ENFit®
Compatible

RELiZORB®

(iMMOBILIZED LIPASE) CARTRIDGE

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PLEASE READ AND FULLY UNDERSTAND THESE INSTRUCTIONS FOR USE BEFORE USING RELiZORB®.

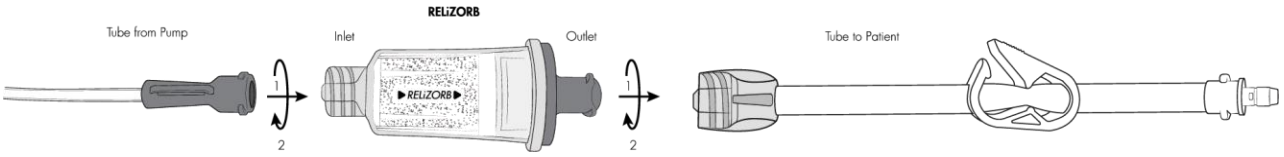
1.0 INDICATIONS FOR USE

RELiZORB is indicated for use in pediatric patients (ages 2 years and above) and adult patients to hydrolyze fats in enteral formula.

2.0 DESCRIPTION

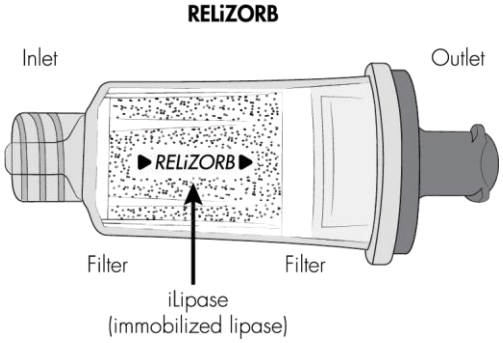
RELiZORB is a single-use, point-of-care digestive enzyme cartridge that connects in-line with existing enteral feeding pump tubing sets and patient extension sets or enteral feeding tubes. RELiZORB is designed to hydrolyze (digest) fats contained in enteral formulas, mimicking the function of the digestive enzyme lipase that is normally secreted by the pancreas, the body's digestive organ. By hydrolyzing (digesting) fats from enteral formulas, RELiZORB allows for the delivery of absorbable fatty acids and monoglycerides to patients.

FIGURE 1: RELiZORB (center) connects with enteral feeding pump tubing set (left) and patient extension set or enteral feeding tube (right).



RELiZORB is comprised of a clear cylindrical, plastic cartridge with a single inlet connection port and a single purple outlet connection port. The inlet and outlet ports of RELiZORB are intended to connect in-line with enteral feeding pump tubing sets and patient extension sets or enteral feeding sets. Inside the cartridge, there are small white beads. The digestive enzyme, lipase, is covalently bound to the small white beads. The lipase-bead complex, iLipase® (immobilized lipase), is retained within the cartridge during use by filters on both ends of the cartridge. The fat in enteral formulas is hydrolyzed as it comes in contact with iLipase as the formula passes through the cartridge.

FIGURE 2: RELiZORB and its major components.



3.0 CONTRAINDICATIONS

None.

4.0 WARNINGS

- RELiZORB is for use with enteral feeding only.
- RELiZORB should not be connected to any intravenous (IV) line, setup, or system.
- Medications should not be administered through the RELiZORB cartridge. Do not add medications to the enteral feed line in between the pump and RELiZORB (before RELiZORB). The passage of medications through RELiZORB may adversely affect the medications or the ability of RELiZORB to hydrolyze fats.

- Fibrosing Colonopathy -- Fibrosing colonopathy is a rare, serious adverse reaction associated with high--dose use of pancreatic enzyme replacement therapy in the treatment of patients with cystic fibrosis. The underlying mechanism of fibrosing colonopathy remains unknown. Patients with fibrosing colonopathy should be closely monitored because some patients may be at risk of progressing to stricture formation. RELiZORB contains lipase enzyme that is not from a porcine source. The lipase is bound to the beads, and this lipase--bead complex (iLipase) is retained within the RELiZORB cartridge. Continue to follow your physician's guidance and porcine pancreatic enzyme labeling regarding porcine pancreatic enzyme use when used in conjunction with RELiZORB.

5.0 CAUTIONS AND PRECAUTIONS

- Do not re-use RELiZORB. RELiZORB is a single-use product. Re-use may result in contamination of the product. If re-used, RELiZORB may not effectively hydrolyze fats.
- Do not break, alter, or place excess pressure on any part of the RELiZORB cartridge. Any compromise of the structural integrity of RELiZORB may lead to improper connection to enteral feeding pump tubing sets and patient extension sets or enteral feeding tubes, enteral formula leakage or risk of contamination.
- Do not use RELiZORB after the date marked on the pouch.
- Enteral formulas containing insoluble fiber (including blenderized formulas) should NOT be used. Insoluble fiber may clog the RELiZORB cartridge. A detailed listing of enteral formulas compatible with RELiZORB can be found at www.relizorb.com/formulas.
- RELiZORB is designed for use with enteral feeding pump systems with low flow/no flow alarms. RELiZORB is NOT intended for use with gravity feed systems. A detailed listing of pumps, enteral feeding pump tubing sets and patient extension sets or enteral feeding tubes compatible with RELiZORB can be found at www.relizorb.com/pumps.
- In order to ensure product performance, store RELiZORB in its pouch either refrigerated or at room temperature (2°C to 27°C; 36°F to 80°F).
- RELiZORB is indicated for use with enteral feeding only; patients should follow physician's guidance for pancreatic enzyme replacement therapy (PERT) use for meals and snacks. Patients and patient caregivers should follow physician's guidance regarding the need for pancreatic enzyme replacement therapy (PERT) during enteral feeding.

6.0 PRODUCT USE

- RELiZORB is intended for one time use only. At the conclusion of the feeding, discard the RELiZORB. Do not store or re-use it.
- A single RELiZORB may be used for up to 500 mL of enteral formula. If you use less than 500 mL of enteral formula per feeding, discard the RELiZORB after use.
- For volumes greater than 500 mL and up to 1000 mL, you can connect 2 RELiZORB cartridges together in a tandem configuration.
- Up to 2 RELiZORBs can be used in a day (24-hour period) and there are no requirements on the amount of time between using them.
- RELiZORB has been evaluated with enteral pump flow rates listed in the table below:

	SINGLE RELiZORB* 2 cartridges/day	TANDEM RELiZORB* One tandem configuration (2 cartridges)/day
ENTERAL FORMULA VOLUME:	Up to 500 mL	500-1000 mL
ENTERAL PUMP FLOW RATE:	10-120 mL/hr	24-120 mL/hr

*Do not exceed use more than 24 hours in either single or tandem configuration.

- RELiZORB is intended for use at home or medical institutions such as a hospital. Patients and patient caregivers should consult with their doctor or healthcare provider before making any changes to flow rates or volume of enteral formula used.
- RELiZORB has been evaluated for use with numerous commercially available enteral formulas and been shown to efficiently hydrolyze (digest) fats into absorbable fatty acids and monoglycerides in most formulas.

- A detailed listing of enteral formulas tested with RELiZORB, along with a summary of the hydrolysis achieved, can be found in Table 1 located in the *In vitro* Performance Characteristics section and at www.relizorb.com/formulas.
- RELiZORB has been tested for up to a 1-hour stop in feeding and shown not to change flow rate as measured by the flow of formula through the device or how well RELiZORB breaks down fat.

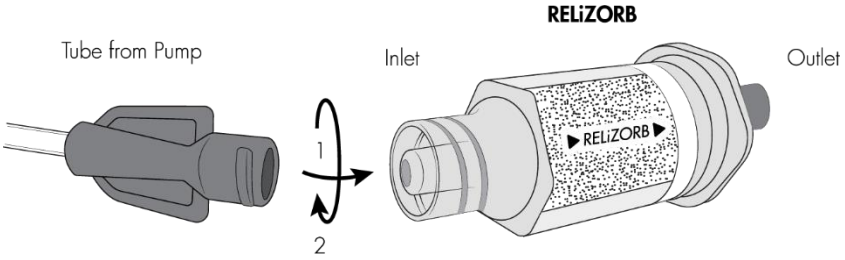
7.0 RELiZORB SETUP PROCEDURE AND USE

Patients and patient caregivers should review the following RELiZORB installation instructions before use.
There are 2 different setup procedures depending on the feeding volume:
(A) Feeding volume up to 500 mL using 1 single cartridge.
(B) Feeding volume greater than 500 mL and up to 1000 mL using 1 tandem configuration.

A. SETUP PROCEDURES FOR RELiZORB USE WITH UP TO 500 mL

1. Set up the pump and enteral feeding pump tubing set per the pump manufacturer's instructions. Prime the enteral feeding pump tubing per the manufacturer's instructions.
2. Remove the RELiZORB pouch from its carton. Examine the RELiZORB pouch. Do not use the RELiZORB if:
    - the pouch seal is broken
    - the current date is past the expiration date shown on the pouch
3. Remove the RELiZORB from its pouch. Examine the RELiZORB. Do not use the RELiZORB cartridge if:
    - the RELiZORB is damaged
    - the RELiZORB has been previously used
4. Secure the RELiZORB to the end of the enteral feeding pump tubing set by inserting the outlet fitting from the pump tubing into the inlet of the RELiZORB with a twisting motion until secure.

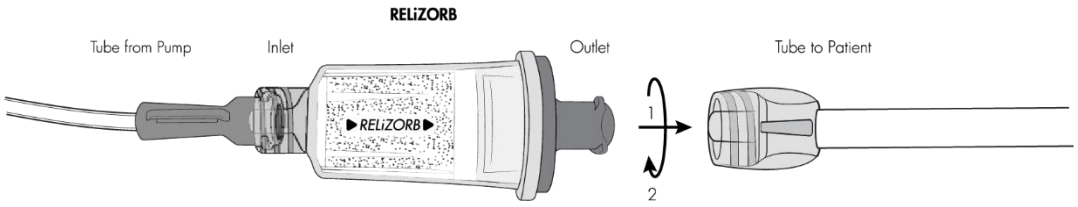
FIGURE 3: Securing RELiZORB inlet to outlet fitting from pump tubing.



NOTE: Do not overtighten the enteral feeding pump tubing set fitting when connecting to RELiZORB. A small gap between the flange on the pump tube fitting and the RELiZORB is normal.

5. Manually prime the enteral formula through the RELiZORB, up to the outlet by holding the prime button on the enteral feeding pump.
6. Connect the RELiZORB outlet fitting to the inlet fitting of the patient extension set or enteral feeding tube that connects to the patient.

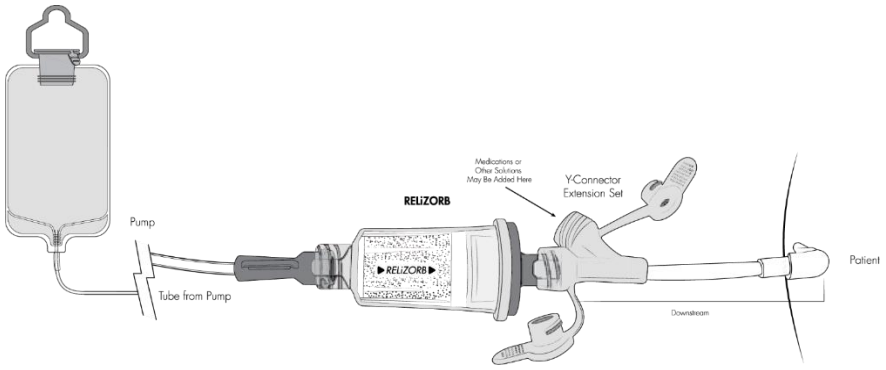
FIGURE 4: Connecting RELiZORB outlet to inlet fitting of patient extension set or enteral feeding tube that connects to patient.



7. If a patient extension set is being used, follow the pump manufacturer's instructions to prime the feeding formula to the end of the patient extension set.
8. Set the pump to the prescribed flow rate and proceed with feeding.

WARNING: If medications, saline flushes or other non-enteral formula materials are to be added, they must be introduced ***AFTER*** RELiZORB (ie, between RELiZORB and the patient). They may be added to the side-port of a Y-Connector extension set located between the RELiZORB and the patient as shown below in Figure 5.

FIGURE 5: Medications may be added between RELiZORB and patient.



NOTE: If medications or flush solutions are added BEFORE the RELiZORB cartridge, then RELiZORB, all tubing and formula must be discarded. You may re-start feeding using a new RELiZORB and a patient extension set. Please follow Steps 1-7 to re-start the process.

NOTE: If a second RELiZORB is required to be installed to replace an existing RELiZORB, use the following steps:

- ○ Pause the pump following the pump manufacturer's instructions
- ○ Disconnect the current RELiZORB from the patient extension set or enteral feeding tube
- ○ Remove the current RELiZORB from the enteral feeding pump tubing set
- ○ Connect the new RELiZORB to the enteral feeding pump tubing set following Step 4
- ○ Prime the enteral formula through to the end of the RELiZORB following Step 5
- ○ Connect the new RELiZORB to the patient extension set or enteral feeding tube following Step 6
- ○ Follow Step 7 if a patient extension set is being used
- ○ Follow Step 8 to re-start enteral formula delivery

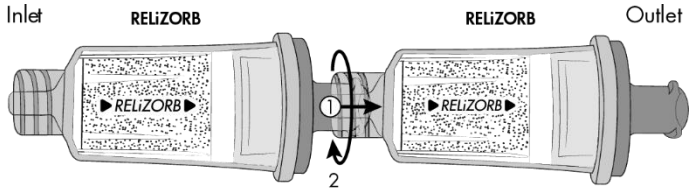
B. SETUP PROCEDURES FOR RELiZORB USE WITH VOLUMES 500-1000 mL

For volumes greater than 500 mL and up to 1000 mL, you can connect 2 RELiZORBs together in a tandem configuration. The tandem configuration (2 cartridges) is limited to 1 such use per day. Tandem RELiZORB may also be referred to as "piggybacking."

TANDEM RELiZORB SETUP PROCEDURE AND USE

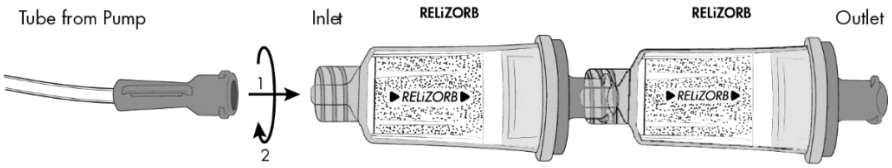
1. Set up the pump and enteral feeding pump tubing set per the pump manufacturer's instructions. Prime the enteral feeding pump tubing per the manufacturer's instructions.
2. Remove 2 RELiZORB pouches from the carton. Examine the RELiZORB pouches. Do not use the RELiZORB if:
    - the pouch seal is broken
    - the current date is past the expiration date shown on the pouch
3. Remove the RELiZORBs from their pouches. Examine each RELiZORB. Do not use the RELiZORB cartridge if:
    - the RELiZORB is damaged
    - the RELiZORB has been previously used
4. Join the 2 RELiZORB cartridges by inserting the outlet fitting from the first RELiZORB into the inlet of the second RELiZORB with a twisting motion until secure as shown in Figure 6.

FIGURE 6: Connecting RELiZORB cartridges together to form a tandem RELiZORB.



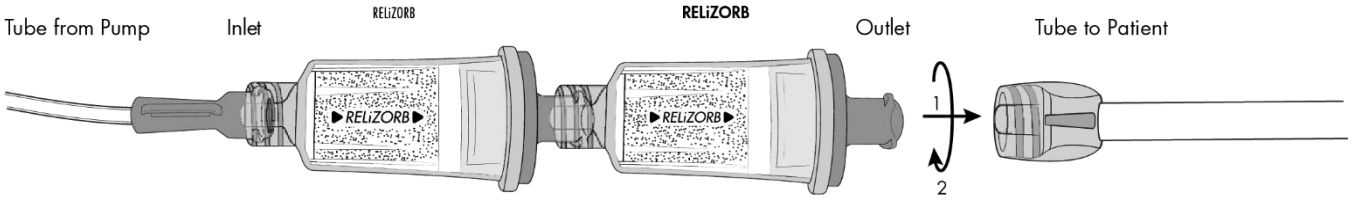
5. Secure the tandem RELiZORB to the end of the enteral feeding pump tubing set by inserting the outlet fitting from the pump tubing into the inlet of the tandem RELiZORB with a twisting motion until secure as shown in Figure 7.

FIGURE 7: Securing tandem RELiZORB inlet to outlet fitting from pump tubing.



6. Manually prime the enteral formula through the RELiZORB, up to the outlet by holding the prime button on the enteral feeding pump.
7. Connect the tandem RELiZORB outlet fitting to the inlet fitting of the patient extension set or enteral feeding tube that connects to the patient as shown in Figure 8.

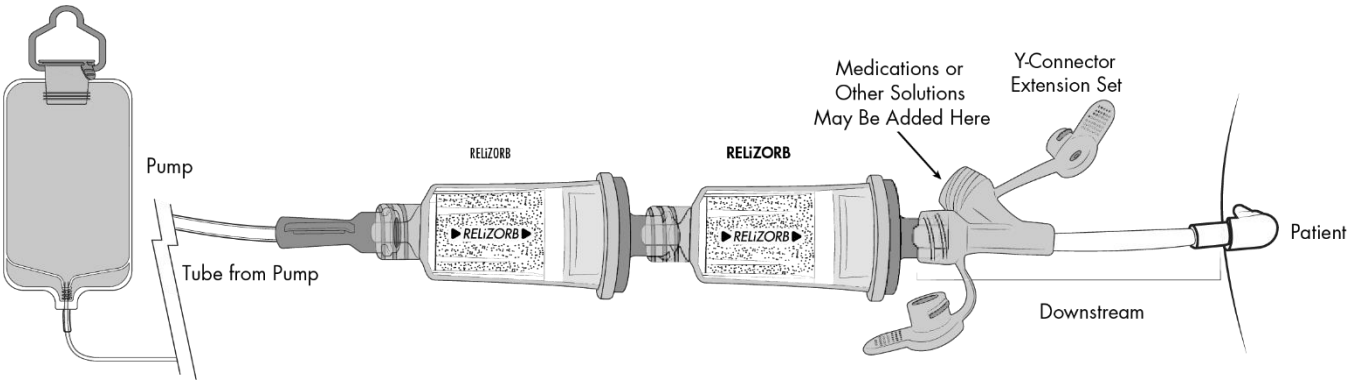
FIGURE 8: Connecting tandem RELiZORB outlet to inlet fitting of tube that connects to patient.



8. If a patient extension set is being used, follow the pump manufacturer's instructions to prime the feeding formula to the end of the patient extension set.
9. Set the pump to the prescribed flow rate and proceed with feeding.

WARNING: If medications, saline flushes or other non-enteral formula materials are to be added, they must be introduced ***AFTER*** the tandem RELiZORB (ie, between tandem RELiZORB and the patient). They may be added to the side-port of a Y-Connector extension set located between the tandem RELiZORB and the patient as shown in Figure 9.

FIGURE 9: Medications may be added between the tandem RELiZORB and patient.



NOTE: If medications or flush solutions are added BEFORE the tandem RELiZORB, then both RELiZORB cartridges, all tubing and formula must be discarded. You may re-start feeding using 2 new RELiZORBs and a patient extension set. Please follow Steps 1-7 to re-start the process.

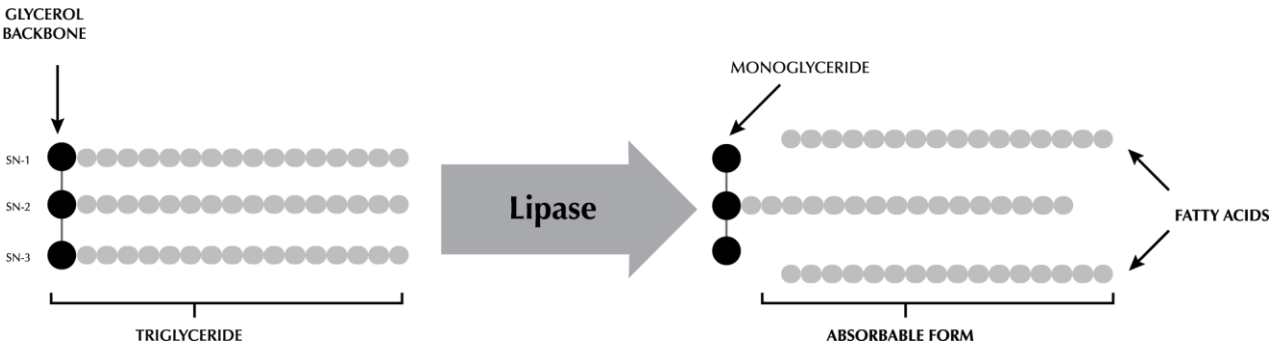
8.0 DISASSEMBLY AND DISPOSAL

- When feeding is complete, disconnect the RELiZORB from the patient extension set or enteral feeding tube set and enteral feeding pump tubing set.
- Discard the RELiZORB.

9.0 MECHANISM OF ACTION

RELiZORB is designed to hydrolyze (digest) fats contained in enteral formulas. RELiZORB contains the digestive enzyme lipase bound to beads (iLipase). By hydrolyzing fats from enteral formulas, RELiZORB allows for the delivery of absorbable fatty acids and monoglycerides. Like human pancreatic lipase, the lipase in RELiZORB has sn-1, sn-3 selectivity in the hydrolysis of triglyceride fats (Figure 10). When enteral formula flows through RELiZORB, the lipase bound to the beads hydrolyzes fats in their triglyceride form, including important long-chain polyunsaturated fats (LCPUFAs), releasing omega-3 (docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)) and omega-6 (linoleic acid (LA) and arachidonic acid (AA)) into their absorbable fatty acid and monoglyceride forms. The iLipase is retained within the RELiZORB cartridge by two filters as enteral formula flows through RELiZORB.

FIGURE 10: Hydrolysis of fat by lipase into monoglyceride and free fatty acids.



10.0 *IN VITRO* PERFORMANCE CHARACTERISTICS

A series of *in vitro* experiments using an enzyme-based fatty acid quantification assay was conducted to measure fatty acid release resulting from the use of the RELiZORB cartridge.

RELiZORB is designed to be compatible with both polymeric and semi-elemental formulas. RELiZORB was tested and is compatible across a range of enteral feeding pump flow rates, 10-120 mL/hr in single configuration and 24-120 mL/hr in tandem configuration, and commercially available enteral formulas with varying product characteristics and components (Table 1). RELiZORB is not compatible with enteral formulas containing insoluble fiber (including blenderized formulas).

Representative Fat Hydrolysis Data Using RELiZORB

TABLE 1: Fat hydrolysis for representative enteral tube feeding formulas and formula volumes using RELiZORB at 120 mL/hour.

ENTERAL TUBE FEED FORMULAS EVALUATED WITH RELiZORB AT 120 mL/HR						
Formula Name	**Per serving**					**Fat hydrolysis (%)* for single and tandem RELiZORB†**
	Fat (g)	**Calories (kcal)**	**Contains pre-hydrolyzed protein**	**MCT:LCT ratio**	**Omega-3 DHA & EPA (g)**	
Impact® Peptide 1.5	15.9	375	✓	50:50	1.23	**89%**
Nutren® 1.5	15	375	-	20:80	-	**69%**
Nutren® 2.0	23	500	-	50:50	-	**51%**
Osmolite® 1.2 Cal	9.3	285	-	NA	-	**61%**
PediaSure® 1.5	16	350	-	NA	0.03	**51%**
PediaSure® Peptide 1.0	9.6	237	✓	NA	-	**76%**
PediaSure® Peptide 1.5	14.4	356	✓	NA	-	**76%**
Peptamen 1.0®	10	250	✓	70:30	-	**86%‡**
Peptamen AF®§	13.5	300	✓	50:50	0.60	**78%**
Peptamen Junior®§	9.5	250	✓	60:40	-	**67%**
Peptamen® 1.5	14	375	✓	70:30	-	**68%**
Peptamen Junior® 1.5	17	375	✓	60:40	0.15	**64%**
TwoCal® HN	21.5	475	-	NA	-	**32%‡**
Vital® AF 1.2 Cal	12.8	284	✓	NA	0.90	**77%**
Vital® 1.5 Cal§	13.5	355	✓	NA	-	**74%**

*Fat hydrolysis (%) is estimated based on label claim fat content.
†Feed volumes tested are ~500 mL using a single RELiZORB and ~1000 mL using tandem RELiZORB.
‡Fat hydrolysis rates are similar over the shelf life of RELiZORB.
§Compatible with EnteraLite® Infinity® Moog pump.

For a more detailed listing of compatible enteral formulas tested with RELiZORB, along with a summary of the hydrolysis achieved, visit www.relizorb.com/formulas.

Please consult with your physician regarding enteral nutrition formulas for use with children

11.0 PRE-CLINICAL STUDIES

The efficacy, safety and intended use of RELiZORB was tested in a well-established pre-clinical porcine model of exocrine pancreatic insufficiency (EPI) that mimics the inability to digest and absorb fats.[1] Ligation of the pancreatic ducts in the EPI porcine model causes a total lack of pancreatic enzymes, leading to arrested growth, fatty acid deficiencies, and GI symptoms including steatorrhea.

In a study conducted in the EPI porcine model, a single feeding (500 mL; 4 hours, 120 mL/hr) of enteral formula administered through RELiZORB resulted in an increase in fat absorption, caloric intake and improvement in uptake of omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) in plasma levels over 24 hours compared with enteral formula that was not administered through RELiZORB. Enteral formula passed through RELiZORB normalized plasma levels of DHA and EPA compared to the healthy control group. RELiZORB was shown to hydrolyze >90% of fats from 500 mL of Peptamen AF® (750 kcal, 32 g fat, 1.8 g DHA and EPA; Nestlé Health Science Europe). The clinical significance of these findings has not been determined.

24-Hour Pharmacokinetic Plasma Fatty Acid Uptake: Safety, tolerability and fat absorption with use of RELiZORB in enteral (tube) feeding.

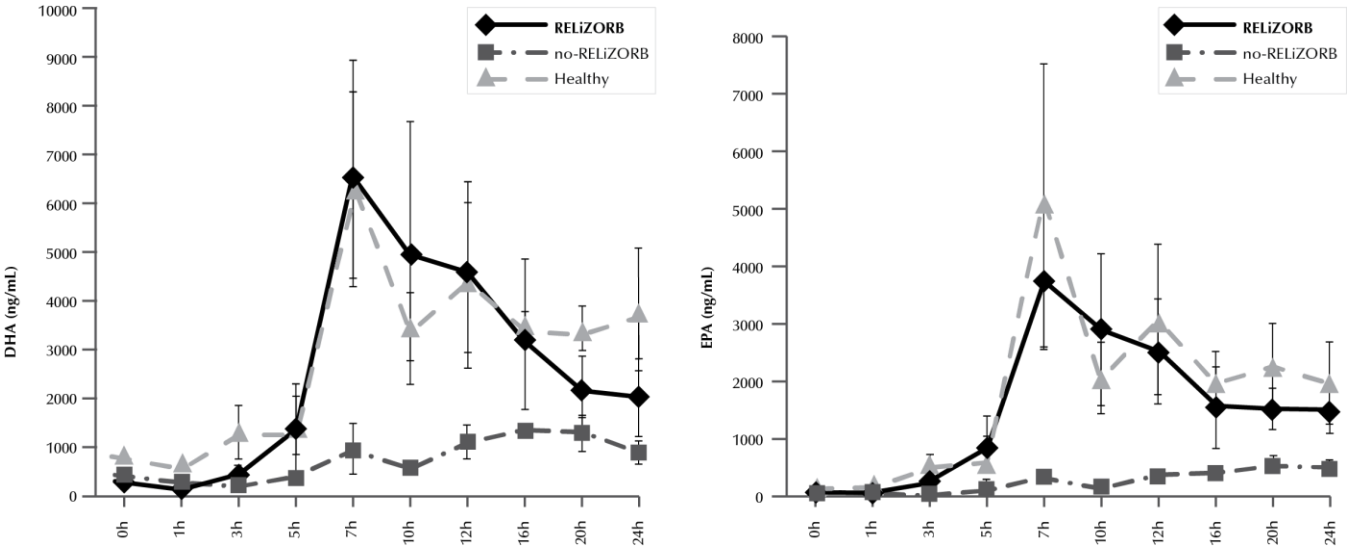
STUDY OBJECTIVE: To measure fat absorption by assessing plasma 24-hour pharmacokinetic changes evaluated by measuring important plasma long-chain polyunsaturated fatty acids (LCPUFA), specifically omega-3 fatty acids DHA and EPA.

STUDY DESIGN AND METHOD: A parallel study consisting of three groups; an EPI group (n=6) receiving formula hydrolyzed with RELiZORB, a second EPI group (n=5) receiving non-hydrolyzed formula without RELiZORB and a third healthy control group (n=3) with normal digestive function receiving non-hydrolyzed formula without RELiZORB. Peptamen AF®, a semi-elemental enteral formula containing hydrolyzed protein was provided over 4 hours (500 mL; pump rate 120 mL/hour). Fat absorption was evaluated by measuring plasma long-chain polyunsaturated fatty acids (LCPUFA), specifically plasma DHA and EPA levels.

RESULTS: RELiZORB use was well tolerated in the porcine model with normal food intake and no serious adverse reactions. No vomiting or diarrhea was recorded during the 24-hour period.

RELiZORB normalized plasma levels of DHA and EPA compared to the healthy control group (Figure 11). Formula hydrolyzed with RELiZORB was associated with a statistically significant increase in total fat absorption and improvement in uptake of omega-3 fatty acids (DHA and EPA) in plasma levels over 24 hours compared with non-hydrolyzed formula without RELiZORB ($p < 0.05$; Table 2). The clinical significance of this observation has not been determined.

FIGURE 11: Plasma DHA and EPA concentration over 24-hour period after single administration of hydrolyzed formula (500 mL) using RELiZORB in a porcine model of exocrine pancreatic insufficiency (EPI).



DHA (docosahexaenoic acid) and EPA (eicosapentaenoic acid) measured as ng/mL. Results are shown as a mean of group.

TABLE 2: Changes in total DHA and EPA fatty acid over 24 hours in a porcine model of exocrine pancreatic insufficiency (EPI).

	DHA			EPA		
	BASELINE	**24 HR.**	**CHANGE**	**BASELINE**	**24 HR.**	**CHANGE**
RELiZORB	0.9 ± 0.2	2.1 ± 0.2	1.2*	1.0 ± 0.1	5.5 ± 0.7	4.5**
NO RELiZORB	1.2 ± 0.2	1.6 ± 0.2	0.4	1.1 ± 0.2	2.1 ± 0.2	0.9
HEALTHY CONTROL	1.6 ± 0.0	2.3 ± 0.2	0.7	1.2 ± 0.2	3.2 ± 0.1	2.0

*DHA (docosahexaenoic acid) and EPA (eicosapentaenoic acid) measured as g of DHA or EPA over 100 g total fatty acids. Results are shown as a mean of group ± SD. *p= 0.0005 difference between RELiZORB vs. No RELiZORB over 24 hours for DHA. **p < 0.0001 difference between RELiZORB vs. No RELiZORB over 24 hours for EPA.*

Increased uptake of specific long-chain polyunsaturated fatty acids with use of RELiZORB resulted in a statistically significant reduction in the omega-6 to omega-3 ratio (Table 3). The clinical significance of this observation has not been determined.

TABLE 3: Change in omega-6 to omega-3 ratio over 24 hours in a porcine model of exocrine pancreatic insufficiency (EPI).

	BASELINE	**24 HR.**
RELiZORB	10.6 ± 0.4	3.6 ± 0.5*
NO RELiZORB	10.5 ± 0.8	7.0 ± 1.2
HEALTHY CONTROL	8.7 ± 0.8	5.2 ± 0.4

*DHA (docosahexaenoic acid) and EPA (eicosapentaenoic acid) measured as g of DHA or EPA over 100 g total fatty acids. Results are shown as a mean of group ± SD. *p<0.0001 for difference between baseline and 24 hours for RELiZORB vs. No RELiZORB.*

Literature from other studies has demonstrated that a balanced ratio of omega-6 to omega-3 fatty acids is beneficial in maintaining normal development, immunological function and overall health.[2]

12-DAY FATTY ACID UPTAKE IN PLASMA AND TISSUES: SAFETY, TOLERABILITY AND FAT ABSORPTION WITH REPEATED USE OF RELiZORB IN NIGHTLY ENTERAL (TUBE) FEEDING.

The safety, tolerability and fat absorption of important long-chain polyunsaturated fatty acids (LCPUFA) in plasma, such as DHA and EPA, with repeated use of RELiZORB with supplemental nightly enteral (tube) feeding were evaluated in a second study conducted in the EPI porcine model.

STUDY DESIGN AND METHOD: This was a parallel study with two groups; a hydrolyzed group (n=6) with use of RELiZORB or non-hydrolyzed group (n=5) without use of RELiZORB. Peptamen® AF, a semi-elemental enteral formula containing hydrolyzed protein was provided over 4 hours (500 mL; pump rate 120 mL/hour). Nightly enteral feedings (750 kcal) administered over 12 consecutive days provided approximately one third of the total daily caloric intake (2,150 kcal). Fat absorption was evaluated by measuring plasma long-chain polyunsaturated fatty acids (LCPUFA), specifically DHA and EPA. The omega-6 to omega-3 ratio was also calculated.

RESULTS: Use of RELiZORB was well tolerated with normal food intake and no serious adverse reactions. No vomiting or diarrhea was recorded with repeated RELiZORB use. A lower stool weight was observed with the group receiving formula hydrolyzed with RELiZORB (317 ± 98 g) compared with non-hydrolyzed formula without RELiZORB (387 ± 77 g; p=0.01).

This study demonstrated that RELiZORB, when evaluated in conditions consistent with the intended use, enhances fat absorption and caloric intake as demonstrated by improved plasma levels of DHA and EPA compared with use of non-hydrolyzed formula without RELiZORB (Table 4). The clinical significance of this observation has not been determined. There was a positive correlation between coefficient of fat absorption (% CFA) and plasma levels of EPA (r_s=0.81), DHA (r_s=0.672) and polyunsaturated fatty acids (r_s=0.736).

TABLE 4: Mean change in DHA and EPA plasma levels after 12 days of nightly feeding with RELiZORB in a porcine model of exocrine pancreatic insufficiency (EPI).

	DHA (DOCOSAHEXAENOIC ACID) (ng/mL)			EPA (EICOSAPENTAENOIC ACID) (ng/mL)		
	BASELINE	**DAY 12**	**CHANGE**	**BASELINE**	**DAY 12**	**CHANGE**
RELiZORB	214.2 ± 141.4	727.6 ± 164.9	513.4*	43.3 ± 23.5	512.6 ± 81.6	469.3**
NO RELiZORB	268.7 ± 129.2	442.8 ± 154.1	174.1	81.5 ± 84.0	190.8 ± 23.1	109.3

*DHA (docosahexaenoic acid) and EPA (eicosapentaenoic acid) measured as ng/mL. Results are shown as a mean of group ± SD. *p= 0.008 difference between RELiZORB vs. No RELiZORB for DHA. **p= 0.001 difference between RELiZORB vs. No RELiZORB for EPA.*

Healthy control (n=3) mean baseline levels were 753.3 ± 102.2 ng/mL for DHA and 138.1 ± 10.0 ng/mL for EPA.

Increased uptake of specific LCPUFAs with use of RELiZORB resulted in a statistically significant reduction in the omega-6 to omega-3 ratio (Table 5). The clinical significance of this observation has not been determined.

TABLE 5: Change in omega-6 to omega-3 ratio after 12 days in a porcine model of exocrine pancreatic insufficiency (EPI).

	BASELINE	**DAY 12**
RELiZORB	10.5 ± 0.7	2.4 ± 0.3*
NO RELiZORB	10.6 ± 0.6	4.2 ± 0.6

*DHA (docosahexaenoic acid) and EPA (eicosapentaenoic acid) measured as g of DHA or EPA over 100 g total fatty acids. Results are shown as a mean of group ± SD. *p<0.05 for difference between RELiZORB vs. No RELiZORB at day 12.*

Healthy control (n=3) mean baseline omega-6 to omega-3 ratio was 8.7 ± 0.8.

Literature from other studies has demonstrated that a balanced ratio of omega-6 to omega-3 fatty acids is beneficial in maintaining normal development, immunological function and overall health.[2]

Higher plasma levels of fat-soluble vitamins (Vitamin D, E) were observed with use of RELiZORB (Table 6). The clinical significance of this finding has not been determined.

TABLE 6: Fat-soluble vitamin levels after 12 days in a porcine model of exocrine pancreatic insufficiency (EPI).

	VITAMIN D (ng/mL)	**VITAMIN E (mcg/mL)**
RELiZORB	6.48 ± 2.8*	0.53 ± 0.3*
NO RELiZORB	3.82 ± 1.0	0.25 ± 0.1

*Results are shown as a mean of group ± SD.*p<0.05 for difference between RELiZORB vs. No RELiZORB for Vitamin D and Vitamin E.*

Normal control values for Vitamin D and Vitamin E were not obtained in this study. The published porcine plasma concentration is 5-30 ng/mL for Vitamin D and 1-7 mg/mL for Vitamin E.[3] Actual levels of vitamins and other nutrients in

a given population may be impacted by dietary intake. Individuals with compromised pancreatic output and fat malabsorption are predisposed to fat-soluble vitamin deficiencies.[4]

An increase in protein absorption (9%; $p<0.05$) was observed when using RELiZORB during administration of Peptamen AF, a semi-elemental formula containing prehydrolyzed protein, compared with protein absorption when Peptamen AF was administered without RELiZORB. Improved fat hydrolysis resulting from the use of RELiZORB may lead to increased absorption of protein; the clinical significance of this observation has not been determined.

In addition, tissue uptake (lung, retina, heart, liver, intestine) of specific important long-chain polyunsaturated omega-3 fatty acids (DHA, EPA) showed a statistically significant increase using formula hydrolyzed with RELiZORB compared with non-hydrolyzed formula without RELiZORB. The clinical significance of this observation has not been determined. Patients with compromised pancreatic output have a higher risk for fatty acid deficiencies in plasma and tissue, which may be related to a variety of adverse physiological effects, such as altered membrane and cellular functions.[5,6]

12.0 CLINICAL STUDY SUMMARY

The safety and efficacy of RELiZORB was assessed in a multicenter, prospective, randomized, double-blind, placebo controlled, cross-over study, conducted in 34 patients with exocrine pancreatic insufficiency (EPI) due to cystic fibrosis (CF). Patients aged 4 to 45 years with CF associated EPI, receiving supplemental enteral nutrition (EN) at least four times a week, and using PERT, were eligible for study inclusion. Exclusion criteria included uncontrolled diabetes mellitus, signs and symptoms of liver cirrhosis, portal hypertension, significant liver disease, history of fibrosing colonopathy or recurring distal intestinal obstructive syndrome.

The study consisted of three distinct periods as follows:

- Baseline current treatment practice (PERT) period (7 days) [Period A]
- Randomized double-blind, placebo controlled, crossover period (11 days) [Period B]
- RELiZORB open-label treatment period (7 days) [Period C]

Both GI and non-GI adverse events (AEs) were collected during entire study conduct.

ENDPOINTS:

1. Change in fatty acid plasma concentration of DHA (docosahexanoic acid) and EPA (eicosapentanoic acid) which are long chain poly-unsaturated fatty acids (LCPUFA)
   omega-3 fats
2. Gastrointestinal symptoms

PERIOD A: This period was used to establish a baseline with respect to overall gastrointestinal (GI) events and non-GI events while patients were asked to maintain their standard PERT dosing along with their standard overnight enteral feeding (up to 1,000 mL per feeding) for 7 days.

PERIOD B: The purpose of the randomized double-blind, placebo controlled, crossover period [Period B] was to obtain plasma measures of DHA and EPA to evaluate the effect of RELiZORB use on fat absorption during enteral formula administration. Patients were randomized to receive a single daytime enteral feeding of 500 mL of an enteral formula containing fixed levels of DHA and EPA as well as total fat [Impact® Peptide 1.5; 32 (g) fat and 2.45 (g) DHA and EPA] without PERT through a RELiZORB cartridge or placebo cartridge, followed by a crossover to a single enteral daytime feeding with the alternate cartridge. The crossover design allowed the patient to serve as their own control, comparing DHA and EPA absorbed by plasma, with and without RELiZORB use. During Period B patients fasted overnight prior to each daytime enteral feeding. Serial plasma measures were collected over 24 hours for both crossover treatment days. Crossover treatment days were separated by a 7-day washout period during which PERTs were taken as usual. Fat absorption from enteral formula was assessed by evaluating changes over 24 hours in plasma fatty acid concentrations of total DHA and EPA.

PERIOD C: The purpose of Period C was to evaluate safety and tolerability, with a focus on GI symptoms with RELiZORB and PERT use, where adverse events during Period C could be compared to the baseline Period A (PERT only). At the completion of the crossover treatment period (Period B) patients entered a 7-day RELiZORB open label treatment period (Period C) and received overnight feedings of a standard enteral formula [32 (g) fat and 2.45 (g) DHA and EPA per 500 mL], up to a maximum volume of 1,000 mL per feeding administered through the RELiZORB cartridge along with the current practice of PERT dosing.

STUDY POPULATION: Thirty-three patients completed the study in the intent-to-treat population (ITT), which included completing receiving one administration of enteral formula through RELiZORB and one administration through a placebo cartridge during Period B. One patient exited the study prior to Period B due to a pulmonary exacerbation. The ITT population ranged from 5 to 34 years of age, with a mean age of 14.5 years, mean BMI (kg/m^2) of 17.5 and mean weight of 41.8 (kg). Of the 33 patients, 14 were between ages 5 and 12, 16 were between ages 13 and 21, and 3 were between 22 to 34 years of age. Twenty patients were male and thirteen were female. Patients enrolled in the study had received enteral nutrition for an average of 6.6 years; the average age of initiation of enteral nutrition was approximately 8 years. Patients self-administered an average of 8-9 PERT capsules (range 2 to 21) with their overnight enteral feeding. There were 12 subjects with a diagnosis of cystic fibrosis-related diabetes (CFRD). Medication use was to be consistent between Period A and Period C.

SAFETY AND TOLERABILITY PERIOD A VS. PERIOD C: Safety and tolerability were addressed by collecting GI symptoms of fat malabsorption from all 33 patients in the ITT population and comparing the frequency of GI events in Period C with events reported in Period A (Table 7). GI events commonly associated with fat malabsorption described in the literature were reported daily by the patients and/or caregivers via use of a Gastrointestinal Symptom Diary (GSD) for 7 days during Period A and Period C. Since there are no validated GI symptom study tools available to address enteral feeding, a study specific tool was completed by caregivers or allowed patients to self-report GI events by choosing from a prospectively identified checklist of fat malabsorption symptoms.[7-9] The GSD also allowed for reporting of other events not prospectively identified in the checklist. Additionally, clinical staff captured both GI and non-GI symptoms during patient visits.

Adverse events were collected in the GSD as patient diary entries during Period A and Period C to allow for a comparison of adverse events associated with fat malabsorption between these two periods.

All 33 patients returned GSDs for both Period A and Period C, though not all patients recorded symptoms for all seven days of diaries. For Period A, 96.1% of daily diaries were completed, and during Period C, 98.3% were completed. A listing of GI events as reported in the GSD for the completed daily diaries is listed in Table 7.

Although patients were asked to maintain their standard dose of PERT in conjunction with RELiZORB use during Period C for enteral feeding, 14 patients (42%) did not take PERT with RELiZORB during Period C (protocol deviations). A subset analysis was performed on patients that used both PERT and RELiZORB (per protocol) and those who used RELiZORB alone in Period C and compared against GI events observed during the baseline Period A (Table 7).

TABLE 7: Gastrointestinal events in Period A vs. Period C by number of events and number of patients reporting events.*

	OVERALL (N=33)		SUBSET (N=19) PERT + RELiZORB		SUBSET (N=14) RELiZORB	
	PERIOD A PERT	PERIOD C	PERIOD A PERT	PERIOD C	PERIOD A PERT	PERIOD C
ABDOMINAL PAIN	29 (13)	19 (10)	15 (8)	13 (6)	14 (5)	6 (4)
BLOATING	14 (5)	7 (3)	6 (2)	4 (2)	8 (3)	3 (1)
CONSTIPATION	8 (6)	0 (0)	2 (2)	0 (0)	6 (4)	0 (0)
DIARRHEA	7 (7)	3 (3)	5 (5)	1 (1)	2 (2)	2 (2)
GAS	30 (12)	38 (10)	10 (6)	21 (6)	20 (6)	17 (4)
INDIGESTION/ HEARTBURN	9 (6)	4 (3)	5 (3)	4 (3)	4 (3)	0 (0)
NAUSEA	9 (6)	6 (4)	3 (3)	5 (3)	6 (3)	1 (1)
STEATORRHEA/ FATTY STOOL	7 (6)	7 (3)	4 (3)	4 (2)	3 (3)	3 (1)
VOMITING	4 (3)	5 (3)	0 (0)	1 (1)	4 (3)	4 (2)
FLATULENCE	1 (1)	7 (1)	1 (1)	7 (1)	0 (0)	0 (0)
SMELLY BURPS	4 (1)	0 (0)	4 (1)	0 (0)	0 (0)	0 (0)
LARGE VOLUME STOOL	0 (0)	4 (2)	0 (0)	4 (2)	0 (0)	0 (0)
ABDOMINAL GAS PAIN	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)
TOTAL FREQUENCY	**122**	**101**	**55**	**64**	**67**	**37**

**Gastrointestinal events are expressed as: number of events (number of patients reporting events).*

Results from Table 7 should be interpreted in light of patients maintaining their standard nutritional practice during Period A and Period C, as differences in symptoms could be partially attributed to other factors including ingestion of solid food accounting for a majority of caloric intake, enteral formula volume, PERT dose and number of completed diaries. The most commonly reported GI events were abdominal pain, gas and bloating.

Non-gastrointestinal adverse events were reported by 6% of patients with RELiZORB during the open-label Period C and by 12% of patients during the baseline only Period A. The most common non-gastrointestinal adverse event reported was headache, which occurred during the baseline period (6.1%) and did not occur during the RELiZORB period (Period C).

SAFETY AND TOLERABILITY CROSSOVER TREATMENT DAYS: While receiving a fixed volume of enteral formula volume over 4 hours during the crossover Period B treatment days, study staff monitored patients (n=33) and recorded adverse events. Non-gastrointestinal adverse events in the crossover treatment period (Period B) were reported by 3% of patients with RELiZORB use and by 18% of patients with placebo.

Gastrointestinal adverse events in the crossover treatment period (Period B) were reported as shown in Table 8.

TABLE 8: Gastrointestinal events in Period B crossover days by number of events and number of patients reporting events.*

	TREATMENT DAY WITH RELiZORB (N=33)	TREATMENT DAY WITH PLACEBO (N=33)
NAUSEA	2 (1)	0 (0)
ABDOMINAL PAIN	1 (1)	0 (0)
GAS	1 (1)	1 (1)
DIARRHEA	0 (0)	1 (1)
CONSTIPATION/NO BOWEL MOVEMENT	1 (1)	1 (1)

**Gastrointestinal events are expressed as: number of events (number of patients reporting events).*

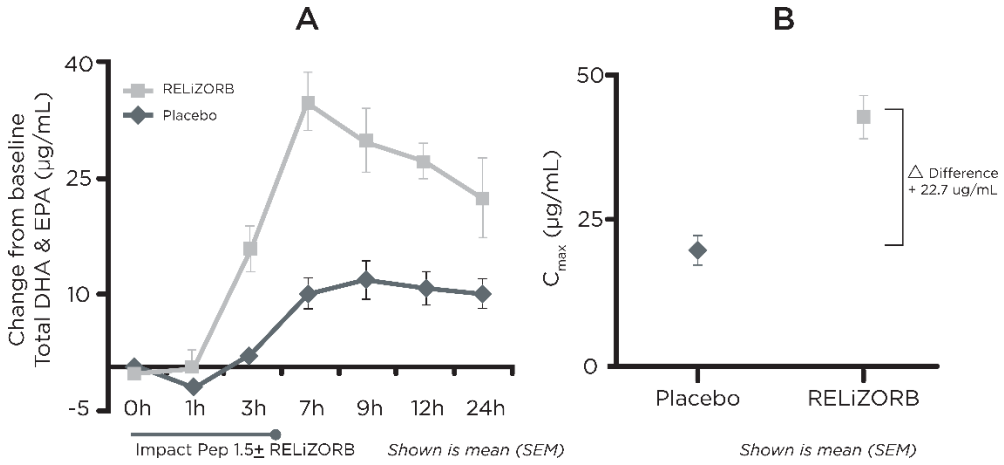
EFFICACY: FAT ABSORPTION EVALUATION: During the randomized double-blind, placebo controlled, crossover Period B patients (n=33) received 500 mL of an enteral formula [Impact® Peptide 1.5; 32 (g) fat and 2.45 (g) DHA/EPA] with fixed quantities of DHA and EPA* as well as total fat over 4 hours (120 mL/h). Efficacy was evaluated with the ITT population (n=33) comparing serial plasma concentrations of DHA and EPA (omega-3 fatty acids) over 24 hours when patients were on RELiZORB as compared to placebo. The ITT population included all patients (n=33) who received one administration of enteral formula through RELiZORB and one administration through a placebo cartridge.

Plasma concentrations of DHA and EPA were analyzed using ultra high performance liquid chromatography (UHPLC). The sum of total DHA and EPA plasma concentrations at each time point (baseline, 1, 3, 7, 9, 12 and 24 hours) was used to measure the absorption of fats by assessing the plasma absorption kinetics and bioavailability profile, represented by the area under the curve ($AUC_{0\text{-}24h}$) and maximum measured plasma concentration (C_{max}) during the 24-hour period for DHA and EPA using the crossover design with period and treatment effects in the model. $AUC_{0\text{-}24h}$ was calculated using a time-weighted average for each patient and compared enteral formula administered through RELiZORB or a placebo. Due to inter-subject variability in baseline DHA and EPA plasma concentrations, values for DHA and EPA plasma concentrations were baseline-adjusted prior to analysis. Results are shown in Figures 12 and 13.

Baseline plasma concentrations of DHA and EPA were 30.8 ± 16.1 for DHA and 17.5 ± 11.2 µg/mL for EPA. Baseline concentrations of DHA and EPA were low, and were consistent with observations from other published studies in patients with CF.[10-15]

**DHA and EPA (omega-3 fatty acids) in plasma provide a strong correlation with overall fat absorption and correlates with levels incorporated in membranes (eg, erythrocyte, monocyte, and thrombocyte membrane).[16] People with CF have abnormal fatty acid metabolism with increased release and turnover of arachidonic acid (AA) and decreased levels of DHA, EPA and linoleic acid (LA) in plasma, erythrocytes, platelets and tissues.[10,17,18]*

FIGURE 12: Changes in plasma concentrations of DHA & EPA (omega-3 fatty acids).



A. *Mean (SEM) baseline-adjusted plasma profile change for total EPA + DHA concentration over 24h. Represents change with use of RELiZORB or placebo over 24-hour period, with Time 0 representing the baseline value prior to enteral feeding (pre-dose value). For each period the baseline level is subtracted so that each point on the graph represents the change from baseline.*
B. *Mean (SEM) baseline adjusted maximum measured plasma concentration (C_{max}) for total DHA + EPA. Error bars display standard error of the mean. Baseline levels are subtracted so that C_{max} represents the change from baseline.*

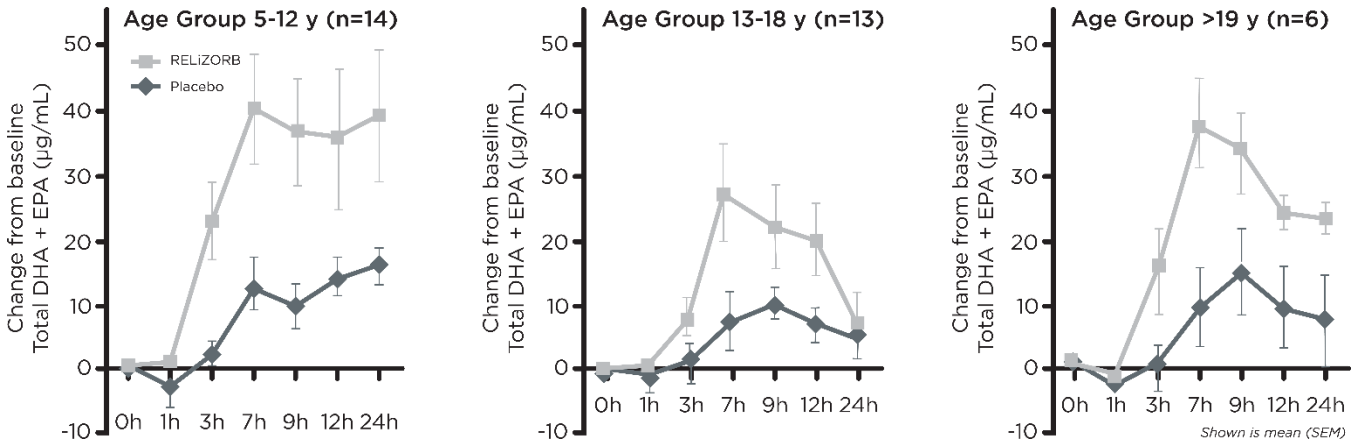
Mean plasma concentrations of total DHA and EPA (omega-3 fatty acids) significantly increased with administration of enteral formula through RELiZORB compared with administration through placebo. Calculated net $AUC_{0\text{-}24h}$ for baseline adjusted changes for DHA and EPA was significantly increased ($p<0.001$) with formula administered through RELiZORB (537± 400 µg*hr/mL) compared with formula administered through placebo (192 ± 199 µg*hr/mL) resulting in a 2.8 fold change.

The maximum plasma concentration of DHA and EPA in 24 hours (C_{max}) occurred at 7 hours after initiation of enteral feeding. C_{max} for DHA and EPA was higher with formula administered through RELiZORB (42.8 ± 22.9 µg/mL) compared with formula administered through placebo (20.2 ± 13.5 µg/mL) resulting in a 2.1 fold change.

The increase from baseline to the mean C_{max} observed with RELiZORB use (Figure 12) resulted in a plasma concentration that approximates plasma reference concentrations of DHA and EPA in the literature[15, 17, 18, 19].

The difference in fat absorption between placebo and RELiZORB, as represented by the area under the curve for baseline adjusted plasma concentrations of total DHA and EPA over 24 hours ($AUC_{0\text{-}24h}$) was consistent across age groups, *$p<0.001$* (Figure 13).

FIGURE 13: Changes in plasma concentrations of DHA and EPA (omega-3 fatty acids) by age group.



Mean (SEM) baseline-adjusted plasma profile change for total DHA + EPA concentration over 24h. Error bars display standard error of the mean. Represents change with use of RELiZORB or placebo over 24-hour period with Time 0 representing baseline value prior to enteral feeding (pre-dose value). For each treatment period, baseline level is subtracted so that each point on the graph represents the change from baseline.

Fat absorption with RELiZORB, as represented by the $AUC_{0\text{-}24h}$ for plasma concentrations of total DHA and EPA was of a similar magnitude in those patients with CFRD (n=12) or without CFRD (n=21).

13.0 HOW SUPPLIED/STORAGE AND HANDLING

CONTENTS:	Primary package: One (1) RELiZORB
STORAGE:	2°C to 27°C (36°F to 80°F). Do not freeze.

14.0 SPECIFICATIONS

	SINGLE RELiZORB* 2 cartridges/day	**TANDEM RELiZORB*** One tandem configuration (2 cartridges)/day
ENTERAL FORMULA VOLUME:	Up to 500 mL	500-1000 mL
ENTERAL PUMP FLOW RATE:	10-120 mL/hr	24-120 mL/hr
OPERATING TEMPERATURE:	Room temperature	

*Do not exceed use more than 24 hours in either single or tandem configuration

15.0 TROUBLESHOOTING

SYMPTOM	PROBABLE CAUSE(S)	CORRECTION(S)
Flow Error Alarm	See pump instructions for probable cause.	If none of the corrective actions offered by the pump instructions correct the Flow Error Alarm, remove the RELiZORB and replace it with a new RELiZORB.
Leakage from RELiZORB Connections	Improper connection of inlet or outlet fitting.	Disconnect and re-connect RELiZORB with a twisting motion until secure.
Incomplete Priming	Auto prime may not pump formula completely through the cartridge.	Use manual prime to completely prime the RELiZORB and patient extension set.

16.0 REFERENCES

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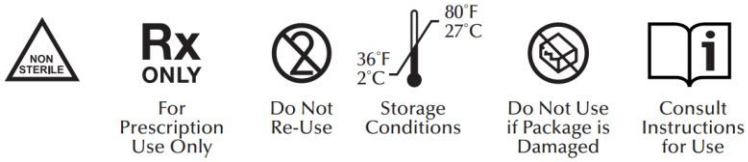

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