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MEDICAL REVIEW(S)

Pages: 1 through 25

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

AUG 14 1997

NDA: 20-772
Orphan Drug No.: 93-786

Date Submitted: May 6, 1997

Sponsor: Orphan Medical, Inc.

Drug: SUCRAID™ (sacrosidase) oral solution

Pharmacological Category: Enzyme Replacement Therapy

Proposed Indication: Enzyme Replacement Therapy for Use in the Treatment of Confirmed or Suspected Congenital Sucrase-Isomaltase Deficiency (**CSID**) and the Prevention of the Associated Symptoms of Sucrose Malabsorption such as Watery Stools, Gas, Bloating, Abdominal Cramping, Explosive Diarrhea and Growth Retardation.

Material Reviewed:

Section	Vol. No.
1. Index to Application	1
2. Summary	1
5. Non-Clinical Pharmacology/Toxicology Summary	8
6. Human Pharmacokinetics and Bioavailability Summary	9
8. Clinical Section	10 to 14
11. Case Report Tabulations	16
12. Case Report Forms	19 to 25

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

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ON ORIGINAL

SUCRAID™ (sacrosidase) Oral Solution
Enzyme Replacement Therapy for Congenital Sucrase Deficiency

Table of Contents

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I. BACKGROUND

The sponsor of the present NDA is seeking approval of SUCRAID™ (sacrosidase) oral solution as an enzyme replacement. This enzyme is intended for use in the treatment of confirmed or suspected congenital sucrase-isomaltase deficiency (**CSID**). Before characterizing **CSID** it is important to briefly introduce the subject of digestion and absorption of carbohydrates.

Digestion and Absorption of Carbohydrates

Carbohydrates (CHOs)[1] are aldehyde or ketone compounds with multiple hydroxyl groups. The principal dietary CHOs are polysaccharides, disaccharide and monosaccharides. Starches (glucose polymers) and their derivatives are the only polysaccharides that are digested to any degree in the human g.i. tract. In **glycogen**, the glucose molecules are mostly in long chains (glucose molecules in 1,4α linkage), but there is some chain branching (produced by 1,6α linkages). **Amylopectin** which constitutes of dietary starch, is similar but less branched, whereas **amylose** is a straight chain with only 1,4α linkages. Glycogen is found in animals, whereas amylose and amylopectin are of plant origin. The disaccharides **lactose** (milk sugar) and **sucrose** (table sugar) are also ingested, along with the monosaccharides fructose and glucose.

The digestion of CHOs proceeds as follows. **Starch** is attacked by **ptyalin**, the α-**amylase** in the saliva. However, the optimal pH for this enzyme is 6.7, and its action is inhibited by the acid gastric juice when food enters the stomach. In the small intestine, the potent pancreatic α-**amylase** also acts on the ingested polysaccharides. Both the salivary and the pancreatic α-amylases hydrolyze 1,4α linkages but spare 1,6α linkages, terminal 1,4α linkages, and the 1,4α linkages next to branching points. Consequently, the end products of α-amylase digestion are oligosaccharides; the disaccharide **maltose**, the trisaccharide **maltotriose**, some slightly larger polymers with glucose in 1,4α linkage, and α-**limit dextrins**, branched polymers containing an average of about 8 glucose molecules (Fig. 1).

The oligosaccharidases responsible for the further digestion of the starch derivatives are located in the outer portion of the brush border, the membrane of the microvilli of the small intestine. α-**Limit dextranase** hydrolyzes the α-**limit dextrins**, and **glucomylase** splits glucose from maltose, maltotriose, and other polymers of glucose in 1,4α linkage. Most of the glucose molecules that are formed enter adjacent mucosal cells, although some remain in the intestinal lumen and are absorbed farther along. Ingested disaccharides are hydrolyzed by lactase or sucrase on the luminal surface of mucosal cells (Fig. 2).

[1] CHOs serve as energy stores, fuels and metabolic intermediates. Ribose and deoxyribose sugars form part of the structural framework of RNA and DNA. Polysaccharides are structural elements in the cell walls of bacteria and plants, and in the exoskeletons of anthropoids. CHOs are linked to many proteins and lipids. CHO units on cell surfaces play key roles in cell-recognition processes. Recently, CHOs have entered the limelight as information-rich molecules, full of significance in development and repair.

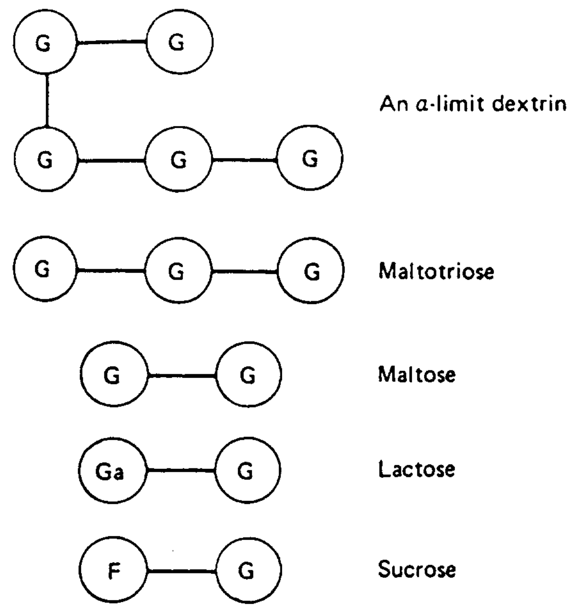


Fig. 1 - *Principal end products of carbohydrate digestion in the intestinal lumen. Each circle represents a hexose molecule. G, glucose; F, fructose; Ga, galactose*

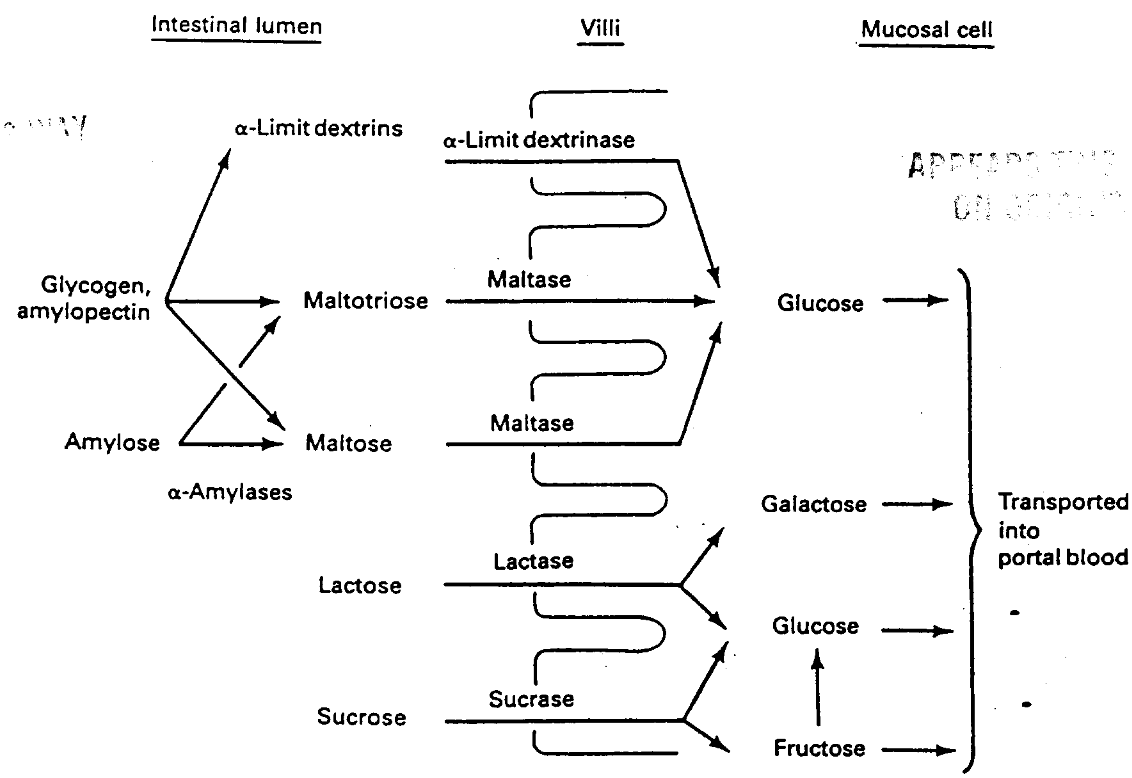
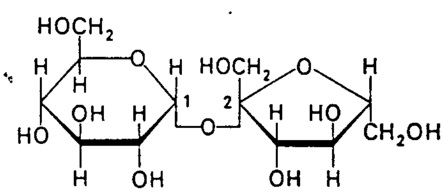


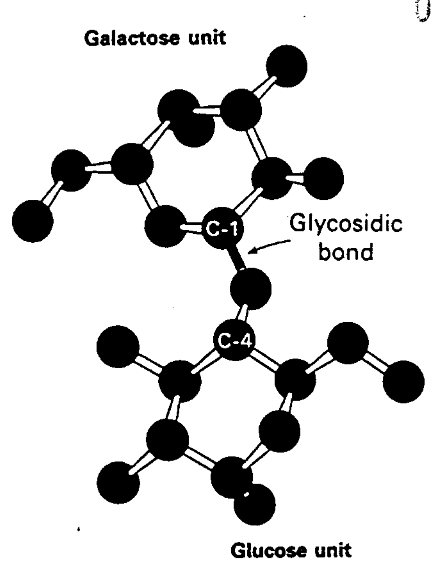
Fig. 2 - *Outline of carbohydrate digestion and absorption. Some of the monosaccharides are also released into the intestinal lumen. Modified from [G.M. Gray, Carbohydrate digestion and absorption NEJM 292:1225 (1975)].*

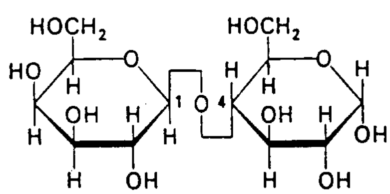
The common disaccharides, which consist of two sugars jointed by an O-glycosidic bond, are sucrose, lactose and maltose. **Sucrose** (common table sugar) is obtained commercially from cane or beet. The anomeric carbon atoms of a glucose unit and a fructose unit are jointed in this disaccharide; the configuration of this glycosidic linkage is α for glucose and β for fructose. *Consequently, sucrose lacks a free reducing group (an aldehyde or ketone end), in contrast with most other sugars.* The hydrolysis of sucrose to glucose and fructose is catalyzed by ***sucrase*** (also called ***invertase*** because hydrolysis changes the optical activity from dextro- to levorotatory).

Lactose, the disaccharide of milk, consists of galactose joined to glucose by a β-1,4 glycosidic linkage (Fig. 3). Lactose is hydrolyzed to these monosaccharides by *lactase* in humans (by **β-galactosidase** in bacteria). In *maltose,* two glucose units are joined by an α-1,4 glycosidic linkage. Maltose comes from the hydrolysis of starch and is in turn hydrolyzed to glucose by ***maltase***. Sucrase, lactase and maltase are located on the outer surface of epithelial cells lining the small intestine. These cells have many finger like folds called ***microvilli*** that markedly increase their surface area for digestion and absorption of nutrients.

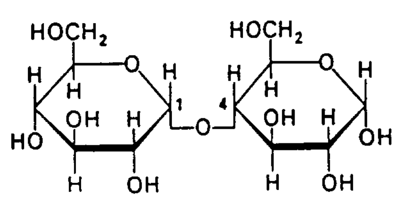


Sucrose
(α-D-Glucopyranosyl-(1→2)-β-D-fructofuranoside)





Lactose
(β-D-Galactopyranosyl-(1→4)-α-D-glucopyranose)



Maltose
(α-D-Glucopyranosyl-(1→4)-α-D-glucopyranose)

<u>*Fig. 3*</u> - *Formulas of three common disaccharides; sucrose, lactose and maltose. The α configuration of the anomeric carbon atom at the reducing end of maltose and lactose is shown here. The Fig. on the right is a model of lactose. Galactose is linked to glucose by a β-1,4 glycosidic bond.*

Hexoses[2] and pentoses are rapidly absorbed across the wall of the small intestine (Fig. 4). Essentially all of the hexoses are removed before the remains of a meal reach the terminal part of the ileum. The sugar molecules pass from the mucosal cells to the blood in the capillaries draining into the portal vein.

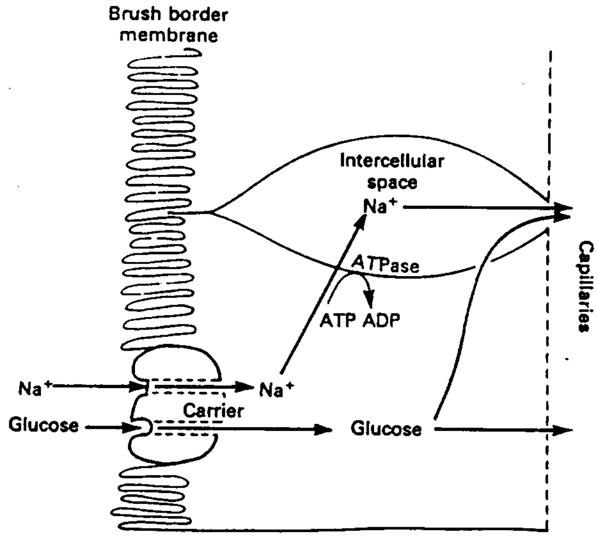


Fig. 4 - *Mechanism for glucose transport across intestinal epithelium. Glucose transport into the intestinal cell is coupled to Na^+ transport, utilizing a common carrier protein. Na^+ is then actively transported out of the cell, and glucose diffuses into the capillaries. [G.M. Gray, Carbohydrate digestion and absorption NEJM 292:1225 1975)]*

[2] The transport of some sugars in uniquely affected by the amount of Na^+ in the intestinal lumen; a high concentration of Na^+ on the mucosal surface of the cells facilitates and a low concentration inhibits sugar influx into the epithelial cells. This is because glucose and Na^+ share the same **symptom**. Intracellular Na^+ is low, and Na^+ moves into the cell along its concentration gradient. Glucose moves with the Na^+ and is released in the cell. The Na^+ is transported into the lateral intercellular spaces, and the glucose diffuses into the interstitium and thence to the capillaries. Thus, glucose transport is an example of secondary active transport; the energy for glucose transport is provided indirectly, by the active transport of Na^+ out of the cell. This maintains the concentration gradient across the luminal border of the cell, so that more Na^+ and consequently more glucose enter. The glucose mechanism also transports galactose. Fructose utilizes a different carrier, and its absorption is independent of Na^+ or the transport of glucose and galactose; it is transported instead by facilitated diffusion. Some fructose is converted to glucose in the mucosal cells. Pentoses are absorbed by simple diffusion.

Insulin has little effect on intestinal transport of sugars. In this respect, intestinal absorption resembles glucose reabsorption in the proximal convoluted tubules of the kidneys; neither process requires phosphorylation, and both are essentially normal in diabetes but depressed by the drug phlorhizin. The maximal rate of glucose absorption from the intestine is about 120 g/h.

II. RATIONALE

As shown in Table 1, there exist five brush border enzymes, which cleave specific bonds in the listed substrates and produce monosaccharides or malto-oligosaccharides. Deficiency of one or more to the disaccharidases may cause diarrhea, bloating and flatulence after ingestion of sugar. The diarrhea is due to the increased number of osmotically active oligosaccharide molecules that remain in the intestinal lumen, causing the volume of the intestinal contents to increase. In the colon, bacteria break down some of the oligosaccharides, further increasing the number of osmotically active particles. The bloating and flatulence are due to the production of gas (CO_2 and H_2) from disaccharide residues in the lower small intestine and colon.[3]

TABLE 1
NDA 20-772

Role of Brush-Border Enzymes in Digestion of Disaccharides and Starch

Enzyme	Bond Cleaved	Substrate	Products
Lactase	beta-(1-4) galactosidase (beta-glucosidase)	Lactose	Glucose, galactose
Sucrase	alpha-(1-4) glucosidase	Sucrose, maltose, maltotriose, alpha-limit dextrins with terminal alpha 1-4 links	Glucose, fructose, malto-oligosaccharide with alpha 1-6 linkage
Glucoamylase	alpha-(1-4) glucosidase	Maltose, maltotriose malto-oligosaccharide (glucose polymers with maximal affinity for chains of 6-10 residues)	Glucose, malto-oligosac-charide with terminal alpha 1-6 linkage
Isomaltase (alpha-dextranase)	alpha-(1-6) glucosidase	Maltose, isomaltose, alpha-limit dextrins (malto-oligosaccharide with terminal alpha 1-6 links)	Glucose, malto-oligosac-charides
Trehalase	alpha- and beta-glucosidase tested on renal trehalase	Trehalose (found principally in mushrooms)	Glucose

[3] The problem of milk intolerance can be relieved by administration of commercial lactase preparations, but this is expensive. Yogurt is better tolerated than milk in intolerant individuals because it contains its own bacterial lactase.

Lactase is of interest because, in most mammals and in many races of humans, intestinal lactase activity is high at birth, declines to low levels during childhood, and remains low in adulthood. The low lactase levels are associated with intolerance to milk (lactose intolerance). Most Europeans and their American descendants retain their intestinal lactase activity in adulthood; the incidence of lactase deficiency in northern and western Europeans is only about 15%. However, the incidence in blacks, American Indians, Orientals and Mediterranean populations is

Congenital Sucrase-isomaltase Deficiency (CSID)

The clinical condition, which is the subject of this application, is congenital sucrase-isomaltase deficiency (CSID). CSID is an autosomal recessive disease of the small intestine most likely caused by alteration of pro-sucrase-isomaltase on the way to the brush border membrane. The molecular defects in patients with CSID are summarized in Table 2. Most patients with this disorder express the high-mannose-containing proenzyme, but its intracellular processing is defective, leading to missorting of the enzyme, reduction in its expression on the brush border enzyme, and premature intracellular degradation [M.L. Lloyd and W.A. Olsen, NEJM 316:438-442 (1987)] (Fig. 5).

TABLE 2
NDA 20-772

Molecular Defects in Patients With CSID

Molecular phenotype					
	I	II	III	IV	V
Location	Golgi	RER	Brush border	Brush border	RER, basolateral membrane
Form	High-mannose precursor	High-mannose and complex precursors	Mature enzyme (catalytically altered sucrase subunit)	Complex precursor (intracellular)	High-mannose precursor
Intracellular degradation products	Present	Present	Absent	Present (sucrase subunit)	?
Microvillus membrane	Absent	Absent	Present (both subunits)	Present (isomaltase subunit only)	Absent
Sucrase activity	0	0	0	0	0
Isomaltase activity	Low	0	Normal	Normal	0

RER, rough endoplasmic reticulum
[E.E. Sterch et al., Molecular aspects of disaccharidase deficiencies. Baillieres Clin Gastroenterol 4:79-96 (1990); A.M. Fransen et al., Naturally occurring mutations in intestinal sucrase-isomaltase provide evidence for the existence of an intracellular sorting signal in the isomaltase subunit. J. Cell Biol 115:45-57 (1991)]

CSID is characterized by complete or almost complete lack of sucrase activity, a very marked reduction in isomaltase activity [S. Auricchic et al., J. Pediatr. 66:555-564 (1965)] and a moderate decrease in maltase activity. The residual maltase activity is caused by the maltase-glucoamylase complex.

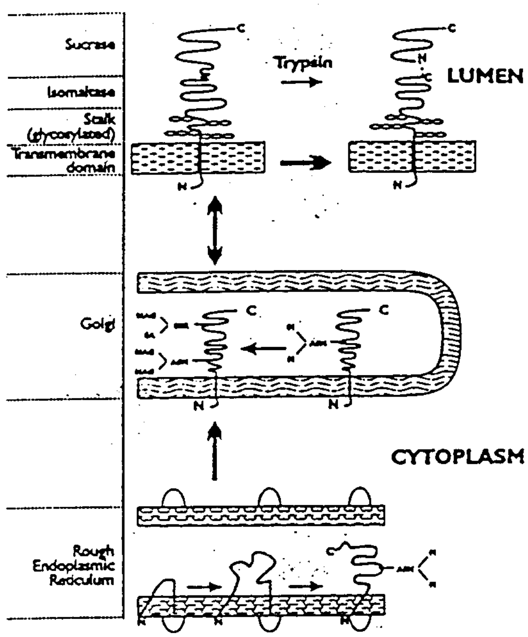


Fig. 5 - *Cotransitional modification and posttranslational processing of sucrase isomaltase (SI) in the enterocyte organelles and intestinal lumen. SI is synthesized as a long polypeptide chain carrying two similar but not identical, active sites (pro-sucrase-isomaltase). The pro-SI is inserted into the rough endoplasmic reticulum (RER) via the same N-terminal hydrophobic region, acting as a targeting protein to the RER, which will later act as the anchor in the brush-border membrane. In the RER, the polypeptide elongates and is glycosylated at asparagine sites (ASN) with mannose (M) residues. The glycoprotein then migrates to the Golgi complex, where mannose residues are trimmed and complex glycosylation with N-acetyl galactosamine (NAG) and sialic acid (SA) residues at ASN and serine (SER) sites takes place. After complex glycosylation, the pro-SI is inserted into the enterocyte membrane, with the sucrase catalytic domain protruding furthest out into the lumen. Pro-Sl is then rapidly processed by trypsin, yielding the two subunits of isomaltase and sucrase associated by noncovalent strong ionic interactions.*

This Fig. and legend are reproduced from [W.R. Treem, J. Pediatr. Gastroenterol. Nutr. 21:1-14 (1995)].

The clinical manifestations in infants exposed to sucrose are severe watery diarrhea, chronic malabsorption and failure to thrive. **CSID** may also cause milder chronic diarrhea in older children with normal growth and development (Table 3). The prevalence of **CSID** in various populations is summarized below.

Prevalence of CSID in Various Populations

Group	Percentage
Greenland Eskimos	
Native Alaskans	3.0
Canadian native peoples	
Danes	<0.1
North Americans	<0.2
Data compiled from sponsor's references (2), (52 through 57)	

TABLE 3
NDA 20-772

Presenting Symptoms in 23 Patients With CSID

Symptoms	Frequency	Mean age at diagnosis (y)
Chronic diarrhea and failure to thrive	7/23	2.0 ± 1.1
Chronic diarrhea with normal growth	9/23	5.6 ± 3.5
Irritable bowel syndrome, abdominal pain	7/23	15.4 ± 7.3

Although common in the Eskimo populations of Greenland and Canada, **CSID** is probably rare in most human populations. However, Welsh et al. found a 2% frequency of heterozygotes in a large series of small intestinal biopsy specimens from white American study subjects. Also, it is possible that **CSID** is not diagnosed in some affected adults with chronic symptoms dating back to childhood.

Diagnosis of CSID

The sponsor notes and the MO agrees that **CSID** is often a difficult disease to diagnose.

- In pediatric patients with chronic diarrhea of unknown origin, studies by Davidson and Robb[4] and those by Larcher et al.[5] have shown that 4-10% of these patients had **CSID**.

- The definitive test for diagnosis of **CSID** is the measurement of intestinal disaccharidases following small bowel biopsy.

- However, a positive breath hydrogen test (**BHT**) following oral challenge with sucrose and a negative **BHT** following oral challenge with lactose along with a stool pH of less than 6 provides an acceptable diagnosis of **CSID**.[6]

- Measurement of expired BH under controlled conditions following a sucrose challenge (a measurement of excess hydrogen excreted in exhalation) in **CSID** patients has shown levels as great as 6 times that of normal subjects.

- It is important to note that in some situations it may be clinically inappropriate, difficult or inconvenient to perform a small bowel biopsy or BHT to make a definitive diagnosis of **CSID**.[7]

- It is also of interest to note that prior to the advent of the **BHT**, oral sucrose tolerance tests were utilized for the noninvasive diagnosis of **CSID**. In children, a rise of blood glucose of >20 mg/dl after a 2.0 g/Kg sucrose load is considered an indication of sucrose malabsorption. However, there is a high incidence of false-positive tests using sucrose challenge followed by glucose blood levels due to delayed gastric emptying.

- In clinical practice, for the diagnosis of disaccharidase deficiency, some physicians have utilized the so-called **differential urinary disaccharide testing**. According to the publications of Maxton in 1989

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4 [G.P. Davidson and T.A. Robb. Med. J. Aust. 2:29-32 (1983)]

5 [V.F. Larcher et al., Arch. Dis. Child. 52:597-605 (1977)]

6 [R.P.K. Ford and G.L. Barnes. Arch. Dis. Child. 58:595-597 (1983)]
[J.A. Perman et al., J. Pediatr. 93:17-22 (1978)]
[W.R. Treem. J. Pediatr. Gastroenterol. Nutr. 21:1-14 (1995)]

7 [W.R. Treem (locus cited) 1995)]
[P.A. Krasilnikoff et al. Acta Pediatr. Scand. 64:693-698 (1975)]
[A.J. Gardiner et al., Arch. Dis. Child. 56:368-372 (1981)]

and 1990 and Treem in 1995,[8] this is done by administering lactulose, lactose, sucrose, isomaltose and rhamnose after an overnight fast followed by collection of urine for 10 h. Separation of the sugars by TLC, has shown excellent agreement with small intestinal biopsy for diagnosis of **CSID**.

No enzyme replacement therapy exists for patients with **CSID**. Currently, the treatment of **CSID** consists of life-long adherence to a sucrose-free diet (Table 4). Compliance with this diet is difficult, and there appears to be a high incidence of chronic gastrointestinal complaints, decreased weight for height and decreased weight for age in patients with **CSID**. Therefore, there is interest in a simple, palatable, enzyme substitution therapy that allows infants and children to ingest more normal diets.

TABLE 4
NDA 20-772

No-No's for a Sucrose-Free Diet

- Ice cream
- Flavored yogurt
- Soda, chocolate milk
- Cakes, pies, cookies, pastries, candy
- Breakfast cereals
- Multiple fruits, fruit juice
- Mayonnaise, salad dressing, maple syrup, catsup
- Peanut butter
- Hot dogs, cold cuts, hams
- Jams, jelly, honey
- Certain vegetables

The sponsor of this NDA is requesting approval of an enzyme replacement therapy for use in the treatment of confirmed or suspected CSID. An initial study by Harms et al. [NEJM 316:1306-1309 (1987) of eight children with **CSID** showed that a small amount of lyophilized baker's yeast (*Saccharomyces cerevisiae)* eliminated or lessened symptoms of diarrhea, cramps or bloating and also lowered breath hydrogen excretion when administered with an oral sucrose load. However, baker's yeast is not palatable in this form and is poorly accepted, especially by young children.

Thus, the rationale for the SUCRAID™ drug product is straightforward - replacement of the missing endogenous sucrase with an exogenous sucrase that retains enzymatic activity when given orally.[9] . It is important to note, however, that although SUCRAID™ provides replacement therapy for the deficient

[8] [D.G. Maxton et al. Dig. Dis. Sci. 34:129-131 (1989)]
[D.G. Maxton et al. J. Clin. Pathol. 43:406-409 (1990)]
[W.R. Treem (locus cited) (1995)]

[9] This approach is analogous to the OTC use of oral lactase supplements in the treatment of **lactose intolerance.**

sucrase enzyme, it does not provide specific replacement therapy for isomaltase deficiency. Therefore, it may be necessary to continue a restriction in the starch content of the diet in order for patients to optimize the reduction of disease symptoms [H.L. Greene et al., Biochem. Med. 6:409-418 (1972)].

CSID: Summary on Diagnostic/Treatment Implications

It is worth summarizing and re-emphasizing certain clinical/pathophysiologic aspects of **CSID**. This is done in an attempt to help understand the design and conclusions drawn from the clinical trials and the eventual wording in the sponsor's proposed package insert, which has been extensively modified by the reviewer.

CSID in terms of enzyme activity - which is measured in intestinal biopsy - is a very variable disease. **CSID** is phenotypically heterogenous. As a consequence, several types of combination of levels of enzymes can be found. Although the common denominator is the absence of sucrase, some patients have neither sucrase nor isomaltase (zero levels of both enzymes), others have no sucrase but residual isomaltase and yet other patients have no sucrase but normal levels of isomaltase (activity). These variations are due to different effects on enzyme synthesis and processing. The enzyme defect can occur in different places and this can be shown on electron microscopic processing of the biopsy specimens: a) The EM may show that the enzyme has been properly synthesized but that it remains in the endoplasmic reticulum and never makes it out of the ER; b) In other instances the enzyme can be shown to be present in the Golgi apparatus but is unable to travel to the membrane where it is needed (it never makes it there); c) Yet in other cases, the EM shows that the membrane is loaded with enzyme. However, although physically present there, the enzyme is not functioning.

The above-described enzyme defects result into different levels of deficiency, particularly in isomaltase activity. All in all, sucrase is less variable (it is absent or barely present in the majority of **CSID** patients).

The two main dietary components that bring about symptoms in the **CSID** patient are sucrose and starch. These two challenging agents can be used to demonstrate that **CSID** makes the patients more susceptible to symptoms of watery diarrhea, gas, cramps, bloating and the like. But the patients experience more severe symptoms more frequently when exposed to sucrose as opposed to starch. After all, starch can be hydrolyzed by a number of enzymes, including salivary amylase, pancreatic amylase and glucoamylase (an enzyme found in the small intestinal wall). The net consequence of this situation is that even in patients with no demonstrable sucrase activity, there may be some isomaltase activity. Therefore, if sucrase is given, the patient may experience no symptoms of disaccharide intolerance even when challenged with starch, because there may be <u>some</u> residual isomaltase activity. It is important to reiterate that the symptoms elicited by sucrose challenge are always greater than those elicited by other challenges.

From the preceding, it is clear that, technically speaking, SUCRAID™ is not really treating **CSID** but a component (part) of it: the deficiency of sucrase but not of isomaltase and that this may matter in some patients who would need to be protected when challenged with starch in their diets.

It is worth diagnosing isomaltase deficiency? Probably not. One reasonable way is the objective testing of breath hydrogen output after starch challenge and measurement of stool pH. But this approach is cumbersome and not practical. According to the experts on **CSID**, such as Dr. William R. Treem who has published extensively on these matters, the most practical approach is, if in some patients isomaltase deficiency is suspected, still treat the sucrase deficiency first: do a therapeutic trial, challenging the patient with sucrose. If there is good symptomatic response, one can say that sucrase deficiency predominates and that the isomaltase deficiency, although it may be present, it is not - in itself - giving the patient symptoms of disaccharide intolerance. Such a therapeutic trial is highly recommended because, even if intestinal biopsy were to be done and the levels of isomaltase activity measured, unfortunately the enzyme activity levels cannot predict the degree of symptomatology. On the other hand, if after sucrase treatment, the patient experiences the expected marked reduction but not complete amelioration of symptoms, dietary restriction of starch may be needed.

Further Notes on the Rationale for Development of SUCRAID™

The sponsor notes that the impetus for the current drug development program can be traced to the 1987 study by H.K. Harms et al., [NEJM 316:1306-1309 (1987)]. In this pilot study (referred to within this application as **Study S-5**, eight fasted **CSID** patients were given two sucrose BHTs, one with and one without the co-administration of a small amount (0.3 g) of lyophilized baker's yeast which contains a high concentration of sucrase activity. The administration of baker's yeast with sucrose caused a marked reduction in the amount of hydrogen in the expired air and a similar marked reduction in the gastrointestinal symptoms compared to when sucrose alone was given. Unfortunately, the dried baker's yeast was not palatable and thus not acceptable for repeated therapeutic use, especially by young children.

The palatability issue has been addressed. Dr. William Treem, a pediatric gastroenterologist, attempted to improve the therapeutic effectiveness and patient acceptance by using a highly palatable solution of yeast-derived sucrase. This solution, containing sucrase in high activity, was already being produced by Red Star Yeast & Products Division of Universal Foods Corp. for use in the commercial baking and candy manufacturing industries.

Dr. Treem's first clinical investigation, initiated in 1990, was a multicenter, randomized, controlled trial .

In 1993, W.R. Treem published an account of an evaluation of liquid yeast-derived sucrase enzyme replacement in patients with **CSID**. In this publication, the following pertinent information is included.

S. cerevisiae contains sucrase activity, but most of the enzyme activity is lost in the preparation of nutritional yeast products because of the drying process. However, the yeast can be grown under conditions designed to increase its sucrase content, and "belt-dried" to preserve this enzyme activity. As a by-product of this manufacturing process, a liquid preparation containing high concentrations of yeast-derived sucrase is obtained. Currently, this liquid preparation is used to hydrolyze unrefined sucrose solutions (i.e., sugar cane juice to produce molasses); it has also been used in the preparation of cream-center candies.

- The 1993's publication by Treem is referred to in this application as **Trial S-1 (or OMC-SUC-1)**. The sponsor notes that based upon the positive results from S-1, a second larger multicenter controlled trial was initiated in 1992 with the support of an FDA Orphan Drug grant and Orphan Medical, Inc. This second trial is identified in this application as **Trial S-2 (or OMC-SUC-2)**. Patients from both Trials S-1 and S-2 were allowed to continue on long-term open-label sucrase therapy following completion of the randomized controlled trials. This open long-term trial is referred to as **Trial S-3 (OMC-SUC-3)** in this application.

III. NON-CLINICAL PHARMACOLOGY/TOXICOLOGY

- SUCRAID™ oral solution had a different life and development path than the development of the usual NCEs. No animal model of **CSID** exists. In addition, **CSID** had been known for years before the logic of replacing the missing endogenous digestive enzyme was clinically attempted. The availability. of the yeast-derived enzyme as a food grade product obviated the requirement for animal testing.[10]

The MO agrees with the sponsor that given the existence of substantial human data, there is no scientific need to retrospectively evaluate and measure the enzyme for its nonclinical efficacy. Other pharmacological tests were not deemed necessary because of safety data obtained in humans, the food status of the enzyme, and the large benefit to risk ratio of the enzyme in patients with the rare disease congenital sucrase-isomaltase deficiency.

Thus, the sponsor is requesting a waiver of nonclinical pharmacology tests based on the following:

1. The enzyme is an exogenous replacement or substitution of a missing endogenous one.

2. There are no appropriate animal models.

3. Efficacy has been clearly demonstrated in humans.

<u>NOTE:</u> Subject to verification of 3. above, the MO recommends that a waiver of nonclinical pharmacology be granted.

[10] The sponsor notes that enzyme replacement in diseases such as Gaucher's Disease originally involved a difficult extraction of the enzyme from human tissue (placenta), but the enzyme sucrase was readily available from yeast manufacturers, and in fact is widely used in commercial bakeries, confection and candy makers.

NON-CLINICAL TOXICOLOGY

Because at this point in time, a pharmacology/toxicology review is not available, what follows was transferred from the sponsor's Summary.

- Orphan Medical has reviewed the scientific literature via computerized database searches and has determined that no studies have been published that examine the toxicity of the enzyme sacrosidase (sucrase, invertase). This includes both endogenous human sacrosidase as well as exogenous yeast-derived sacrosidase.

  As discussed with FDA at the pre-NDA meeting held in October 1996, Orphan Medical and FDA agreed that no additional nonclinical toxicity studies are warranted based upon the following:

  (1) Yeast-derived sacrosidase (sucrase, invertase) has been widely utilized within the human food industry for decades. It is a **GRAS** food material under FDA provision 21 CFR § 170.30 due to its long history of safe use in human food. The sponsor state that they do not know of any reported toxicity associated with the use of sacrosidase as a food product.

  (2) It is however clear that, since sacrosidase is a large macromolecule, it will not be transported across the gastrointestinal mucosa and into the systemic circulation following oral ingestion. Thus, no systemic toxicity directly from the sacrosidase molecule is feasible.

  (3) It is also clear that, because sacrosidase is a naturally occurring enzyme with a glycoprotein structure, it will be digested to peptides and eventually amino acids within the small intestine. These metabolic products will be absorbed into the circulation and utilized as nutrients.

  (4) Also mentioned is the fact that several years of clinical experience with the yeast-derived oral sacrosidase solution, in patients as young as 5 months of age, have revealed no evidence of significant toxicity or intolerance.

- The major excipient in the sacrosidase solution is glycerol (glycerin) which is present at a 50% (Wt/v) concentration and contributes to the stability of the enzyme within the drug product. A separate literature search and toxicity assessment was done on glycerol. Therefore, individual toxicology summaries for sacrosidase and glycerol are presented below along with bibliographic references for each substance.

Sucrase

- **Sucrase** is a natural enzyme present within the intestinal wall, and is responsible for the metabolism of sucrose during and after the process of absorption. Sucrase is localized within the brush border membrane of the intestinal villus cells[11]. A variety of exogenously administered materials can inhibit the activity of or increase the degradation of

[11] [J. Kralovansky and N. Prajda Biochemical Changes of Intestinal Epithelial Cells Induced by Cytostatic Agents in Rats. Arch Toxicol Suppl. 8:94 (1985)]

sucrase, including propane-1,2-diol[12], hexachlorobenzene,[13] and hexitol derivatives[14] while epidermal growth factor was shown to potentiate the effect of hydrocortisone on the expression of sucrase activity[15] (Foltzer-Jouradainne and Raul 1990). In 1985, Goda et al.[16] noted that the activity of sucrase in the jejunum could be increased in suckling rats by feeding mannitol and other sugars, but attributed the effect to stress (caused by diarrhea) rather than to substrate induction.

- Regarding **toxicological data** the literature review did not identify any information studying the effects of exogenously administered sacrosidase.

- There were considerable numbers of references relative to the effects of various materials on sacrosidase activity, but none of these references provide information with regard to the safety of sacrosidase, and thus are not summarized.

- As repeatedly noted by the sponsor, however, it could be expected that orally administered sacrosidase at clinically relevant doses would be utilized physiologically for its enzyme activity and would subsequently be metabolized as any other protein disaccharidase.

  NOTE: [The absorption of proteins → polypeptides → small peptides → di-peptides → individual amino acids is well characterized and addressed in the literature and textbooks and will not be repeated in this review.]

Toxicology Summary for Glycerol

- Orphan Medical has used glycerol as a vehicle for the oral delivery of sacrosidase at a concentration of 50% in sacrosidase drug product. The purpose of the following section is to provide a summary of the available nonclinical toxicology information on glycerol.

- **Glycerol**, chemically identified as 1,2,3-trihydroxypropane (Merck Index, 1983), has a variety of clinical uses as a result of its ability to elevate osmotic pressure. Administration of oral and parenteral

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[12] [K.M. Morshed et al., The Effect of Propane-diols on the Intestinal Uptake of Nutrients and brush Border Membrane Enzymes in the Rat. Biochem. Med. Metab. Biol. 45:161 (1991)]

[13] E. Ivanov et al., Changes in Some Intestinal Enzyme Activities in Experimental Hexachlorobenzene-Induced Porphyria and Modifying Effects of Diet. IARC Scientific Publication, 77:611-18 (1986)]

[14] [J. Kralovansky and N. Prajda (locus cited) (1985)]

[15] [C. Foltzer-Jourdainne and F. Raul. Effect of Epidermal Growth Factor on the Expression of Digestive Hydrolases in the Jejunm and Colon of Newborn Rats. Endocrinology 127:1763 (1990)]

[16] [T. Goda et al. Precocious Increase of Sucrase Activity by Carbohydrates in the Small Intestine of Suckling Rats. I. Significance of the Stress Effect of Sugar-Induced Diarrhea. J. Pediatr. Gastroenterol. Nutr. 4:468 (1985)]

glycerol elevates plasma osmolality, resulting in enhanced flow of water from the extravascular spaces into plasma, and has been used for the treatment of cerebral edema. Other uses include ophthalmic solutions (to reduce superficial corneal edema) as an aid in ophthalmoscopic examinations, and to lower ocular tension in glaucoma [Goodman and Gilman (1980)].

- The sponsor notes: **Glycerol** is deemed Generally Recognized as Safe (GRAS) by the Food and Drug Administration as a multiple purpose food substance in food for human consumption (21 CFR 182.1320).

- **Glycerol** is currently approved for use in multiple therapeutic products [Physicians Desk Reference (1996)], and is available as an OTC product (NDC# 0472-0763).

- The acute oral and intravenous LD_{50} of **glycerol** in the rat is reported to be >20 and 4.4 mL/Kg, respectively [Merck Index (1983)]. The oral and intraperitoneal LD_{50} in the rat has also been reported to be 12.6 and 4.42 g/Kg, respectively, while the intravenous LD_{50} is put at 5.566 g/Kg. In the mouse, the oral, intraperitoneal and intravenous LD_{50} is reported as 4.09, 8.7, and 4.25 g/Kg, respectively. The oral and intravenous LD_{50} in the rabbit is reported to be 27 and 53 g/Kg, respectively [all reported in the Registry of Toxic Effects of Chemical Substances (1996)]. Thus, glycerol has a low order of acute toxicity in animals.

- The literature reviewed did not identify any recent repeated dose toxicity studies performed on **glycerol**. However, in 1973, Informatics, under contract with the FDA, produced a report entitled "Generally Recognized as Safe Food Ingredients; Glycerine and Glycerides". The information in this report, along with a report prepared by the FASEB ("Evaluation of the Health Effects of Glycerin and Glycerides as Food Ingredients"), indicated that the literature at that time showed that glycerol was safe, and formed the basis of the GRAS affirmation.

- The principal toxicological effect of **glycerol** on repeated administration of high doses is potent renal vasoconstriction which ultimately leads to acute renal failure[17]. From a mechanistic standpoint, Yamada[18] showed that a dose of administered subcutaneously resulted in increased levels of renal **malondialdehyde** as an index of lipid peroxidation and was associated with the development of a mild necrosis in the proximal tubules.

- **Glycerol** as a 10% solution, when injected intravenously into rats for nine days produced increased levels of succinate dehydrogenase and acid

[17] [Cassarret and Doull, Toxicology: The Basic Science of Poisons. (1993)]

[18] [T. Yamada. Studies on the Mechanism of Renal Damage Induced by Nephrotoxic Compounds. Nippon Hoigaku Zasshi 49:447 (1995)]

phosphatase in the kidney, and histopathology indicated degeneration of the renal tubular epithelium[19]. Recovery animals held for 19 days showed no histopathological effects in the kidney, suggesting the lesions were reversible.

There is information available on the topical effects of glycerol, particularly as it related to its effects on the eye. Because of its osmotic effects, glycerol is known to produce a variety of effects when introduced into the anterior chamber of the eye, including edema of the cornea with wrinkling of the posterior surface and damage to the endothelial cells when administered full strength[20]. A 50% solution produces less severe reactions.

A battery of mutagenicity studies have been performed with glycerol. Essentially all of these studies have shown glycerol to be devoid of mutagenic activity.[21]

- In a recent review document, BIBRA Toxicology International produced a toxicity profile on **glycerol** [BIBRA (1993)],[22] although much of the data discussed was generated in studies conducted prior to 1975. The following was excerpted from their document.

Acute Toxicity

- Oral LD_{50} data is similar to that previously described. In addition, they report LD_{50} values of 15-38 g/Kg in mice, with 10 g/Kg producing no signs of toxicity. The LD_{50} in rabbits is with 4 g/Kg producing elevations in blood glucose. Dogs tolerated a dose of 8 g/Kg with no signs of toxicity, but emesis was noted at 11 g/Kg. Intravenous injections are well tolerated at doses up to 4 g/Kg in multiple species.

Repeated Exposure

- Rats have tolerated glycerol for up to two years at oral doses of 5 g/Kg/day without serious effects; increases in liver and kidney weights were seen in one such study, and increased heart weights were seen in another. The administration of **glycerol** in the drinking water (5%) for six months was without serious effects except for the presence of calcium deposits in the kidneys. There was no indication of a

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19 [H. Nowak et al., Patol. Pol. 30:61 (1979)]

20 [Grant, Toxicology of the Eye (1986)]

21 [S. Haworth et al., Salmonella Mutagenicity tests Results for 250 Chemicals, Environmental Mutagen 5(Suppl 1):3-142 (1983)]
[M. Ishdate et al., Primary Mutagenicity Screening of Food Additives Currently Used in Japan. Food and Chemical Toxicology 22:623-636 (1984)]
[D.J. Doolittle et al., The Genotoxic Activity of Glycerol in an In Vitro Test Battery. Food and Chemical Toxicology 26:631-635 (1988)]

22 [BIBRA Working Group, Glycerol: Toxicity Profile, BIBRA Toxicology International (1993)]

carcinogenic effects in any of these studies. Studies with higher oral doses (20-50 g/Kg/day) for a week or more produced decreased growth, increased blood glucose and phospholipids, liver enlargement, increased liver enzymes and liver glycogen.

Mice were treated with 10 g/Kg/day (in drinking water) for 25 weeks, and showed no significant effects. Pulmonary lesions were seen in another study at this dose after two weeks of treatment.

In dogs, no signs of toxicity were seen following treatment by dietary admixture at 5 g/Kg/day for one year, except for increased water consumption and diuresis. In another study, three dogs given **glycerol** at 35% of the diet also showed no toxic effects.

Other studies reported included studies where **glycerol** was given by the inhalation, topical, intravenous and subcutaneous routes of administration. In most cases, the doses were relatively high, but still demonstrated no significant signs of organ toxicity.

Reproductive Toxicity

Reproduction studies were reported where **glycerol** was a component of a cosmetic formulation (4.5%), and the material was applied topically. No effects upon reproductive processes were reported.

Mutagenicity

Negative results have been seen in the Ames test (multiple studies), tests for DNA damage and chromosomal aberration studies.

A Soviet study reported that the administration of 1 g/Kg by gavage to male rats showed a low incidence of chromosomal damage in the bone marrow and an increase in fetal deaths when male rats at this dose were bred to female rats. Other compounds tested in this study with similar positive responses would not have been expected to produce positive responses.

Absorption, Distribution, Metabolism and Excretion

Orally administered **glycerol** is absorbed from the gastrointestinal tract and is rapidly distributed in plasma with peak serum concentrations occurring within 60-90 min. The majority of an orally administered dose is incorporated into body fat, with of the dose excreted unchanged in the urine. The elimination half-life of **glycerol** is 30-40 minutes (USP).

Primary metabolism takes place in the liver (approaching 80%) and is either eliminated as carbon dioxide and water, or is utilized in glucose or glycogen synthesis. When radiolabeled **glycerol** is administered intravenously to pregnant rats, the conversion to glucose was enhanced as was the disappearance of glucose from the blood.[23]

[23] [J.M. Chaves et al., Biology of the Neonate 37:172 (1980)]

SUMMARY OF GLYCEROL TOXICITY RELEVANT TO CLINICAL DOSAGES

- Based upon the animal toxicity data reviewed above, it would appear that the most sensitive species is the dog in which it was shown that an oral **glycerol** dosage of 5/Kg/day administered chronically was the lowest dosage at which signs of minimal toxicity first appeared. Thus, 5 g/Kg/day could be considered the maximum tolerated oral dose (MTD).

- The proposed clinical dosage of the SUCRAID™ oral solution is 1-2 ml with each meal and snack. For patients weighing less than 15 Kg the usual dose is 1 ml while patients weighing 15 Kg or greater the dose is 2 ml. The solution contains 50% **glycerol** by volume.

  Thus, for an infant weighing 5 Kg (11 lb) and taking five 1 ml doses of SUCRAID™ per day, the total amount of **glycerol** consumed would be 2.5 ml per day. Since **glycerol** has a specific gravity of 1.249 g/ml, this dose is equal to 3.123 g/5 Kg b.w./day or 0.625 g/Kg b.w./day. Therefore, the ratio of the maximum tolerated dose in dogs to the maximal dosage likely in a very young human subject is 5.0/0.625 or 8.

  Similarly, if a child weighs 15 Kg (33 lb) and receives five 2 ml doses of SUCRAID™ per day or 10 ml per day, the **glycerol** content is 5 ml/day or 6.245 g/day. For a 15 Kg child this converts to 0.416 g/Kg/day. In this case, the ratio is 5.0/0.416 = 12.

CONCLUSION

The reviewer agrees with the sponsor that the dosages of **glycerol** to be ingested by SUCRAID™ patients are very small in relation to the dosages known to produce any evidence of toxicity.

IV. HUMAN PHARMAKINETICS AND BIOAVAILABILITY

- SUCRAID™ (sacrosidase, derived from baker's yeast) oral solution is an enzyme replacement, with action in the small intestine where it catalyzes the hydrolysis of the disaccharide sucrose to glucose and fructose. SUCRAID™ has an apparent molecular weight of 97 kD (513 amino acid residues) and hence is too large a macromolecule to be systemically absorbed. Like any other orally ingested protein, the eventual fate of this replacement enzyme is degradation to some small peptides and simple amino acids by proteases (including pepsin, trypsin and peptidases) normally present in the gastrointestinal luman (having been produced by the pancreas) or produced by the gastrointestinal mucosa. The resultant individual amino acids are absorbed into the systemic circulation as nutrients. Since SUCRAID™ oral solution cannot be absorbed into the portal circulation as intact macromolecules, systemic bioavailability is a moot issue and, therefore, human PK studies based on plasma drug concentration vs time profiles are not warranted with this product.

- None of the underlying mechanisms proposed to explain drug-drug interactions[24] apply to SUCRAID™ oral solution because this product is not absorbed as such. The MO agrees with the sponsor that there is no need to conduct in vivo drug-drug interaction studies. After all, in healthy humans not suffering from **CSID**, the hydrolysis of sucrose normally would be catalyzed by naturally occurring sucrase and this endogenous enzyme has not been reported to participate in any drug-enzyme interaction(s).

Drug-Food Interaction Studies

- It is to be noted that endogenous sucrase is produced by the mucosa of the small intestine, whereas SUCRAID™ oral solution must pass through the stomach before reaching the small intestine, its expected site of action. The hydrolysis of proteins generally begins in the lumen of the stomach where the active enzyme pepsin (arising from pepsinogen released from chief cells) acts on many proteins but produces only slight hydrolysis. This is because pepsin acts only at linkages between *l*-glutamyl and *l*-tyrosyl residues within a protein. In other words, exogenous β-D-fructofuranoside fructohydrolase in SUCRAID™ oral solution is expected to be subjected to slight hydrolysis by pepsin in the stomach lumen after ingestion. This appears to justify the rational behind the recommendation that one half of the SUCRAID™ oral solution dose be taken with a beverage before solid food intake. The introduction of the solid food to the stomach is expected to induce a higher HCl secretion and activate pepsin (the protease). There is no assurance, however, that the beverage would not induce secretion of HCl. But definitive answers to these questions would require extensive experimentation in infants and children.

- In addition, the sponsor notes results of clinical studies suggesting that a greater portion of a SUCRAID™ oral solution dose is delivered to the small intestine if the product is diluted with milk rather than water (OMC-SUC-2, BHT results). This beneficial effect is believed to be due to decreased activity of intragastric pepsin in the presence of milk protein. Diluting the product with infant formula which contains emulsified soy proteins, should accomplish the same result.

  [<u>NOTE:</u> Although the BHT results of Study S-2 do suggest that more enzyme may be delivered to the intestine when diluted in milk rather than water, this interesting finding has not been replicated].

V. CLINICAL TRIALS IN NDA 20-772

In support of the efficacy, safety and tolerance of SUCRAID™ (sacrosidase), an oral liquid yeast-derived sucrase enzyme preparation as a treatment for CSID,

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[24] Drug-drug interactions can be classified into several types based on underlying mechanisms. These include (I) displacement interactions, i.e., a second drug displacing the first drug from tissue or protein binding sites resulting in higher free concentration of the first drug, (ii) induction of hepatic microsomal enzymes by another drug resulting in the lowering of plasma concentration of the first drug, (iii) enzyme inhibition by a second drug resulting in the elevation of plasma levels of the first drug, and (iv) interference of the absorption process of the first drug by a second drug in the gastrointestinal tract.

the sponsor has submitted results from six clinical studies. These are identified as **S-1, S-2, S-3, S-4, S-5** and **S-6**. Of these, studies **S-1 (Protocol OMC-SUC-1)** and **S-2** (OMC-SUC-2) are adequate and well-controlled trials that, according to the sponsor, provide evidence of the efficacy SUCRAID™ drug product in the treatment of CSID (see next section).

- **Study S-3** is a long-term, open trial that included patients who had previously completed participation in either trial S-1 or S-2. Study S-3 is expected to provide supportive evidence of the long-term safety, tolerance and effectiveness of SUCRAID™ in CSID patients consuming a normal diet.

- **Study S-4** is a retrospective survey study involving the patients, parents, pediatric gastroenterologists and primary care pediatricians involved in the care of the CSID patients in S-1 and S-2, the two controlled trials. According to the sponsor, the results of this written survey provide additional supportive data regarding the efficacy of the sucrase (sacrosidase) oral solution therapy.

- **Study S-5** is an additional supportive efficacy study designed to demonstrate the efficacy of a different form of sucrase enzyme in treating CSID. This published study was conducted by Harms et al. (1987) using lyophilized baker's yeast (*Saccharomyces cerevisiae)*, the same organism used in the production of SUCRAID™.

- **Study S-6** is a supportive safety study that involved the administration of single-doses of liquid yeast-derived sucrase to six adult HIV-positive subjects.

VI. <u>MAIN FEATURES OF PIVOTAL TRIALS</u>

Refer to Table 5. As pivotal, the sponsor has submitted results of two clinical trials, identified in this Table as S-1 (OMC-SUC-1) and S-2 (OMC-SUC-2) conducted . Both were multicenter, randomized, controlled, double-blind, essentially 4-arm trials in CSID patients in whom the diagnosis was confirmed primarily upon the determination of disaccharide enzyme activity in duodenal biopsy samples obtained during UGI endoscopy. The CSID patients enrolled in these trials had sucrase activity levels of <10% of normal, isomaltase (palatinase) levels that were low, lactase levels that were normal and maltase levels that were either normal or reduced.

Both controlled trials, S-1 and S-2 made use of a similar experimental design. This included an initial BHT phase. During this phase, patients were given a standard sucrose loading dose under fasting conditions one week apart combined with either sucrase or placebo. In the second trial (S-2) a third BHT was conducted in which the sucrase was combined with milk. This approach was based upon the presumption that the milk would buffer pepsin in the gastric juice and allow a greater proportion of the sucrase dose to reach the small intestine, thereby improving effectiveness. In this manner, the BHT phase provided double-blind, placebo-controlled, single-dose efficacy data with respect to both the objective BH excretion and the subjective symptomatic response. In addition, these results verified that the patient had the correct diagnosis.

In the second phase of both trials, four serial dilutions were administered in a randomized crossover design. This double-blind dose-response phase utilized the collection of daily stooling and symptom information on patient diaries. The two primary efficacy parameters, total number of stools and total GI symptoms, were calculated from the stooling and symptom diaries along with a number of secondary ratings of individual symptom severity and stool characteristics. During the dose-response phase, the patients were also instructed to consume a diet that was essentially normal with respect to sucrose and carbohydrate content. Separate dietary records were also collected in this phase. From the dietary records, a registered dietitian was able to quantify the daily sucrose and carbohydrate intake and thereby verify that the patients were consuming a normal diet.

The sponsor notes that a placebo treatment design was not used during the dose-response phase because it was considered unethical to experimentally induce severe and prolonged GI symptoms in this population of young children. It is also noted that each trial covered a 1000-fold dosage range. This approach seemed to make it unnecessary to include a true placebo in this second phase of these trials.

At the pre-NDA meeting of October 30, 1996, the FDA requested that a "success per patient analyses" be added to the efficacy assessments. In response to this request, the sponsor has included a post-hoc defined "success/failure responder" assessment in the analysis of each controlled trial.