS for patients ingesting more than 30 g of sucrose would produce an effect similar to the pilot data for younger patients. Thus, it was concluded that a sample of 25 to 30 patients should provide greater than 90% statistical power to demonstrate group differences in BH levels between placebo and YS challenges with an alpha level of 0.010.

- Daily averages were calculated for number of stools, individual symptoms, and the total symptoms score by dividing the period total for a patient by the number of days the patient had nonmissing data.

- Total stools, average daily stools, and total stool consistency measures were summarized at baseline and for each treatment with descriptive statistics for continuous variables.

- Totals and averages of individual symptoms, the total symptoms score, and the daily average of the total symptoms score were each categorized, and then summarized with frequencies and percentages. The cut points of the categories were defined such that each category contained at least 10% of responses across the treatments.

- Statistical treatment comparisons were performed for total stools, averages of individual symptoms, and the total symptoms score.

- For the primary analysis, p-values for pairwise treatment comparisons were obtained from a Wilcoxon signed-rank test of the difference in response between the two treatments. The two higher concentrations (full-strength enzyme and 1:10 dilution) were also compared to the two lower concentrations (1:100 and 1:1000 dilutions) with a Wilcoxon signed-rank test.

Testing for Crossover Effects

- A supportive analysis was performed using an ANOVA model for crossover designs with effects for carryover, period, treatment, Principal Investigator's location, and patient within Principal Investigator's location.

- P-values for Principal Investigator's location were obtained by testing Principal Investigator's location against patient within Principal Investigator's location.

- If carryover was nonsignificant (p-value >0.15), then a reduced model was fit without this effect.

- Pairwise treatment comparisons, and the comparison of the two higher versus the two lower concentrations, were obtained from the ANOVA model least squares means. Due to the non-normal distribution of the efficacy measure responses and the extensive response of zero (none) for most symptoms, the ANOVA model was fit to categorized data. For average individual symptoms and the period-total symptoms score, the categories were defined using similar 10% cut-point guidelines as defined for the total symptoms score above, with a value of zero applied to the first category, one to the second, etc. A similar method was used to create categories for total stools. An ANOVA was not performed for average nausea and average vomiting since over 90% of the responses were equal to zero for these measures.

- An ANOVA model of the categorized data was also fit to the baseline data. The model contained effects for Principal Investigator's location, patient within Principal Investigator's location, and treatment received during the first period. P-values from the ANOVA F-test for overall treatment effects were obtained to assess imbalance of baseline values across patients.

- The MRANK procedure (a multivariate extension of Friedman's test) specified in the protocol was replaced by Wilcoxon signed-rank tests and a supportive ANOVA for three reasons: so that information on the magnitude of response differences was utilized, so that carryover and period effects could be tested, and so that efficacy measures could be evaluated individually, rather than combined in a multivariate test.

- Multiple comparisons were addressed by a step-down procedure. The primary comparisons were for the two higher versus the two lower dose levels for total stools and the total symptoms score. Within each of these measurements, if the primary comparison was significant (p-value ≤0.050), the six pairwise treatment comparisons were also evaluated for significance. Given that the primary comparison was significant for the total symptoms score, this comparison was also evaluated for each individual symptom, and, when significant, pairwise treatment comparisons for the individual symptom were then evaluated.

- The number and percentage of patients who were asymptomatic were summarized by treatment group. Additionally, p-values for pairwise treatment comparisons were obtained from McNemar's test, a nonparametric procedure.

11. Results

[NOTE: As in the review of Study S-1, for simplification of presentation purposes, only reviewer's Tables or key Tables and/or Figures presented by the sponsor, are reproduced in this review.]

A. Patient Accountability/Protocol Deviations

Refer to Table 15.

- A total of 40 patients were screened for this trial.
- Of these 40, 3 withdrew prior to randomization so 37 were randomized to the dose-response phase.
- 6 withdrew prior to phase 1 treatment; 34 entered the BH phase. Of these 34 (safety population), 32 entered and completed the BH phase of the trial (received enzyme).
- 28 entered the dose-response phase of the trial (efficacy population). Of these,
    - 26 completed the dose-response phase, having received all 4 treatments
    - 2 withdrew from the dose-response phase of the trial.
- A listing of the 6 patients who withdrew from the trial after treatment was presented in sponsor's Table 2.0. In summary, one (#6) was W/D for wheezing, an AE that resulted in hospitalization. His sibling (#5) was W/D by his mother because of the symptoms experienced by his brother. Patients #2 and #29 were W/D from the trial by their families due to difficulties in compliance with some of the trial procedures. Patients #22 and #36 were W/D because they did not meet trial selection criteria.
- The sponsor presented a summary of protocol violations in general and a by-patient listing of specific protocol violations in their Tables 4.0 and 4.1. From these the following is summarized:
    - 20/28 (71%) patients had one or more protocol violations.
    - None of the patients in the efficacy population was randomized with respect to treatment sequence in the BH phase of the trial.
    - 10 patients (36%) were non-compliant in taking the trial medication on one or more occasions.

- 8 (29%) had a baseline (time 0) BH output ≥10 ppm.

- 7 (25%) had a different actual treatment sequence than the assigned randomized treatment sequence.

- 5 (18%) had sucrose loading dosage deviations.

- 3 (11%) were non-compliant with visit scheduling.

TABLE 15
Study S-2 (OMC-SUC-2)

Patient Accountability

Measure	Principal Investigator's Location		
	Hartford	Duke	Total
Patients Screened	28	12	40
Randomized to the Dose-Response Phase[a]	24	13	37
Withdrew Prior to Randomization	2	1	3
Breath Hydrogen Phase			
Withdrew Prior to Treatment	4	2	6
Patients Entered (Safety Population)[b]	24	10	34
- Completed[c]	18	9	27 (79%)
- Did Not Complete	6	1	7 (21%)
- Withdrew After Treatment[b]	4	2	6 (18%)
Received Enzyme	23	9	32 (94%)
Dose-Response Phase			
Patients Entered (Efficacy Population)[d]	18	10	28 (82%)
Completed[e]	18	8	26 (76%)
Did Not Complete	0	2	2 (6%)

This Table was abstracted from sponsor's Table 1.0, with major modifications.
a) Patients #26 and #27 completed the BH phase at Hartford, but were randomized to the dose-response phase at Duke.
b) Received at least one of the following treatments: placebo, enzyme, milk/enzyme
c) Received all three treatments (placebo, enzyme, milk/enzyme).
d) Received at least one of the following treatments: full-strength enzyme [A], 1:10 dilution [B], 1:100 dilution [C], 1:1000 dilution [D].
e) Received all four treatments [A, B, C AND D].

Percentages are based on the number of patients in the safety population.

B. Demographics/Disease History/Concomitant Medications

- Demographic characteristics of the efficacy population are summarized in Table 16.

  - Of the 28 patients, 16 were females, 12 males. All were infants or children.

- The mean age was 49.3 mo. (4.1y).

- The mean weight was 16.6 Kg

TABLE 16
Study S-2 (OMC-SUC-2)

Demographic Characteristics at Baseline
Efficacy Population

Characteristic	Principal Investigator's Location		
	Hartford [n=20]	Duke [n=8]	Total [n=28]
Gender			
M	11	1	12 (43%)
F	9	7	16 (57%)
Age (mo.)	20	8	28
	46.7 (32)[a]	55.9 (34)	49.3 (34)
	4 to 120[b]	16 to 138	4 to 138
Weight (Kg)	20	8	28
	15.7 (14.4)	18.7 (13.4)	16.6 (13.9)
	6.8 to 34.0[c]	8.0 to 46.5	6.8 to 46.5

This Table corresponds to sponsor's Table 5, with major modifications (The S.E.M. has been omitted)

a) Mean (median)
b) Minimum to maximum age in months
c) Minimum to maximum weight

- In this study, as in S-1, tests were performed to determine if patients had CSID at baseline and could therefore participate in this trial. The results of these evaluations were presented in sponsor's Table 3.0. From this Table, the following can be summarized.

  - The diagnosis of CSID was made by DEA only in 22/34 patients, by BHT only in 3/34 patients and by BHT plus DEA in 3/34 of the patients.

  - No saccharidase levels (=0) were found in 14 of the patients and no paltinase levels in 15 of the patients.

  - Except for one patient (#33) who had a low lactase level (13.0), all patients had normal levels of lactase and therefore met the disaccharidase-level criteria per protocol.

  - Although in 16 patients, the pathology report was normal, in 14 the pathology report was listed as not available.

- In two patients [#17 and #34], the pathology reports revealed abnormal villous architecture. However, both met the other diagnostic criteria for disaccharidase levels [#17 on the basis of DEA and #34 on the basis of BHT plus DEA].

- In their Table 6.0, the sponsor presented a by-patient listing of patients with concomitant medications.

  - 16 patients received one or more additional medications during the trial.

  - Most frequent was the use of antibiotics for the treatment of infections commonplace in children and infants. The start and/or stop dates of many of these concomitant medications were not available. As mentioned previously, patients were not to be treated with antibiotics within one week of BHT. In spite of this, 11 patients[39] were known to have been treated with antibiotics during the trial.

C. Efficacy

1) Primary Efficacy Parameters (Tables 17 and 18)

- Comparisons of the four treatment periods with respect to the mean number of total stools (Table 17) showed fewest for the more concentrated solutions (18.2 ± 1.6 for full-strength enzyme and 22.0 ± 2.5 for the 1:10 dilution) and greatest for the least concentrated solutions. This was also the case for average stools per day as well as for the mean number of watery and soft stools. Conversely, the mean number of formed stools was greatest for full-strength enzyme and the 1:10 dilution, and fewest for the 1:100 and 1:1000 dilutions. In addition, the mean number of hard stools was greatest for full-strength enzyme and fewest for the 1:100 dilution. The average stools for each of the four treatment groups are summarized in Table 17.

TABLE 17
Study S-2 (OMC-SUC-2)
Dose-Response Phase: Mean Number of Stools

Sucrose Treatment (Dilution)	Total	Average No. Day	Number of Stools			
			Watery	Soft	Formed	Hard
Full-strength	18.2	1.84	3.8	6.1	7.9	0.4
1:10	22.0	2.22	7.0	7.0	7.7	0.3
1:100	25.8	2.60	12.0	8.3	5.1	0.1
1:1000	24.4	2.45	9.7	9.0	5.4	0.3

[39] 8 of these patients were treated with antibiotics after the BH phase of the trial and were therefore not in violation of the protocol; however, it could not be determined if the remaining 3 patients were in compliance with this criterion because complete start and/or stop dates of concomitant medication were not available.

- As summarized in Table 18 (upper panel), there were statistically significant differences between groups A and C, A and D and B and C and the most concentrated solutions (A+B) in comparison to the least concentrated solutions (C+B) re: total stools (summed up over a 10-day period for the dose-response phase) and the average stools per day (averaged over a 10-day period for the dose-response phase).

- Refer to the lower panel of Table 18. With respect to total symptoms, the two most concentrated solutions were clinically and statistically superior to the two least concentrated solutions. Thus, A > C, A > D, B > C and A+B > C+D. There was no statistically significant difference between formulation C and D.

TABLE 18
Study S-2 (OMC-SUC-2)

Results of Primary Efficacy Parameters

	Baseline	Treatment/Dilution			
		Full Strength [A]	1:10 [B]	1:100 [C]	1:1000 [D]
I. Total Stools[a]///Average Stool per Day[b]					
Mean (median)	[n=23] 15.5 (13)	[n=27] 18.2 (16)	[n=27] 22.0 (19)	[n=28] 25.8 (22)	[n=28] 24.4 (22)
Mean (median)	2.3 (2.0)	1.8 (1.6)	2.2 (2.1)	2.6 (2.2)	2.5 (2.2)
Statistics (p-value)[c]	A vs B N.S.	A vs C 0.001	A vs D 0.006	B vs C 0.004	B vs D N.S.	C vs D N.S.	A+B vs C+D 0.001
II. Total Symptoms					
	[n=23]	[n=27]	[n=27]	[n=28]	[n=28]
0	7 (30%)	8 (30%)	10 (37%)	5 (18%)	6 (21%)
1-2	4 (17%)	2 (7%)	3 (11%)	5 (18%)	4 (14%)
3-7	8 (35%)	9 (33%)	4 (15%)	5 (18%)	5 (18%)
8-10	2 (9%)	4 (15%)	5 (19%)	2 (7%)	0
11-15	1 (4%)	3 (11%)	2 (7%)	5 (18%)	3 (11%)
16-20	0	0	2 (7%)	5 (18%)	4 (14%)
>20	1 (4%)	1 (4%)	1 (4%)	1 (4%)	6 (21%)
Statistics (p-value)[d]	A vs B N.S.	A vs C 0.020	A vs D 0.009	B vs C 0.035	B vs D 0.034	C vs D N.S.	A+B vs C+D 0.003

Reviewer's Original Table

a) Stool were summed up over a 7-day period (for baseline) and over a 10-day period (for the dose-response phase)

b) Total stools were averaged over a 7-day period (for baseline) and over a 10-day period (for the dose-response phase).

c,d) p-values obtained from a nonparametric Wilcoxon signed-rank test on pairwise comparisons.

NOTE: Five patients were not assessed at baseline; two patients missed one treatment period. Four patients had missing data on one or more days in the dose-response phase.

2) Secondary Efficacy Parameters

a) Breath Hydrogen Phase

- The BHT results are summarized in Table 19. Depicted are the mean and the median at 6 time-points, starting at 30 min. from baseline (time 0) to 180 min. Whether one compares the mean or the median, the BH output was always higher with placebo than with either the enzyme or the milk/enzyme.

- As in Study S-1, the BH excretion results are better appreciated in Fig. 7. The median changes (upper graph) indicate that in these CSID patients, significant BH excretion - indicative of sucrose malabsorption began about one hour after the sucrose solution was ingested, reached a peak at 150 min. and then began to decline. In contrast, when the sucrase enzyme was taken together with the sucrose load only a slight increase in BH excretion (<15 ppm) occurred. When the sucrase enzyme was given together with milk, essentially no changes were detected in BH excretion (median) over the three hours of observation.

- In the lower graph in Fig. 7 the BH data are plotted as mean and S.E.M. As in the case of results of Study S-1, the pattern in this graph is not very dissimilar to that seen when plotting median data. But the mean data give an indication of a) the intersubject variability in BH excretion and b) the greater effect of individual outlier responses on the mean values as compared to the median values shown in the upper graph.

  The reviewer agrees with the sponsor that overall, these data indicate that the liquid yeast-derived sucrase markedly attenuates the large increase in hydrogen expiration seen in the CSID patient in response to unmetabolized sucrose. In addition, these two graphs in Fig. 7 suggest (but do not prove since this finding needs replication) that giving milk along with the sucrase may further enhance this inhibition of hydrogen production.

TABLE 19
Study S-2 (OMC-SUC-2)

Results of Secondary Efficacy Parameters
Breath Hydrogen Phase: Breath Hydrogen Output

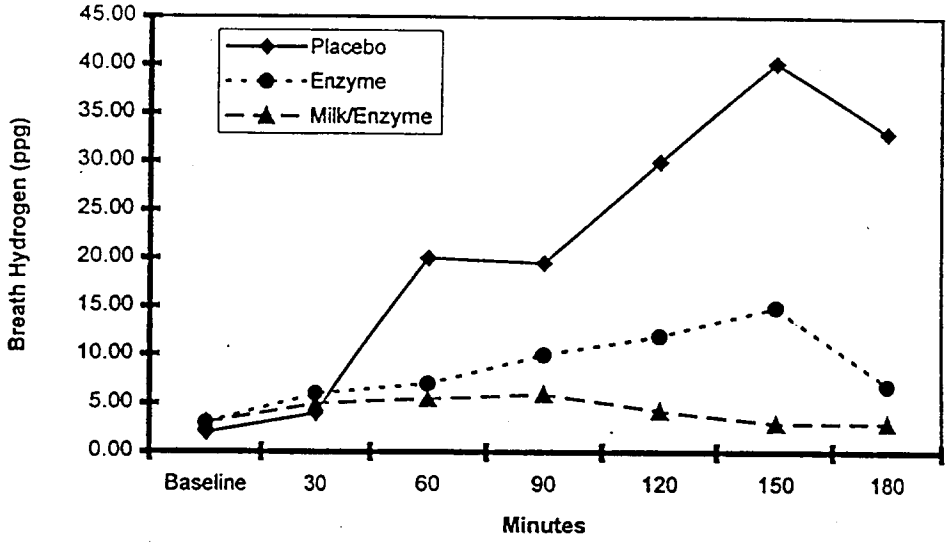
Treatment Group	Evaluation Parameter	Baseline [n=28]	Time Point From Baseline (min.) 30 [n=28]	60 [n=28]	90 [n=28]	120 [n=28]	150 [n=28]	180 [n=28]
BREATH HYDROGEN OUTPUT (ppm)								
Placebo	n	27	27	27	26	27	26	25
	Mean	7.1	18.5	33.1	36.5	47.4	50.2	43.1
	Median	2.0	4.0	20.0	19.5	30.0	40.2	33.0
Enzyme	n	27	27	27	27	27	25	27
	Mean	4.5	10.4	13.3	20.7	21.1	22.7	21.6
	Median	3.0	6.0	7.0	10.0	12.0	15.0	6.9
Milk/Enzyme	n	26	26	26	26	26	25	25
	Mean	4.0	13.0	10.0	9.5	10.6	8.8	9.3
	Median	3.0	5.0	5.4	6.0	4.3	3.0	3.0

	Evaluation Parameter	Peak [n=28]	Peak-Baseline [n=28]	AUC[a] [n=28]
BREATH HYDROGEN OUTPUT (ppm)				
Placebo	n	27	27	27
	Mean	61.9	56.1	6285.1
	Median	39.0	38.0	3945.0
	95% C.I.	(48.7, 78.9)	(43.2, 73.7)	(5115.1, 7833.1)
Enzyme	n	27	27	27
	Mean	34.4	30.1	2999.7
	Median	22.0	14.0	2130.0
	95% C.I.	(21.2, 51.4)	(17.2, 47.7)	(1829.7, 4547.7)
Milk/Enzyme	n	26	26	26
	Mean	17.8	13.8	1767.1
	Median	7.5	4.0	945.0
	95% C.I.	(7.8, 38.6)	(3.0, 34.0)	(827.4, 3594.9)
Statistical Analysis (p-values):				
Site Effect		N.S.	N.S.	N.S.
Treatment Effect		**0.001**	**0.002**	**0.001**
Placebo vs Enzyme		**0.009**	**0.015**	**0.001**
Placebo vs Milk/Enzyme		**0.001**	**0.001**	**0.001**
Enzyme vs Milk/Enzyme		N.S.	N.S.	N.S.

Reviewer's Table, based on sponsor's Table 7.0, with major modifications. The S.E.M., min. and max. values have been omitted and fractions of ppm have been rounded off to one decimal, for clarity of presentation.

a) AUC = Area under the curve. Missing values before the last time point were interpolated. Missing at the last time point were assigned the value of the previous time point.

NOTE: Negative values for peak minus baseline and AUC were converted to zero.
Patient #20 received twice the amount of sucrose than as per protocol.
Since it was not certain whether Pt #27 received PL or ENZ during the first two tests, these data were excluded from the analysis; 2 pts did not receive milk/enzyme; 4 pts had missing data at various time points.
p-values and 95% confidence intervals (C.I.) about least squares means were obtained from ANOVA models with effects for site, treatment, and patient.



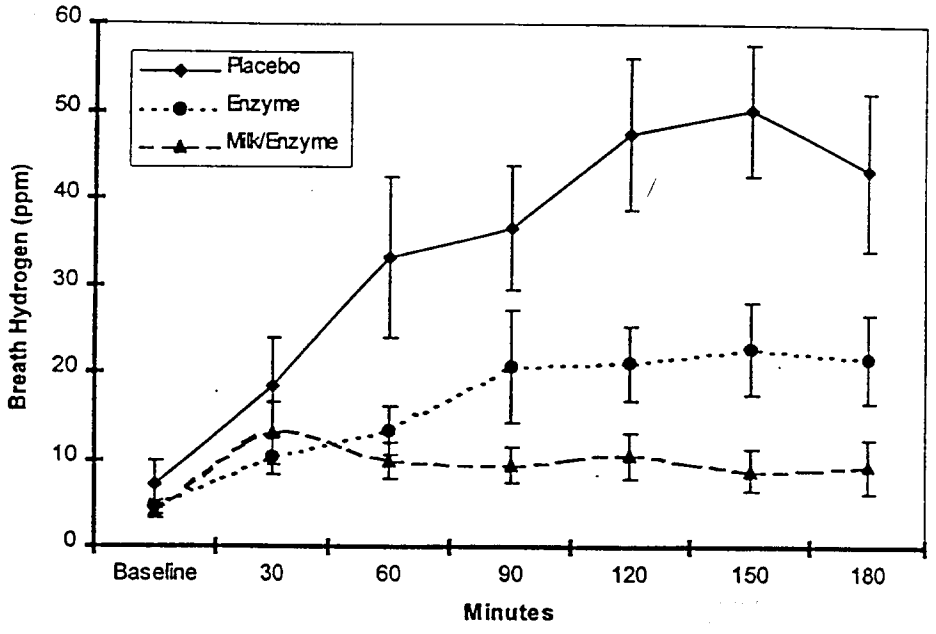


Fig. 7 - Study S-2 (OMC-SUC-2): Breath Hydrogen Excretion Following Pre-Treatment With the Oral Sucrose Loading Dose of 2 g/Kg and Oral Treatment With Either Sucrase, Sucrase plus Milk or Placebo (Water) Test Dose.

Upper Graph: median values
Lower Graph: mean ± S.E.M.

- Refer to the lower panel of Table 19, where statistical analyses (comparisons) are made among the three treatments (sucrase vs milk/sucrase vs placebo) with respect to the three key BH measures [peak, peak minus baseline and total output (AUC)].

  - The results did not show significant site (Principal Investigator's location) effects.

  - Highly significant treatment effects were shown. Treatment effect p-values for peak and AUC were ≤0.001. For peak minus baseline the p-value was 0.002.

  - Significant pairwise differences were present for each endpoint between placebo and yeast sucrase and between placebo and YS+milk.

  - **No significant pairwise differences were found between sucrase and YS+milk with respect to any of the three efficacy endpoints.**

- The severity ratings of gastrointestinal symptoms occurring during the BH phase were summarized in sponsor's Table 7.1. From this Table, the following was abstracted:

  - The majority of patients in each treatment group (77% for placebo, 100% for sucrase, 92% for sucrase + milk) had a total symptoms score (sum of the maximum severity scores for each symptom) of six or less.

  - The percentage of patients with a total symptom score of zero increased across the placebo (8%), yeast sucrase (35%), and yeast sucrase plus milk (46%) groups. These important therapeutic gains represented a highly significant difference (p≤0.001).

- Individual GI symptoms were examined next:

  - 19% of the patients in the placebo group reported having no symptoms of diarrhea. In the yeast sucrase (YS) and YS+milk groups, a larger percentage of patients reported having no symptoms 62% and 65%, respectively). The therapeutic gain represented a very meaningful clinical difference.

  - For gas, 42% of patients in the placebo group had no symptoms. In the YS group, 65% had no symptoms and, in the YS+milk group, 58% had no symptoms. Again, these are clinically meaningful therapeutic gains.

  - For bloating, the percentage of patients who reported having no symptoms was 62% for placebo, 88% for YS and 73% for YS+milk. Once again, although the PL response is high, treatment with the enzyme resulted in a clinically meaningful therapeutic gain.

- With respect to cramps, 46% of patients in the placebo group had no symptoms, and in both the YS and YS+milk treatment groups, 77% of the patients had no symptoms (Table 20, upper panel). As per the other symptoms, these are clinically meaningful therapeutic gains.

In summary, the above represented important therapeutic gains (sucrase better than placebo) of 43%, 23%, 26% and 31% for diarrhea, gas, bloating and cramps, respectively (Table 20, middle panel). P-values for pairwise comparisons are shown in the lower panel of Table 20.

- Significant treatment differences were shown between placebo and YS for the total symptoms score (p-value ≤0.001), diarrhea (p-value ≤0.001), bloating (p-value = 0.012), and cramps (p-value = 0.014).

- Treatment differences were also present between placebo and YS+milk for the total symptoms score (p-value ≤0.001), diarrhea (p-value ≤0.001), gas (p-value = 0.014), and cramps (p-value = 0.016).

- There were no significant treatment differences between sucrase and sucrase plus milk for the total symptoms score or for any of the individual symptoms.

TABLE 20
Study S-2 (OMC-SUC-2)

Breath Hydrogen Phase
Percentage of Patients With No Gastrointestinal Symptoms

Treatment	Diarrhea	Gas	Bloating	Cramps	
Placebo	19%	42%	62%	46%	
Sucrase (YS)	62%	65%	88%	77%	
YS+milk	65%	58%	73%	77%	
Comparison	Therapeutic Gain				
Sucrase - Placebo	43%	23%	26%	31%	
(YS+milk) - Placebo	46%	16%	11%	31%	
Treatment Comparison	Statistics[a]				Total Symptom Score
Placebo vs YS	0.001	N.S.	0.012	0.014	0.001
Placebo vs YS+milk	0.001	0.014	N.S.	0.016	0.001
YS vs YS+milk	N.S.	N.S.	N.S.	N.S.	N.S.

Reviewer's Table

a) p-values calculated by the Wilcoxon signed-rank test.

b) Dose-Response Phase

Refer to Table 17. A summary of the average stools for each treatment group was given in this Table. At baseline, the mean number of total stools was 15.5 ± 1.7. The mean number of soft stools was 6.8 ± 1.8; formed stools (5.8 ± 1.1); watery stools (2.4 ± 1.0); and hard stools (0.4 ± 0.2). The mean number of average stools per day was 2.31 ± 0.23.

- As already mentioned, during the four treatment periods, the mean number of total stools was fewest for the more concentrated solutions (18.2 ± 1.6 for full-strength enzyme and 22.0 ± 2.5 for the 1:10 dilution) and greatest for the least concentrated solutions (25.8 ± 2.9 for the 1:100 dilution and 24.4 ± 2.5 for the 1:1000 dilution). The test medication had also the same effect on average stools per day and for the mean number of watery and soft stools.

- The inverse was seen when assessing results on formed stools and hard stools. The mean number of formed stools was greatest for full-strength enzyme and the 1:10 dilution, and fewest for the 1:100 and 1:1000 dilutions. Furthermore, the mean number of hard stools was greatest for full-strength enzyme and fewest for the 1:100 dilution.

- Total scores for **gastrointestinal symptoms** were computed and were presented at the bottom of Table 21. Although not shown in this Table, the following was seen:

  - At baseline, the majority of patients (83%) had a total symptom score of 7 or less.

  - Similarly, for the four treatment periods (full-strength enzyme, 1:10 dilution, 1:100 dilution, and 1:1000 dilution), 70%, 63%, 54% and 54% of the patients, respectively, had a total symptoms score of 7 or less.

The following is shown in Table 21:

- The percentage of patients with a **total gas score** of 7 or less at baseline was 96%.

  - There were more patients with a total gas score of 7 or less in the full-strength, 1:10 dilution and 1:100 dilution groups than in the 1:1000 dilution group: 78%, 74% and 79%, respectively, vs 64%.

- The percentage of patients with a **total bloating score** of 7 or less at baseline was 96%. Results for the full-strength and 1:10 dilution groups were 96% and 93%, respectively, compared to 86% and 82% for the 1:100 and 1:1000 dilution groups, respectively.

- The percentage of patients with a **total cramps score** of 7 or less at baseline was 96%. Results for each of the four treatment groups were similar: 96%, 100%, 93% and 89%, respectively.

- With respect to **nausea and vomiting**, the majority of patients reported having no symptoms either at baseline (≥83%) or during treatment (≥89%). Consequently, there were no differences between or among the groups with respect to nausea or vomiting.

- The sponsor presented the **average scores** for gastrointestinal symptoms in their Table 9.1. Results were similar to those of the total scores (results displayed in Table 21).

- Primary treatment comparisons (statistics) for total stools and gastrointestinal symptoms are presented in the lower panel of Table 21.

    - As already mentioned, results from Wilcoxon's signed-rank test showed significant treatment differences for the primary outcome variable **total stools** when comparing the two more concentrated solutions with the two less concentrated solutions (p-value ≤0.001) (see right hand column).

    - In addition, significant pairwise treatment differences were present between full-strength enzyme and the 1:100 dilution (p-value ≤0.001), between full-strength enzyme and the 1:1000 dilution (p-value = 0.006), and between the 1:10 and 1:100 dilutions (p-value = 0.004).

- Also displayed in the lower panel of Table 21 are the significant treatment differences between the two highest doses (full-strength enzyme/1:10 dilution) and the two lowest doses (1:100/1:1000 dilutions) that were evident for the total symptoms score (p-value = 0.003), average gas (p-value = 0.042), average bloating (p-value = 0.006), and average cramps (p-value = 0.028).

    - With respect to the total symptoms score (bottom of Table 21), Wilcoxon's signed-rank test further indicated significant treatment differences between full-strength enzyme and the 1:100 dilution (A vs C. p-value = 0.020), full-strength enzyme and the 1:1000 dilution (A vs D, p-value = 0.009), the 1:10 and 1:100 dilutions (B vs C, p-value = 0.035), and, the 1:10 and 1:1000 dilutions (B vs D, p-value = 0.034).

NOTE: In Table 21, upper panel the **total scores** of gastrointestinal symptoms in the dose-response phase of the trial are depicted. These total scores were very similar to the **average scores** (not shown). The results of statistic analyses summarized in the lower panel of Table 21 used the average scores.

TABLE 21
Study S-2 (OMC-SUC-2)

Dose Response Phase: Total Scores of Gastrointestinal Symptoms
Efficacy Population

Symptom[a]	Baseline [n=28]	Treatment Group/Dilution: Full-Strength]n=28]	1:10 [n=28]	1:100 [n=28]	1:1000 [n=28]
Average Score of Gastrointestinal Symptoms					
Gas [n →]	23	27	27	28	28
0	11 (48%)[b]	11 (41%)	12 (44%)	11 (39%)	8 (29%)
1-2	5 (22%)	3 (11%)	5 (19%)	8 (29%)	6 (21%)
3-7	6 (26%)	7 (26%)	3 (11%)	3 (11%)	4 (14%)
8-10	0	4 (15%)	5 (19%)	4 (14%)	2 (7%)
>10	1 (4%)	2 (7%)	2 (7%)	2 (7%)	8 (29%)
Bloating [n →]	23	27	27	28	28
0	15 (65%)	22 (81%)	23 (85%)	20 (71%)	19 (68%)
1-7	7 (30%)	4 (15%)	2 (7%)	4 (14%)	4 (14%)
>7	1 (4%)	1 (4%)	2 (7%)	4 (14%)	5 (18%)
Nausea [n →]	23	27	27	28	28
0	21 (91%)	26 (96%)	26 (96%)	26 (93%)	26 (93%)
>0	2 (9%)	1 (4%)	1 (4%)	2 (7%)	2 (7%)
Vomiting [n →]	23	27	27	28	28
0	19 (83%)	27 (100%)	25 (93%)	25 (89%)	25 (89%)
>0	4 (17%)	0	2 (7%)	3 (11%)	3 (11%)
Cramps [n →]	23	27	27	28	28
0	17 (74%)	20 (74%)	19 (70%)	16 (57%)	17 (61%)
1-2	1 (4%)	5 (19%)	3 (11%)	3 (11%)	3 (11%)
3-7	4 (17%)	1 (4%)	5 (19%)	7 (25%)	5 (18%)
>7	1 (4%)	1 (4%)	0	2 (7%)	3 (11%)

	Statistics: Treatment Comparisons = p-value[c]						
	A vs B	**A vs C**	**A vs D**	**B vs C**	**B vs D**	**C vs D**	**A+B vs C+D**
Total Stools[d]	N.S.	0.001	0.006	0.004	N.S.	N.S.	0.001
Gas[e]	N.S.	N.S.	0.049	N.S.	N.S.	0.022	0.042
Bloating[e]	N.S.	0.048	0.018	0.016	0.023	N.S.	0.006
Nausea[e]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Vomiting[e]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Cramps[e]	N.S.	0.025	0.050	N.S.	N.S.	N.S.	0.028
Total Symptoms[f]	N.S.	0.020	0.009	0.035	0.034	N.S.	0.003

This Table is based on sponsor's Tables 9.0 and 10.0, put together, with major modifications.

a) Severity scores summed over a 7-day period (for baseline) and over a 10-day period (for the dose-response phase). Original scale was: 0=None, 1=Mild, 2=Moderate, 3=Severe.

NOTE I: Five patients were not assessed at baseline; two patients missed one treatment period. Three patients had missing data on one or more days in the dose-response phase.

b) Percentages are based on the number of patients with nonmissing data for that symptom. It represents the sum of gas, bloating, nausea, vomiting and cramps scores summed over 7 days (for baseline) and over 10 days (for the dose-response phase).

c) p-values obtained from a nonparametric Wilcoxon signed-rank test on pairwise treatment comparisons.

NOTE II: A = full strength enzyme, B = 1:10 dilution, C = 1:100 dilution, D = 1:1000 dilution.

d) Based on total number of stools over a 10-day period.

e) Based on **average severity scores** over a 10-day period.

f) Represents the sum of total gas, total bloating, total nausea, total vomiting and total cramps scores over a 10-day period.

Additional Comparison for individual symptoms are noted:

- For **average gas** pairwise treatment differences were significant between full-strength enzyme and the 1:1000 dilution (p-value = 0.049), and between the 1:100 and 1:1000 dilutions (p-value = 0.022).

- For **average bloating** treatment differences were significant between full-strength enzyme and the 1:100 dilution (p-value = 0.048), between full-strength enzyme and the 1:1000 dilution (p-value = 0.018), between the 1:10 and 1:100 dilutions (p-value = 0.016), and between the 1:10 and 1:1000 dilutions (p-value = 0.023).

- Finally, for **average cramps** results indicated a significant treatment difference between full-strength enzyme and the 1:100 dilution (p-value = 0.025), and between full-strength enzyme and the 1:1000 dilution (p-value = 0.050).
- As pointed out above, no significant treatment differences were found for the outcome variables average nausea or average vomiting.

c) Supportive Treatment Comparison on Stools and Gastrointestinal Symptoms During the Dose-Response Phase (Table 22)

- Results from an ANOVA displayed in this Table indicated that PI's location and treatment were nonsignificant at baseline for all of the efficacy variables. This analysis indicated no imbalance of baseline values across PI's location or treatments.

  - With respect to the treatment period, carryover was marginally significant for total stools (p-value = 0.054), average cramps (p-value = 0.085), and the total symptoms score (p-value = 0.109). Hence for these measures, results for PI's location effect, period effect, overall treatment effect, and pairwise treatment comparisons were adjusted for carryover (Table 22).

  - For the efficacy variables average gas and average bloating, carryover was found to be nonsignificant, and was therefore removed from the model.

- Overall, results for pairwise treatment comparisons (Table 22) were supportive of those displayed in Table 21. Effects for PI's location (site) and period were non-significant. For average gas, the overall treatment effect showed a trend (p-value = 0.056)[40] but this is listed as N.S. in Table 22.

[40] The sponsor presented supplementary efficacy tables in their Appendix 17.5. These tables include by-day analyses for each individual symptom, and in general, were consistent with and supportive of the efficacy results discussed above.

TABLE 22
Study S-2 (OMC-SUC-2)

Dose-Response Phase: Stools and Gastrointestinal Symptoms
Supportive Treatment Comparison p-Values

Statistical Analysis/p-values	MEASUREMENT				
	Total Stools[a]	Average Gas[b]	Average Bloating[b]	Average Cramps[b]	Total Symptoms[c]
Baseline[d]					
Site Effect	N.S.	N.S.	N.S.	N.S.	N.S.
Treatment Effect	N.S.	N.S.	N.S.	N.S.	N.S.
Dose-Response Phase[e]					
Carryover Effect	0.054	N.S.	N.S.	0.085	0.109
Site Effect	N.S.	N.S.	N.S.	N.S.	N.S.
Period Effect	N.S.	N.S.	N.S.	N.S.	N.S.
Treatment Effect	**0.018**	N.S.	N.S.	N.S.	**0.029**
A vs B	N.S.	N.S.	N.S.	N.S.	N.S.
A vs C	**0.003**	N.S.	N.S.	N.S.	N.S.
A vs D	**0.019**	N.S.	**0.042**	**0.016**	**0.009**
B vs C	N.S.	N.S.	N.S.	N.S.	N.S.
B vs D	N.S.	**0.013**	**0.033**	N.S.	**0.013**
C vs D	N.S.	**0.023**	N.S.	N.S.	N.S.
A + B vs C + D	**0.007**	N.S.	**0.011**	**0.016**	**0.007**

This Table corresponds to sponsor's Table 10.1, with major modifications.

a) Based on total number of stools over a 7-dy period (for baseline) and over a 10-day period (for the dose-response phase).
b) Based on average severity scores over a 7-day period (for baseline) and over a 10-day period (for the dose-response phase).
c) Represents the sum of total gas, total bloating, total nausea, total vomiting, and total cramps scores over a 7-day period (for baseline) and over a 10-day period (for the dose-response phase).
d) p-values obtained from ANOVA model fit to transformed variables with effects for site and Period 1 treatment assignment.
e) For total stools, average cramps, and total symptoms, p-values were obtained from ANOVA models fit to transformed variables with effects for carryover, site, period, treatment and patient. For average gas and average bloating, p-values for carryover were also obtained from this model; all other p-values were obtained from ANOVA models with effects for site, period, treatment and patient.

NOTE: A = Full-strength enzyme, B = 1:10 dilution, C = 1:100 dilution, D = 1:1000 dilution. Due to the large number of zero responses, average vomiting and average nausea were not analyzed.

d) Post-hoc Responder Analysis (Table 23)

- 78% of patients were asymptomatic at baseline.
- During the treatment period, a higher percentage of patients (81%) were asymptomatic while receiving full-strength enzyme, than while receiving any of the other three dilutions: 1:10 dilution (56%), 1:100 dilution (43%) or 1:1000 dilution (50%).
- Significant pairwise treatment comparisons were present between full-strength enzyme and the 1:100 dilution (A vs C, p-value = 0.002), and between full-strength enzyme and the 1:1000 dilution (A vs D, p-value = 0.007).
- No other significant differences were found.

D. Safety

1) Completeness/Limitation of Data

The safety data collected in Study S-2 are limited in several respects. Firstly, neither clinical laboratory evaluations nor vital sign changes were collected during the trial. Although this is mentioned here, no changes in these parameters are expected. Therefore, only AEs, withdrawals due to AEs and serious AEs were presented by the sponsor. Secondly, probably due to the study population per se (infants and children), the fact that in some instances the PI depends upon the parent/guardian to get a complete description of the AE, etc. the PI did not indicate whether the AE was or was not related to test medication. In some cases, resolution of the AE was not indicated. Thirdly, most AEs appeared to be symptoms of sucrose malabsorption that are expected in CSID patients. Therefore, these events may not have been considered unexpected for this patient population (the PI may have felt less compelled to monitor such an AE closely). Nonetheless, with the data on hand, some conclusions appear possible.

TABLE 23
Study S-2 (OMC-SUC-2)

Dose-Response Phase: Responder Analysis

Measurement	Baseline [n=28]	Treatment Group/Dilution			
		Full-Strength [A] [n=28]	1:10 [B] [n=28]	1:100 [C] [n=28]	1:1000 [D] [n=28]
Asymptomatic[a]	23	27	27	28	28
YES	18 (78%)[b]	22 (81%)	15 (56%)	12 (43%)	14 (50%)
NO	5 (22%)	5 (19%)	12 (44%)	16 (57%)	14 (50%)

STATISTICS

Treatment Comparisons:	p-value[c]
A vs B	N.S.
A vs C	**0.002**
A vs D	**0.007**
B vs C	N.S.
B vs D	N.S.
C vs D	N.S.

This Table corresponds to sponsor's Table 11, with major modifications.
a) A patient was asymptomatic if on at least 70% of the days in a period with nonmissing data, he/she had no watery stools and ratings of none or mild for all gastrointestinal symptoms.

NOTE: Five patients were not assessed at baseline. Two patients missed one treatment period. Four patients had some missing data on one or more days in the dose-response phase.

b) Percentages are based on the number of patients with nonmissing data for that period.
c) p-values obtained from a nonparametric McNemar's test on pairwise treatment comparisons.