CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020772

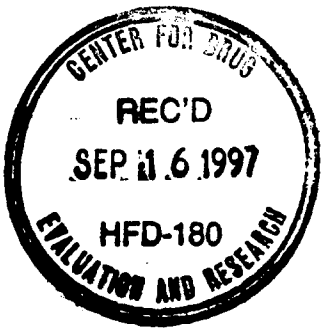
STATISTICAL REVIEW(S)

STATISTICAL REVIEW & EVALUATIONS

NDA #: 20-772 **Date**: SEP 16 1997

SEP 15 1997

Drug: Sacrosidase (Sucraid™) Oral Solution



Applicant: Orphan Medical, Inc

Indication: Treatment of Congenital Sucraid-Isomaltase Deficiency (CSID)

NDA Drug Classification: 1P

Statistical Reviewer: A. J. Sankoh, Ph.D.

APPEARS THIS WAY ON ORIGINAL

Clinical Reviewer: The issues addressed in this review have been discussed with the medical reviewer, Hugo Gallo-Torres, M.D., Ph.D.

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Keywords/Phrases: Cross over study designs; multiple doses, multiple endpoints; orphan drug;

Introduction

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Congenital sucraid-isomaltase deficiency (CSID) is a chronic malabsorption disease characterized by an autosomal recessive inheritable disease of the sucrase and isomaltase deficiency. CSID patients are associated with lack of endogenous sucrase activity, a marked reduction in isomaltase activity, and a moderate decrease in maltase activity.

Sucrase is normally produced in the brush border lining of the small intestine and is responsible for the metabolism of sucrose, a disaccharide commonly known as table sugar, into two component monosaccharides (glucose and fructose) which are then absorbed into the circulation. Without the sucrase enzyme, sucrose cannot be absorbed, and passes unchanged into the large intestine. Unabsorbed sucrose in the large intestine is broken down by colonic bacteria, producing among other products the gases hydrogen, methane, and carbon dioxide. These gases generate gastrointestinal discomfort including excessive gas, bloating, abdominal cramps, watery diarrhea, nausea, and vomiting.

Thus children born with CSID develop a malabsorption syndrome upon first exposure to sucrose in their diet. The primary symptoms of CSID include severe watery diarrhea, gas, bloating, abdominal cramps, abdominal pain and sometimes nausea and vomiting. Prior to this product (Sucraid™), the only feasible treatment was a diet totally free of sucrose.

The definitive test for diagnosis of CSID has remained the measurement of intestinal disaccharidases following small bowel biopsy. However, a positive breath hydrogen test following oral challenge with sucrose and a negative breath hydrogen test following oral challenge with lactose along with a stool pH of less than 6 provide an acceptable diagnosis of CSID.

The rationale for the sucraid drug product is the replacement of the missing endogenous sucrase with extrogenous sucrase that retains enzymatic activity when given orally. It should be noted that sucraid does not provide specific replacement therapy for isomaltase deficiency. Thus continued restriction in the starch content of the diet may be necessary for patients to optimize diminishment of disease symptoms.

This NDA submission consists of two pivotal studies OMC-SUC S-1 and S-2 in support of the efficacy and safety of Sucraid™ in the treatment of CSID .

Key Words & Phrases: Crossover designs; breath hydrogen test; milk challenge, sucrase deficiency

I. STUDY DESIGN

1.1 Protocol #OMC-SUC-1 (conducted 5/24/90 to 11/10/92)

This was a two-phased, randomized, multi-center, multi-dose, (patient) blinded crossover study to assess sucrase enzyme replacement in patients with congenital sucrase-isomaltase deficiency (CSID). The first phase (Phase I) was a diagnostic phase [by a breath hydrogen test (BHT)] and consisted of two single-dose treatments (liquid yeast sucrase (YS) and a matching placebo arm) which were to be assigned to patients in a random order; the second phase (Phase II) was a dose-finding phase consisting of four consecutive 14-day treatments (1:100 dilutions, 1:1000 dilutions, 1:10,000 dilutions and 1:100,000 dilutions of the full strength sucrase) which were to be administered to each patient in a random sequence. Prior to the BHT phase, patients were to be evaluated to confirm CSID diagnosis and trial eligibility.

During the BHT phase, patients were to undergo two randomized BHTs: (a) 2 mg/kg body weight of oral sucrose followed immediately by 1 mL of full strength YS in 29 mL of water, and (b) 2 mg/kg body weight of oral sucrose followed immediately by 30 mL of water and no YS (placebo). The tests, entailing ingestion of sucrose followed by placebo or YS, were to be separated by one week, and were to be conducted following a 12-hour fasting and a 3-day sucrose free period. During each test, and for a period of eight hours thereafter, gastrointestinal (GI) symptoms were to be recorded on a symptom diary. The BHT phase was to last for two

weeks (two single tests given one week apart).

During the dose-finding phase (Phase II), patients were instructed to maintain a normal sucrose diet while receiving each of four strengths of sucrase [1:100 (A), 1:1000 (B), 1:10,000 (C), and 1:100,000 (D) dilutions] in a random order, for a period of 14 days each; no wash-out period between doses was allowed. Stool frequency, stool consistency measures, GI symptoms were to be recorded on a daily basis. Adverse events were to be collected throughout the trial. During each of the 14 days, all patients received 1 mL of each sucrase dilution with meal and snack. The dose-ranging phase was to last for eight weeks (two weeks on each of the four sucrase doses).

The objective of the study was to assess the effect of YS on breath hydrogen excretion and gastrointestinal symptoms following the ingestion of a large sucrose load, and to establish a dose range of YS which allows the consumption of a normal sucrose containing diet. The mode of administration was oral with each meal or snack added to one ounce of liquid (water, milk, juice, infant formula).

Patients of any age with CSID qualified for this study if they had an appropriate clinical trial history, small intestinal biopsy with measurement of disaccharidase levels showing sucrase activity of <10% of decrease maltase activity, normal villous architecture or only mild villous atrophy of the small bowel, and a positive BHT showing a rise in breath hydrogen of greater than 20 parts per million (ppm) over baseline after an oral sucrose challenge of with a negative lactose breath hydrogen test.

Randomization & Blinding

It is not clear to this reviewer how the randomization for this study was done. However, sponsor's documentation on page 73 of Vol 1.10 (& page 68 of Vol 1.15) indicated numerous violations of pre-established randomization rules: treatment sequences in the database were based on documentation provided by the primary investigator, William R. Trem, M.D. (who was unblinded to treatment assignments); a number of these treatment sequences did not necessarily agree with the order of dates of the BHTs recorded on the case report forms (CRFs). Regarding the dose-response phase of the study, the treatment sequence actually used was different for some patients than the pre-determined randomized sequence. In fact, 11 (73%) patients had unknown randomization treatment sequence (see Table below), or did not receive treatment according to pre-determined randomization scheme; 12 (92%) of the 13 ITT patients were classified as protocol violators by the sponsor (see page 113 of Vol 1.10). Thus, it is clear that the actual conduct of this trial was different from that stipulated in the protocol, and was far from being satisfactory.

Patient Randomized versus Actual Treatment Sequence (Phase II)

Pat #:	1	2	3	4	5	6	7	8	9	10	11	12	13	15	16
RandSeq:	NI	NI	NI	NI	NI	NI	NI	NI	ABCD	NI	ADBC	ACDB	NI	DABC	NI
ActtrtSeq:	ABCD	CBDA	NI	NI	ABCD	NI	NI	ABCD	ABCD	DABC	NI	NI	ABCD	ABCD	ABCD

RandSeq=Randomized Sequence; ActtrtSeq= Actual treatment Sequence; NI= No sequence Identified; A=1:100, B=1:1000, C=1:10000, D=1:100000

1.2 Primary Efficacy Endpoints

The protocol defined primary endpoints are total stools and total symptoms score collected during the dose-ranging phase of the study. The secondary endpoints included peak hydrogen output, peak minus baseline hydrogen output, total breath hydrogen output (area under the curve), as well as individual and total symptom score during the breath hydrogen test phase, and total watery, soft, formed, and hard stools, average daily stools, etc., during the dose-ranging phase of the study.

Note that while one could infer treatment effectiveness from the dose-ranging (phase II) of the study (provided there is a significant dose response: A<B<C<D), in this reviewer's assessment, Phase I of the study presents a better vehicle for assessing treatment effectiveness because of the presence of a placebo arm in this phase of the study. The establishment of a significant dose response trend in Phase II strengthens the findings in Phase. This reviewer's efficacy assessment will, therefore, emphasize both the Phase I (short term) and Phase II (long term) efficacy findings.

1. Breath Hydrogen Test (BHT)

Following three days of a sucrose-restricted diet and a 12-hour fasting interval, each patient underwent two breath hydrogen tests, separated by one week apart. Breath samples were to be collected at baseline, at 30 minutes intervals for a 3-hour period, immediately following ingestion of a standardized sucrose load, for a total of 7 readings. The following measurements were to be derived from these seven breath hydrogen readings:

(i) Peak: the peak of the seven half-hourly breath hydrogen readings
(ii) Total breath H_2 (AUC) - the sum of the six half-hourly (plus baseline) breath H_2 readings
(iii) Peak - Baseline BHT (the difference between the peak and baseline breath H_2 reading).

2. Symptom Evaluations

During the tests, and for eight hours following each breath hydrogen test, patients were to also record their symptom severity [i.e., symptoms of diarrhea, abdominal pain, gas, nausea, and vomiting]; the most severe response for each symptom was to be assessed for each patient.

Patients were required to keep daily diary entries indicating the absence or presence [if present, to record the intensity on a 4-point scale: none (0), mild (1), moderate (2) and severe (3), and the number of stools] of the following GI symptoms: gas, abdominal cramps, bloating, nausea, vomiting during the dose ranging phase of the study.

Symptom severity was scored on a 4-point scale: 0 for none, 1 for mild, 2 for moderate, and 3 for severe; a symptom was described as "mild" if it lasted for less than five minutes and did not interfere with normal activity, "moderate" if it lasted for 5-30 minutes and did interfere with normal activities but resolved rapidly, and "severe" if it lasted for more than 30 minutes and resulted in cessation of normal activities for a prolonged period of time.

Daily averages were calculated for each individual symptom, and for the total symptom score by dividing the period total per patient by the number of days a patient had nonmissing data (total symptoms score is the sum of total responses of all 5 symptoms for all patients).

1.3 Sponsor's Analysis Methods & Results

Patient Population & Sample Size Determination

Patients for inclusion into the study were to be recruited from the clinical practices of the members of the North American Society for Pediatric Gastroenterology and Nutrition (NASPGN). Physicians caring for those patients were to be designated as co-investigators; a pilot study over a 6-12 month period of 20 patients with congenital sucrase-isomatase deficiency (CSID) was anticipated. Sixteen (16) patients were screened, one withdrew before randomization to the dose-ranging phase of the study. Of the fifteen that entered the dose-response phase, 11 (73%) are females.

Two patient populations were identified for analysis by the sponsor: efficacy population (13 patients who received at least one of the four treatment assignments, A, B, C and D in the dose response phase) and safety population (14 patients received either placebo or enzyme); see Table S1.1 below. Of the 13 (77% female, average age 8.2 years) patients in the sponsor's efficacy population, 11 (85%) received all four treatments (A, B, C and D).

Table S1.1/ Patient Disposition & Analysis Data Sets

Screening Phase	Breath H_2 Phase (safety Population)	Dose-Response Phase (Efficacy Population: n=13) Problems				
		Protocol Violators	TSU*	Diary Data	Loading Dose	No BHT
16	14	12 (92%)	5(38%)	7 (54%)	1 (8%)	1 (8%)

TSU=Treatment sequence unknown/different from randomization; #: Sucrase loading dose non-compliance.

The efficacy analysis section of the study report (Vol 1.10, page 84) indicated that negative values for 'peak BHT minus baseline BHT' and 'total breath hydrogen' endpoints were set to zero (0) before the calculation of descriptive statistics. The total breath hydrogen output was calculated as the area under the curve (AUC) using the trapezoidal rule. For the AUC calculation, missing values before the last time point were interpolated while those that occurred at the last time point were assigned the last available reading from the previous time point. Analysis of variance (ANOVA) models with effects for treatment and patient were used to analyze peak, peak minus baseline, and AUC endpoints.

For the analyses of (average of the) individual symptom, the total symptoms score, and total stools endpoints, Wilcoxon signed-rank tests were used to compare placebo and enzyme in the BHT phase, and to compare the two higher concentrations (1:100 and 1:1000 dilutions) and the two lower concentrations (1:10,000 and 1:100,000 dilutions).

No adjustment for multiple primary endpoints was considered. But multiple comparisons were addressed by a step-down procedure. That is, pairwise comparisons among the individual concentrations (A vs B, A vs C, A vs D, B vs C, B vs D and C vs D) were only considered if the

primary comparisons for the two higher (A+B) versus two lower (C+D) concentrations were significant at the .05 α-level. Similarly, pairwise comparisons for the individual symptoms (gas, bloating, nausea, diarrhea, and cramps) were only carried out if the primary comparisons for total symptoms score was significant at the .05 α-level.

The sponsor reported all analysis results as statistically significant (in favor of sucraid) if calculated 2-sided p-values were ≤.05.

Table S1.2 below summaries sponsor's efficacy results for the breath hydrogen test (BHT) data. Note that this reviewer has not been able to locate the efficacy data used by the sponsor to generate the results in this table (see reviewer's Tables R1.1 & R1.2).

Table S1.2/Sponsor's BHT Phase Efficacy Analysis Results (For N=13 Patients)

Endpoint/ Measure	Peak: Means±SE			'Peak - Baseline': Means ±SE			Total (AUC): Means ±SE		
	Sucrase	Placeb	p-value	Sucrase	Placeb	p-value	Sucrase	Placeb	p-value
BH Output	83±33	130±31	001	78±32	109±26	014	7209±2968	13647±3608	001

Data extracted from Sponsor's Table 7.0, pp 119, Vol 1.10

Sponsor's corresponding Wilcoxon-signed-rank test for the symptom data showed no difference between placebo and sucrase 2-sided p-value= **0.750 for diarrhea, 0.625 for gas, 0.750 for bloating, .999 for abdominal cramps, and .672 for total symptoms** (see Table 7.1, pp 120, Vol 1.10 for details).

Table S1.3 below summaries sponsor's dose-ranging (Phase II) efficacy results.

Table S1.3/ Phase II Symptoms Score Analysis Results (P-Values Only For N=13 Patients)

Symptoms/Treatment	A vs B	A vs C	A vs D	B vs C	B vs D	C vs D	A+B vs C+D
Total Symptoms	0.334	0.879	0.020	0.445	0.700	0.492	0.621
Gas	0.057	0.622	0.117	0.656	0.999	0.594	0.820
Bloating	0.750	0.107	0.664	0.188	0.859	0.464	0.793
Nausea	0.750	0.999	0.999	0.875	0.000	0.999	0.750
Cramps	0.250	0.266	0.031	0.625	0.125	0.250	0.125
Total Stools	0.151	0.747	0.832	0.941	0.289	0.589	0.820

Data Extracted from Sponsor's Table 10.0, pp 132, Vol 1.10.

Note that for completeness of result presentation, the individual symptom scores analysis results are presented above even though the primary comparisons on the primary endpoint indicate no significant result. [Sponsor's analyses plan (addressing multiplicity of endpoints) required analyses of individual endpoints only if the total symptoms score primary endpoint was significant at the .05 α-level.]

1.4 Reviewer's Evaluations & Comments

1. Breath Hydrogen Test (BHT) [Diagostic Test]

Sponsor's analysis results summarized in Table S1.2 above indicate that sucrase (enzyme) is significantly more effective than placebo in reducing the expected rise in breath H_2 (following a

sucrose containing meal) as measured by the breath hydrogen (BH) total output derived measurements (i.e., peak BH, difference between peak and baseline BH, and AUC BH). For all these three measurements, sponsor's analysis of variance (ANOVA) results (with effects for treatment and patients) indicate significant sucrase advantage over placebo. However, this reviewer's analysis results (data from SAS data set CV_BHT.XPT contained in the NDA) summarized in Tables R1.1 and R1.2 below (based on ANCOVA model with effect for treatment and baseline BH, or simply by a simple t-test) indicate no significant sucrase advantage over placebo in controlling the rise in BH following a sucrose containing meal. Note that there is a significant baseline BH effect for all comparisons (2-sided p-value $\leq$ .005) by the analysis of covariance (ANCOVA) model; thus least squares means (LSMEANS) are more appropriate than ordinary means (i.e., means unadjusted for baseline BH imbalance) as in this case.

Thus, contrary to sponsor's significant findings favoring sucrase in the reduction of breath hydrogen concentration, both analysis results by this reviewer summarized in Tables R1.1 and R1.2 above indicate no significant difference between placebo and sucrase regarding all three breath hydrogen output derived measurements: peak, peak - Baseline, and cumulative breath hydrogen concentration.

Table R1.1/ Phase I ANCOVA Model W/Treatment & Baseline BH Effect (For N=14 Patients)

Response	Peak BH_2			Peak - Baseline			Cumulative BHT		
	LSMEANS*		2P-val*	LSMEANS*		2-P-val*	LSMEANS*		2P-val*
	Placebo	Enzyme	P-value	Placebo	Enzyme	P-value	Placebo	Enzyme	p-value
	97.5	102.8	0.874	86.3	91.6	0.874	9472	9706	0.927

Note: Data from CV_BHT.XPT Data set File;
*: adjusted for baseline imbalance in BH (which is highly significant: 2p≤.005) by ANCOVA model.

Table R1.2/ Comparisons of Breath Hydrogen Test Levels by Simple T TEST: Placebo vs Enzyme#

Endpoint	Treatment	N@	Mean	Plac - Enz	95% CI	T-test 2P-Val
1. Baseline BHT	Placebo	14	18.1	13.7		0.053
	Enzyme	14	4.4			
2. Peak BHT	Placebo	14	122.9	45.5	(-17.1, 108)	0.254
	Enzyme	14	77.4			
3. (Peak - Baseline) BHT		14	104.8	31.8	(-30.8, 94.3)	0.372
	Enzyme	14	73.0			
4. Cumulative BH	Placebo	14	12417	5707	(-176, 1159)	0.174
	Enzyme	14	6710			

From 'CV_BHT.XPT' SAS data set file; #: 95% CI by Dunnett; @: Pat #4 w/ missing data excluded from analyses;

2. Breath Hydrogen Phase Symptom Data [Efficacy Assessment]

This reviewer's analysis results for the breath hydrogen phase symptom data [based on sponsor's SAS data set files CV_BHT (for maximum symptom severity scores) and CV_BSYMP (for differences in symptom severity scores between sucrase and placebo)] are consistent with those of the sponsor; that is, sucrase has no advantage over placebo in reducing gastrointestinal symptoms secondary to sucrose malabsorption following a sucrose containing meal (see reviewer's Table R1.3 below).

Table R1.3/ Phase 1 Symptom Assessment ANOVA Results (For N=14 Patients)

Endpoint	Treatment	Maximum Score [Data From CV_BHT.XPT] N@	Mean	Plac-Enz 2p (ANOVA)		[Data From CV_BSYMP.XPT] N	Pla-Enz	W-S-R 2p
Total Symptom		13	3.08	0.46	0.737	13	.46	0.832
		13	2.62					
1. Diarrhea	Placebo	13	1.00	-0.08	0.879	13	-.08	1.00
	Enzyme	14	1.08					
2. Gas	Placebo	13	0.69	0.07	0.862	13	.08	1.00
	Enzyme	13	0.62					
3. Bloating	Placebo	13	0.54	0.08	0.834	13	.08	0.938
	Enzyme	13	0.46					
4. Cramps	Placebo	13	0.85	0.39	0.346	13	.39	0.313
	Enzyme	13	0.46					

@: pt #s3&4 w/ missing obs not included in analyses; W-S-R=Wilcox Signed-Rank.

Dose-Finding Symptom Results [Phase II Data]

Sponsor's symptom data results (summarized in Table S1.3 above) indicate no significant dose differential sucrase among the four doses taken under normal dietary conditions as measured by the total symptoms score primary endpoint; the primary treatment comparison (A+B vs C+D) show no advantage of the two higher (A, B) over the two lower (C, D) dose concentrations (A=1:100, B=1:1000, C=1:10,000, D=1:100,000 sucrase dilutions). This reviewer's analysis results (summarized in Table R1.4 below) are consistent with those by the sponsor.

Table R1.4/ Primary Dose Comparisons: A+B vs C+D

Endpoint	Mean Difference	W-S-R t-test 2-Sided P-Value
Average Stools	1.23	0.820
Total Symptoms	-2.0	0.621

W-S-R=Wilcoxon-Signed-Rank Test

Replication Of Sponsor's Diagnostic & Efficacy Results:

In faxed responses by the sponsor (8/13/97 & 9/3/97) on this reviewer's requests for explanation on the comparability of the efficacy data used in the sponsor's analyses (see Table S1.2 for pertinent results summary), and those used in this reviewer's analyses (sponsor submitted SAS data set file CV-BHT), the sponsor indicated that *"the raw breath hydrogen data (BT data) was used to generate the statistics on the first two pages of Table 7.0. The created variable file (CV_BHT) was used to generate the statistics on the third and fourth pages of Table 7.0."*

The table below summarizes the statistics generated from SAS data set *BT.XPT* (top 2 rows) and SAS data set *CV_BHT.XPT* (bottom 2 rows) mentioned in the sponsor's faxed memos. Note that the summary statistics in this table (means and SD's) are different from those in Table 7.0 Vol 1.10 (page 117) by the sponsor. In fact those from CV_BHT.XPT are a little closer but still different (especially as measured by the SD).

Mean Breath Hydrogen Output Overtime From SAS Data Set BT.XPT

	Baseline		30 Mins		60 Mins		90 Mins		120 Mins		150 Mins		180 Mins	
	N	Mean±SD	N	Mean±SD	N	Mean±SD	N	Mean±SD	N	Mean±SD	N	Mean±SD	N	Mean±SD
Plac	14	16.0±25	14	20.1±28	14	44.0±56	13	70.4±75	14	79.8±98	13	80.7±111	13	83.8±118
Enzy	14	6.7± 7	14	13.9±22	14	39.5±38	13	55.3±62	14	77.8±84	13	77.4±104	13	80.5±107
Pla	14	18.1±25	14	27.8±31	14	63.0±53	14	78.2±73	14	99.6±98	14	90.8±104	14	91.1±111
Enzy	14	4.4± 5	14	6.1± 6	14	20.5±28	14	43.6±56	14	58.1±82	14	62.1±106	14	61.5±108

II. STUDY DESIGN

2.1 Protocol #OMC-SUC-2 (conducted 4/4/92 to 11/7/96)

This was a two-phased, randomized, multi-center, multi-dose, (patient) blinded, crossover study to assess sucrase enzyme replacement in patients with congenital sucrase-isomaltose deficiency (CSID). The first phase (Phase I) was a diagnostic phase [by a breath hydrogen test (BHT)] and consisted of three single-dose treatments [placebo, yeast sucrase (YS) and YS plus milk arm] which were to be assigned to patients in a random order; the second phase (Phase II) was a dose-response phase consisting of four consecutive 10-day treatments [full-strength YS, 1:10 dilution, 1:100 dilution, and 1:1000 dilution] which were to be administered to each patient in a random sequence.

The objective of the study was to assess the effect of yeast-derived liquid sucrase in treating patients of all ages with congenital sucrase-isomaltose deficiency (CSID) regarding breath hydrogen excretion following the ingestion of a large sucrose load (Phase I), and to establish a dose range of YS which allows the consumption of a normal sucrose containing diet by CSID patients without the associated gastrointestinal symptoms (Phase II). The mode of administration was oral, immediately five minutes after the beginning of each meal, added to 2-4 ounces of water.

Patients of all ages with CSID qualified for this study if they had an appropriate clinical trial history, small intestinal biopsy with measurement of disaccharidase levels showing sucrase activity of <10% of controls with normal lactase levels and normal or decreased maltase activity, normal villous architecture, and a normal lactose breath H_2 test; treatment duration was 14 days for the BHT phase (3 single doses given 7 days apart), and 40 days for the dose-ranging phase (10 days on each of the 4 decrease doses).

Prior to the BHT phase, patients were to be evaluated to confirm CSID diagnosis and trial eligibility; a study dietician was to instruct the patients on the use of a (sucrose-free) diet and symptom history diary. Patients' 1-week diary recordings of their diet, stool, and gastrointestinal symptom patterns (week prior to BHT) were to serve as baseline for the breath H_2 test.

During the BHT phase, patients were to undergo three randomized, (patient) blinded breath hydrogen tests (BHTs), separated one week apart of sucrose and starch restricted diet. The breath tests were to be carried out for three hours, immediately following ingestion of sucrose, and

breath samples obtained every 30 minutes. The tests were: (i) 2 mg/kg body weight of sucrose followed immediately by active YS in water, (ii) 2 mg/kg body weight of sucrose followed immediately by water and no YS (placebo), and (iii) 4.0 mL/kg of whole cow's milk followed by 2 mg/kg body weight of sucrose load and active YS in water. The BHTs were to be conducted following a 12-hour fast and 3-day sucrose -free/low starch diet. Subjects who were on antibiotics within one week of the tests were to be excluded.

Subjects were to record (in their diaries) stool frequency and consistency, and symptoms of gas, bloating, nausea, vomiting, and cramps during the 3-hour breath test, and for 24 hours following each breath test; symptoms were to be recorded by episode frequency and ranked for severity (0=none, 1=mild, 2=moderate, and 3=severe).

After completion of the breath hydrogen test phase, and following a baseline 1-week sucrose-free/low starch diet period, patients were to enter a dose-ranging phase. During the dose-ranging phase, patients were instructed to maintain a normal sucrose diet while receiving each of four strengths/concentrations of sucrase [(1) full-strength , (2) 1:10, (3) 1:100, and (4) 1:1000 dilution] in a (patient) blinded random order for a period of 10 days each; no wash-out period between doses was allowed. Stool frequency, stool consistency measures, GI symptoms were to be recorded on a daily basis. Adverse events were to be collected throughout the trial.

Randomization & Blinding

It is not clear to this reviewer how the randomization for this study was done. However, sponsor's documentation on page 20 of Vol 1.11 (& page 68 of Vol 1.15) indicated numerous violations of pre-established randomization rules: treatment sequences in the database were based on documentation provided by the **same primary investigator** (as in study SUC-1), William R. Trem, M.D. (who was unblinded to treatment assignment); these treatment sequences did not necessarily agree with the order of dates of the BHTs recorded on the case report forms (CRFs). The protocol stipulation that the BHT treatment sequence be randomized was not followed (the yeast plus milk was always given as the final test (see page 332 of Vol 1.11). Regarding the dose-response phase of the study, the study report (page 20 Vol 1.11) indicated that patients were randomly assigned to one of 24 possible treatment sequences (this could not be located in the NDA and/or confirmed by this reviewer); in 6 cases, actual treatment sequences were different from the pre-determined randomized sequences, and one case could not be determined (see page 330 of Vol 1.11). There were a total of 20 patients with one or more protocol violations [9 trial medication non-compliance, 8 baseline breath hydrogen output $\geq$10 ppm, 7 with treatment sequences different from randomized sequences, 5 sucrose dosage non-compliance, and 3 visit non-compliance]. Thus, as in study SUC-1, the actual conduct of this trial was far from being satisfactory.

2.2 Primary Efficacy Endpoints

The protocol defined primary endpoints are total stools and total symptoms score collected during the dose-ranging phase of the study. The secondary endpoints included peak hydrogen output, peak minus baseline hydrogen output, total breath hydrogen output (area under the

curve), as well as individual and total symptom score during the breath hydrogen test phase, and total watery, soft, formed, and hard stools, average daily stools, etc., during the dose-ranging phase of the study.

Note that while one could infer treatment effectiveness from the dose-ranging (phase II) of the study (provided there is a significant dose response: A<B<C<D), in this reviewer's assessment, Phase I of the study presents a better vehicle for assessing treatment effectiveness because of the presence of a placebo arm in this phase of the study. The establishment of a significant dose response trend in Phase II strengthens the findings in Phase. This reviewer's efficacy assessment will, therefore, emphasize both the Phase I (short term) and Phase II (long term) efficacy findings..

1. Breath Hydrogen Test (BHT)

Following three days of a sucrose-restricted diet and a 12-hour fasting interval, each patient underwent two breath hydrogen tests, separated by one week apart. Breath samples were to be collected at baseline, at 30 minutes intervals for a 3-hour period, immediately following ingestion of a standardized sucrose load, for a total of 7 readings. The following measurements were then derived from these seven breath hydrogen readings:

(i) Peak: the peak of the seven half-hourly breath hydrogen readings
(ii) Total breath H_2 (AUC) - the sum of the six half-hourly (plus baseline) breath H_2 readings
(iii) Peak - Baseline BHT (the difference between the peak and baseline breath H_2 reading).

2. Symptom Evaluations

During the tests, and for eight hours following each breath hydrogen test, patients were to also record their symptom severity [i.e., symptoms of diarrhea, abdominal pain, gas, nausea, and vomiting]; the most severe response for each symptom was to be assessed fro each patient.

Patients were required to keep daily diary entries indicating the absence or presence [if present, to record the intensity on a 4-point scale: none (0), mild (1), moderate (2) and severe (3), and the number of stools] of the following GI symptoms: gas, abdominal cramps, bloating, nausea, vomiting during the dose ranging phase of the study.

Symptom severity was scored on a 4-point scale: 0 for none, 1 for mild, 2 for moderate, and 3 for severe; a symptom was described as "mild" if it lasted for less than five minutes and did not interfere with normal activity, "moderate" if it lasted for 5-30 minutes and did interfere with normal activities but resolved rapidly, and "severe" if it lasted for more than 30 minutes and resulted in cessation of normal activities for a prolonged period of time.

Daily averages were calculated for each individual symptom, and for the total symptom score; by dividing the period total per patient by the number of days a patient had nonmissing data (total symptoms score is the sum of total responses of all 5 symptoms for all patients).

2.3 Sponsor's Analysis Methods & Results

Patient Population & Sample Size Determination

Patients for inclusion into the study were to be recruited from the clinical practices of the members of the North American Society for Pediatric Gastroenterology and Nutrition (NASPGN). Physician-members of the American Gastroentrologic Association (AGA) and the American College of Gastroentrology (ACG) were to be informed also.

Physicians caring for those patients were to be designated as co-investigators; a pilot study over a 6-12 month period or 20 patients with congenital sucrase-isomatase deficiency (CSID) was anticipated. Forty (40) patients from two sites (Hartford and Duke) were screened, 37 were randomization to the dose-ranging phase of the study, and 28 were included in the sponsor's efficacy population.

Two patient populations were identified for analysis by the sponsor: efficacy population (28 patients who received at least one of the four treatment assignments in the dose ranging phase of the study) and safety population (28 patients received either placebo, enzyme, or enzyme/milk); see Table S2.1 below. Of the 28 patients in the efficacy population, 43% were male, the mean age was 4.1 years, and the mean weight was 16.6 kg.

Table S2.1/ Patient Disposition & Analysis Data Sets

Screening Phase:		Breath H_2 Phase:		Dose-Response:		Efficacy Population	
Hartford	Duke	Hartford	Duke	Hartford	Duke	Hartford	Duke
28	12	24	10	24	13	20	8

The efficacy analysis section of the study report indicated that negative values for 'peak BHT minus baseline BHT' and 'total breath hydrogen' endpoints were set to zero (0) before the calculation of descriptive statistics. The total breath hydrogen output was calculated as the area under the curve (AUC) using the trapezoidal rule. For the AUC calculation, missing values before the last time point were interpolated while those that occurred at the last time point were assigned the last available reading from the previous time point. Analysis of variance (ANOVA) models with effects for treatment and patient were used to analyze peak, peak minus baseline, and AUC endpoints.

For the analyses of (average of the) individual symptom, the total symptoms score, and total stools endpoints, Wilcoxon signed-rank tests were used to compare placebo and enzyme in the BHT phase, and to compare the two higher concentrations (full strength and 1:10 dilutions) and the two lower concentrations (1:100 and 1:1000 dilutions).

No adjustment for multiple primary endpoints was considered. But multiple comparisons were addressed by a step-down procedure (as discussed in section 1.3 above). The sponsor reported all analysis results as statistically significant (in favor of sucraid) if calculated 2-sided p-values were $\leq .05$.

Table S2.2 below summaries sponsor's efficacy results. Note that sponsor's ANOVA models with effects for treatments, sites, and patients indicate significant overall treatment effect (2-sided p-value $\leq .002$); there was no significant site effect (2-sided p-value$\geq .290$) for all three derived measures of breath hydrogen output. Note that this reviewer has not been able to locate the efficacy data used by the sponsor to generate the results summarized in this table.

Table S2.2/Sponsor's Efficacy Population Analysis Results: Breath Hydrogen Test Phase Comparisons

Endpoint/ Measure	Peak: Means± SE			'Peak - Baseline': Means ± SE			Total BH (AUC): Means ± SE		
	Placebo	Sucrase	Sucrase/Milk	Placebo	Sucrase	Sucrase/Milk	Placebo	Sucrase	Sucrase/Milk
N:	27	27	26	27	27	26	27	27	26
BH_2 Output	62±11	34±7	18±4	56±11	30±7	14±4	6285±1105	3000±587	1767±378
2-p vs Plac	-	.009	.001		.015	.001		.001	.001
2-p vs Sucr		-	.219		-	.194		-	.305

Data from sponsor's Table 7, pp 86-89, Vol 1.11; Means from ANOVA models with effects for site, treatment and patient; BH=Breath H_2.

Sponsor's corresponding (Wilcoxon-signed-rank test) 2-sided p-values for the symptom data are summarized below:

Table S2.2a/Breath Hydrogen Test Phase Symptom Data (P-values Only For N=27 Patients)

	Diarrhea	Gas	Bloating	Cramps:		Total Symptoms
Plac vs Sucrase	**.001**	.052	**.012**	**.014**	⇦	**.001**
Placebo vs Milk/Sucrase	**.001**	**.014**	.057	**.016**	⇦	**.001**
Sucrase vs Sucrase/Milk	.848	.672	.521	.865	⇦	.954

Extracted from sponsor's Table 7.1, pp 91, Vol 1.11; **Boldface** indicates significant findings even after adjustment for multiple symptoms.

Dose Response Phase

Table S2.3 below summaries sponsor's dose-ranging (phase II) efficacy results.

Table S2.3/ Phase II Total Symptoms Score & Total Stools Primary Endpoints Analysis Results (P-values Only)

Symptoms/Treatment	1 vs 2	1 vs 3	1 vs 4	2 vs 3	2 vs 4	3 vs 4	1+2 vs 3+4
Total Symptoms (ANOVA Model)*	0.992 (0.802)	0.020 (0.175)	**0.009** (0.009)	0.035 (0.309)	0.034 (0.013)	0.096 (0.155)	**0.003** (0.007)
Gas	0.356	0.753	0.049	0.796	0.067	0.022	0.042
Bloating	0.999	**0.048**	**0.018**	**0.016**	**0.023**	0.840	**0.006**
Nausea	0.999	0.500	0.500	0.500	0.500	0.999	0.250
Vomiting	0.500	0.250	0.250	0.999	0.250	0.375	0.250
Cramps	0.723	0.025	0.050	0.147	0.197	0.967	0.028
Total Stools (ANOVA Model)*	0.296 (0.123)	**0.001** (0.003)	**0.006** (0.019)	**0.004** (0.198)	0.121 (0.384)	0.107 (0.648)	**0.001** (0.007)

Note:1=Sucrase full strength, 2=1:10, 3=1:100, 4=1:1000 dilution; data from Table 10.0, page 100 of Vol 1.11
()*: model with carryover, period, site treatment and patient [no significant site, period & carryover (except for stools) effect]

Except for bloating, sponsor's analysis results at the individual time points summarized in the table below indicate no significant dose differential.

Table S2.3a/Sponsor's Individual Daily & Average Symptoms Score Analysis Results For Overall Treatment Effect (P-values Only)

Symp/Days	1	2	3	4	5	6	7	8	9	10	Average
Gas Severity	.423	.957	.716	.433	.420	.597	.454	.773	.419	.454	.042
Bloating	.065	**.010**	.160	.057	.094	.453	**.014**	**.010**	**.012**	.051	**.006**
Nausea	.999	.999	.438	.999	.999	.999	.414	.999	.999	.414	.250
Vomiting	.999	.321	.343	.343	.414	.999	.999	.999	.999	.999	.250
Cramps	.480	.475	.874	.642	.752	.587	.097	.527	.545	.514	.028

Data from Appendices 5.0 - 5.1 of Vol 1.11; **Boldface** indicates significance at the .05 level; underline indicates borderline at the .05 level.

2.4 Reviewer's Evaluations & Comments

Breath Hydrogen Test (BHT) [Diagostic Phase]

Sponsor's analysis results summarized in Table S2.2 above indicate that sucrase (enzyme) is significantly more effective than placebo in reducing the expected rise in breath hydrogen (BH) as measured by BH total output derived measurements (i.e., peak BH, difference between peak and baseline BH, and cumulative/AUC BH). For all three derived measures, sponsor's analysis of variance (ANOVA) results (with effects for treatment and patients), indicate significant sucrase advantage over placebo. In particular, the efficacy results indicate consistent significant improvements favoring sucrase alone, or sucrase with milk over placebo, and a numerical trend favoring sucrase with milk over sucrase alone for all three derived measures.

Table R2.1/ Phase I ANCOVA Model (W/Treatment & Baseline BH) Results

Response	Overall LSMEANS*			2_Sided P-values (Based on SS3)		
	Pla	Enzy	Enz/Mil	Pl v En	Pl v En/Ml	En v En/Ml
Peak BH_2 Output	57.5	31.49	19.3	0.045	0.002	0.143[a]
Peak - Baseline BHT	53.1	26.8	4.7	0.043	0.002	0.131[a]
Cumulative BHT	5750	2758	1939	0.014	0.001	0.226[a]

Note: Data from CV_BHT.XPT Data set File; except for enzyme vs enzyme/milk cumulative BH comparison, there is numerical but no significant baseline BH (see Table R2.2 below).
a p-values in favor of enzyme/milk.
*: Lsmeans obtained from ANCOVA model with treatment & baseline BH effects.

Table R2.2/ Phase I Comparisons of Breath Hydrogen Test Levels by Studentized Test

Endpoint	Placebo	Enzyme	Enzyme/Milk
N@	30	30	29
1. Baseline BH: Mean±SD*	6.7±13.4	4.5±3.9	3.7±3.9
Mean Difference From Plac (2p)	-	2.2 (.389)	3.0 (.250)
From Enzyme		-	0.8 (.435)
2. Peak BHT: Mean±SD*	57.7±57.5	31.2±37.6	19.1±23.2
Mean Difference From Plac (2p); [95%CI]	-	26.5 (.039) [1.4,52]	38.6 (.001); [16,62]
From Enzyme (2p); [95%CI]		-	12.1 (.145); [-4.3,28.4]
3. (Peak-Base) BHT Mean±SD*	52.1±56.9	27.1±37.8	15.5±23.3
Mean Difference From Plac (2p); [95%CI]	-	25.0 (.050) [.02,50]	36.6 (.002); [14,59.5]
From Enzyme (2p); [95%CI]		-	11.6 (.162); [-4.8,28.1]
4. Cumulative BH Mean±SD*	5826±5635	2736±2997	1882±2218
Mean Difference From Plac (2p); [95%CI]	-	3090 (.010) [758,5430]	3944(.001); [1697,6192]
From Enzyme (2p); [95%CI]		-	854 (.220); [-525,2233]

Data from SAS data set file 'CV_BHT.XPT' submitted by sponsor (see pages 158-160 Vol 1.15);
*: Lsmeans/Means obtained from ANCOVA model with treatment & baseline BH effects.

Though not as strong as those by the sponsor, this reviewer's analysis results summarized in Table R2.1 above for ANCOVA model with effect for treatment and baseline BH main effect, and in Table R2.2 above for simple t-tests also indicate both sucrase alone and sucrase given with milk are superior to placebo are consistent with those by the sponsor.

Phase I Symptom Data [Efficacy Assessment]

This reviewer's analysis results based on sponsor edited data [contained in sponsor edited SAS data set file CV_BSYMPT.XPT for treatment differences in symptom severity scores] and those based on data sets contained in SAS data set file CV_BHT.XPT for maximum symptom severity scores are consistent with sponsor's findings regarding total symptom severity endpoint. That is, both enzyme alone and enzyme given with milk are superior to placebo in the reduction of GI symptom severity as measured by total symptom score. For the individual symptom severity scores, however, this reviewer's analysis results (based on *CV_BHT.XPT*) indicate consistent sucrase alone superiority over placebo but no sucrase with milk advantage over placebo (except for the diarrhea symptom severity scores); see Table R2.3 below.

As in the sponsor's analysis, this reviewer's analysis results further indicate that there is no significant difference between sucrase alone and sucrase given with milk in reducing gastrointestinal symptom severity secondary to sucrose malabsorption following a sucrose containing meal.

Table R2.3/ Phase 1 Symptom Assessment Analysis Results [From Three Different SAS Data Sets]

		Maximum Score[1]			Sponsor Edited Data Set[2]			
*Difference	Endpoint	N	Mean[a]	t-2P	N	Mean	T*	W-S-R
Plac- Enz	Diarrhea	29,29	1.00	0.001	27	1.148	0.0001	0.001
Plac-Milk/Enz		29,27	0.99	0.001	26	1.038	0.0001	0.001
Enzy-Milk/Enz		29,28	-0.02[b]	0.927	26	0.038	0.8517	0.988
	Gas	29,29	0.48	0.043	27	0.444	0.0431	0.053
		29,27	0.38	0.125	25	0.560	0.0101	0.014
		29,27	-0.10[b]	0.587	25	-0.120	0.5426	0.672
	Bloating	29,29	0.59	0.017	27	0.630	0.0042	0.006
		29,27	0.42	0.092	25	0.480	0.0559	0.057
		29,27	-0.16[b]	0.392	25	-0.160	0.4907	0.522
	Cramps	29,29	0.66	0.008	27	0.704	0.0065	0.009
		29,27	0.60	0.029	25	0.640	0.0126	0.016
		29,27	-0.06[b]	0.761	25	-0.080	0.7314	0.865
Total Symptoms		29,29	2.72	0.001	27	2.926	0.0001	0.001
		29,27	2.63	0.002	26	2.808	0.0002	0.001
		29,28	-0.30[b]	0.593	26	-0.269	0.6541	0.992

*: denotes parametric t-test results; W-S-R=Wilcoxon-Signed-Rank t-test; @: patients w/non-missing data;
1: From SAS Data set CV_BHT.XPT; 2: CV_BSYMP.XPT (used in sponsor's analyses).
b: -ve mean difference indicates at least a numerical enzyme alone edge over enzyme/milk.

Phase II (Dose-Finding) Symptom Data Results [Based On Sponsor Edited Data]

For the primary comparison, doses 1 (full-strength sucrase) + 2 (1:10 dilutions) vs doses 3 (1:100 dilutions) + 4 (1:1000 dilutions) , sponsor's dose-ranging symptom data analysis results (summarized in Table S2.4 above) indicate a significant combined doses 1 and 2

advantage over doses 3 and 4 for both primary endpoints, total stools and total symptoms score. The pairwise dose comparisons also indicate that sucrase given at full strength (dose 1) is superior to dose 3 (1:100 dilutions) and dose 4 (1:1000 dilutions) but not to dose 2 (1:10) as measured by the two primary endpoints. Similarly dose 2 is shown to be superior to doses 3 and 4, but that dose 3 is not different from dose 4. This reviewer's analysis results based on sponsor edited data set (summarized in Table R2.4 below) are consistent with those by the sponsor.

However, except for bloating (and to a limited extent, cramps), this reviewer's analysis results (based on SAS data set *CV_DRES3.XPT*) indicate no significant dose differential for the individual symptom severity score (see Table R2.4 below). Also sponsor's analysis results summarized in Tables S2.3 (for average severity scores over the Phase II 10-day treatment period) and S2.3a (for daily severity scores during the Phase II 10-day treatment period) above are in agreement with this reviewer's findings regarding individual symptom severity scores. That is, of the five (5) symptoms evaluated, only bloating shows significant consistent dose differential favoring full strength sucrase or 1:10 diluted sucrase strength.

Table R2.4/ Dose Comparisons on (Treatment) Mean Differences [Phase II Symptom Data]*

Symptom Severity	1+2 vs 3+4 Mean	2P*	1 vs 2 Mean(2P*)	1 vs 3 Mean(2P*)	1 vs 4 Mean(2P*)	2 vs 3 Mean(2P*)	2 vs 4 Mean(2P*)	3 vs 4 Mean (2P*)
Total Stools:	**5.37**	**0.001**	**-3.58 (.297)**	**-7.56 (.001)**	**-6.07 (.006)**	**-3.89 (.004)**	**-2.74 (.122)**	**1.39 (.107)**
Total Symptom:	**6.54**	**0.003**	**1.65 (.992)**	**-3.59 (.020)**	**-7.26 (.009)**	**-5.04 (.035)**	**-8.85 (.034)**	**-3.61 (.096)**
Individual (Components of Total) Symptoms Score Results:								
Bloating:	**0.24**	**0.006**	0.02 (1.00)	-0.20 (.048)	-0.22 (.018)	-0.23 (.016)	-0.25 (.023)	-0.02 (.840)
Cramps:	**0.20**	**0.028**	0.07 (.723)	-0.13 (.025)	-0.19 (.050)	-0.20 (.148)	-0.26 (.197)	-0.06 (.967)
Gas:	**0.16**	**0.042**	0.07 (.356)	0.00 (.753)	-0.24 (.050)	-0.05 (.796)	-0.29 (.067)	-0.24 (.022)
Nausea:	**0.04**	**0.250**	0.02 (1.00)	-0.01 (.500)	-0.04 (.500)	-0.03 (.500)	-0.06 (.500)	-0.03 (1.00)
Vomiting:	**0.02**	**0.250**	-0.01 (.500)	-0.01 (.250)	-0.04 (.250)	0.00 (1.00)	-0.03 (.250)	-0.03 (.375)

*: See Attachment 2.2 (for alternative t-test); note: 1=Full-strength, 2=1:10, 3=1:100, 4=1:1000 dilutions; 2p=2-sided Wilcox signed-rank test; Averages taken over 10-day Phase II treatment period; **Bold**: indicates primary endpoints/comparisons; Data set from CV_DRES3.XPT.

Replication Of Sponsor's Diagnostic & Efficacy Results:

Note that as in study SUC-1, this reviewer was not able to locate some of the data sets used in the sponsor's analyses, especially for the breath hydrogen test (Phase I) data. For example, this reviewer could not replicate sponsor's Table 7.0 Vol 1.11 (pages 86-87) results.

In faxed responses by the sponsor (8/13/97 & 9/3/97) on this reviewer's requests for explanation on the comparability of the efficacy data used in the sponsor's analyses (see Table S2.2 for pertinent results summary), and those used in this reviewer's analyses (sponsor submitted SAS data set file CV-BHT), the sponsor indicated that *"the raw breath hydrogen data (BT data) was used to generate the statistics on the first two pages of Table 7.0. The created variable file (CV_BHT) was used to generate the statistics on the third and fourth pages of Table 7.0."*

The table below summarizes the statistics generated from SAS data set *BT.XPT* (top 3 rows) and SAS data set *CV_BHT.XPT* (bottom 3 rows) mentioned in the sponsor's faxed memos. Note that

the summary statistics in this table (means and SD's) are different from those in Table 7.0 Vol 1.11 (pages 86-87) by the sponsor.

Mean Breath Hydrogen Output Overtime From SAS Data Set BT.XPT

	Baseline		30 Mins		60 Mins		90 Mins		120 Mins		150 Mins		180 Mins	
	N	Mean±SD	N	Mean±SD	N	Mean±SD	N	Mean±SD	N	Mean±SD	N	Mean±SD	N	Mean±SD
Plac	31	3.9± 3	31	17.6±26	31	28.3±46	31	33.1±41	31	39.2±43	29	40.4±43	30	36.9±45
Enzy	33	7.2±13	33	8.4±11	33	12.5±15	32	17.7±23	33	21.5±26	32	25.8±25	32	20.0±23
Enz/Mil	29	3.7± 4	29	14.7±22	29	10.6±13	29	10.3±12	28	11.4±13	27	9.6±13	27	9.2±15
Plac	30	6.7±13	30	17.6±26	30	30.3±46	30	35.8±35	30	44.4±44	30	44.8±38	30	38.8±43
Enzy	30	4.5± 4	30	9.6±11	30	12.2±14	30	10.8±22	30	19.2±221	30	19.4±25	30	19.6±25
Enz/Mil	29	3.7± 4	29	14.7±22	29	10.6±13	29	10.3±12	28	11.4±13	28	9.8±13	28	9.7±15

IV. SUMMARY OF RESULTS THE TWO ACROSS STUDIES

It should be noted that this reviewer has not been able to replicate some of the sponsor's derived statistics (especially for the breath hydrogen test efficacy data) from both sources of data mentioned in the faxed responses to this reviewer's requests for such data sets. That sponsor's derived summary statistics seem to indicate that a maximum of 28 patients in the breath hydrogen test phase (Phase I of study SUC-2) were included in the analyses (see Table S2.2 above). This reviewer's analyses (based on the available data sources, CV_BHT or BT.XPT) indicate a maximum of 33 and a minimum of 27 patients in Phase I of study SUC-2 had complete Phase I data. While this may not satisfactorily explain the source of the disagreement between this reviewer's and the sponsor's derived statistics, it seems to suggest that the results could not have come from the same patient data base.

Furthermore, sponsor's documentation for both studies indicated treatment sequences in the database were based on documentation provided by the **same** primary investigator, William R. Trem, M.D. (who was unblinded to treatment assignments); these treatment sequences did not necessarily agree with the order of dates of the BHTs recorded on the case report forms (CRFs); Furthermore, the report indicated that a number of patients had unknown randomization treatment sequence, or did not receive treatment according to pre-determined randomization scheme. How these patients were handled in the efficacy analyses is not clear to these reviewer.

Based on the available efficacy evidence as summarized below, however, the following conclusions can be drawn:

A. Breath Hydrogen Test [Diagnostic Parameters]

1. For study SUC-1, sucrase enzyme has no advantage over placebo in reducing breath hydrogen concentration as measured by peak breath hydrogen, difference between peak and baseline breath hydrogen, and cumulative [or area under the curve (AUC)] breath hydrogen.

2. For study SUC-2, the efficacy data indicate that sucrase enzyme or sucrase enzyme given with milk is superior to placebo in reducing breath hydrogen concentration as measured by

peak breath hydrogen, difference between peak and baseline breath hydrogen, and cumulative [or area under the curve (AUC)] breath hydrogen.

3. Compared to a sucrase with (whole cow) milk combined administration, the efficacy data indicate no sucrase alone advantage over the combination in the diagnosis of CSID.

B. Phase I Symptom Severity [Efficacy Parameters]

1. For study SUC-1, the efficacy data indicate that sucrase enzyme has no advantage over placebo in reducing gastrointestinal (GI) symptom severity following a sucrose containing meal.

2. For study SUC-2, the efficacy data support sucrase superiority over placebo following a sucrose containing meal. With regard to sucrase with milk, efficacy is supported by the total symptom efficacy result, primarily due to strong diarrhea symptom efficacy results. Furthermore, the efficacy data indicate that there is no significant difference between sucrase alone and sucrase given with milk.

C. Dose Response [Phase]

1. Note that doses A (1:100) and B (1:1000) in study SUC-1 are identical to doses C and D in study SUC-2; and that doses C (1:10,000) and D (1:100,000) in study SUC-1 are not comparable to doses A (full strength) and B (1:10 dilution) in study SUC-2.

2. For study SUC-1, the efficacy data show no dose differential among the four doses. The primary dose comparison (A+B) versus (C+D) indicate null differentials as measured by total stools and total symptoms.

3. For study SUC-2, the efficacy data indicate a dose differential for the primary dose comparison (A+B) versus (C+D) favoring (A+B) as measured by total stools and total symptoms. However, except for bloating, the data indicate no significant primary comparative differential with respect to the individual parameters after adjustment for multiple endpoints. Furthermore, as in study SUC-1, the data indicate no dose differential between doses A and B.

Summary of Designs and Efficacy Results

Study Protoc	SUC-1: n=16 (12 F/4 M); Efficacy n=13 (10 F/3 M), Ages 8mo-28yr	SUC-2: Screened n=40 (20 F/20 M); Efficacy n=28 (16 F/12 M), Ages 5mo-10yr
Objective	To assess effect of yeast-derived liquid sucrase in patients of all ages with congenital sucrase-isomaltose deficiency (CSID) regarding breath hydrogen excretion following ingestion of a large sucrose load, and to establish a dose range of yeast sucrase that allows consumption of a normal sucrose containing diet by CSID patients without the associated gastrointestinal symptoms.	
Study Type	2-Phased, R, Patient-Blinded, crossover, SC (SUC-1, 16 screened, 14 in Ph2), MC (SUC-2, 40 screened, 37 in Ph2), DR.	
Dosing	Ph1: P, E; Ph2:1:100,1:1000,1:10000, 1:100000 Dilutions	Ph1: P, E, EM; Ph2:Full Strength,1:10,1:100, 1:1000 Dilutions
1st Efficacy Endpoints	Total/Average Symptoms Score, Total/Average stools [both evaluated in Phase II]	Total/Average Symptoms Score, Total/Average stools [both evaluated in Phase II]
Phase I: Pla vs Enz Pla vs En/M En vs En/M	Diagnostic Parameters: Peak BH / Chg_Peak / Cumulat 0.874 / 0.874 / 0.927 Efficacy Parameters: Tot Symp / Dia Gas Blo Cra 0.182 / 1.0 1.0 .94 .32	Diagnostic Parameters: Peak BH / Chg_Peak / Cumulat 0.039 / 0.050 / 0.010 0.001 / 0.002 / 0.001 0.145 / 0.161 / 0.220 Efficacy Parameters: Tot Symp / Diar Gas Bloat Cram 0.001 .001 .043 .017 .008 0.002 .001 .125 .092 .029 0.593 .927 .587 .392 .761
Phase II*: 2 Hi vs 2 Lo 1:100 v 1:000	----------Dose-Response---------- Nothing significant; 2p: total stools=.82, total symptom=.62 average stool=0.151; total symptoms score=.334	----------Dose-Response---------- 2p: total stools=.001, total symptom=.003; average stool=0.297; total symptoms score=.992
Common Doses	Note: A=1:100 and B= 1:1000 in study SUC-1 are the same as doses C=1:100 and D=1:1000 in study SUC-2; doses C=1:10,000 and D=1:100,000 in study SUC-1, doses A (full-strength) and B=1:10 in study SUC-2 are not comparable.	
Summary of Safety Results	No serious adverse events (AE) reported; 8 pts reported 17 AEs attributed to concurrent medication and not to Sucraid™; all 14 pts completed the study.	26 of 34 pts (76%) reported at least one AE; 11 of these 26 pts (42%) experienced (GI symptom related) AEs attributed to Sucraid™.; all but one of the 34 pts completed the study.
Conclusion	While the efficacy data in study SUC-2 seem to support the efficacy of sucrase, the sponsor need to address the data deficiencies/discrepancies and study conduct issues raised in this review.	

Ph1=Phase I; Ph2=Phase II; P=Placebo; E=Enzyme; EM=Enzyme/Milk; R=Randomized; DR=Dose Response, S/MC=Single/Multiple Center; F=Females, M=Males; *: p-values are by Wilcoxon-Signed-Rank; Hi/Lo=higher/lower doses.

V. OVERALL CONCLUSIONS

1. The efficacy data from study SUC-1 do not support sponsor's claim that Sucraid™ is effective for the treatment of congenital sucrase-isomaltase deficiency (CSID) secondary to sucrose malabsorption.

2. The efficacy data from study SUC-2 support sponsor's claim that Sucraid™ is effective for the treatment of congenital sucrase-isomaltase deficiency (CSID) secondary to sucrose malabsorption.

3. However, the sponsor should address the data deficiencies/discrepancies and trial conduct (including the handling of patients with unidentified treatment sequences in the efficacy analyses) issues raised in this review.

4. Twenty six of the 34 patients (76%) in study SUC-2 reported at least one adverse event (classified 'not serious' by the sponsor); 11 of these 26 patients (42%) experienced (GI symptom related) adverse events attributed to the drug Sucraid™.

5. Based on the concerns raised in this review about the conduct of the trial, data handling and efficacy results, this reviewer's recommendation for the purpose of making any definitive

statistical conclusion on the efficacy of this drug is for the sponsor to conduct one more independent study to better assess both the short and long term benefit of the drug in CSID patients secondary to sucrose malabsorption.

A. J. Sankoh, Ph.D.
/S/ 9/15/97

Mathematical Statistician

Concur:

Dr. Huque /S/ 9/15/97

Dr. Smith /S/ 9/15/97

cc: Archival NDA # 20-772
HFD - 180
HFD - 180/Dr. Talarico
HFD - 180/Dr. Gallo-Torres
HFD - 180/Dr. Robie-Suh
HFD - 180/Ms. McNeil
HFD - 344/Dr. Lisook
HFD - 720/Dr. Smith
HFD - 720/Dr. Huque
HFD - 720/Dr. Sankoh
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Sankoh/x73090/AJS/09-15-97.