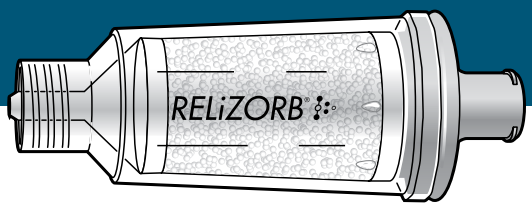


RELiZORB®

(iMMOBILIZED LIPASE) CARTRIDGE

Table of Contents

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

1.0 INDICATIONS FOR USE

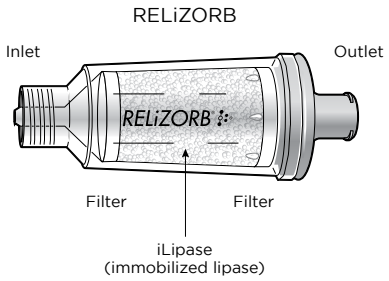
RELiZORB is indicated for use in pediatric patients (ages 2 years and above) and adult patients to hydrolyze fats in enteral formula.

2.0 DESCRIPTION

RELiZORB is a single use, point-of-care digestive enzyme cartridge that connects in-line with existing enteral feeding supplies. 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.

RELiZORB is comprised of a clear cylindrical, plastic cartridge with a single inlet connection port and a single orange outlet connection port. The inlet and outlet ports of RELiZORB are intended to connect in-line with enteral feeding supplies. 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 1: 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 formula or tubing 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 RELiZORB. Any compromise of the structural integrity of RELiZORB may lead to improper connection to enteral feeding supplies, enteral formula leakage or risk of contamination.
- Do not use RELiZORB after the date marked on the pouch.
- Do not use blenderized formulas with RELiZORB. A detailed listing of enteral formulas compatible with RELiZORB can be found at www.relizorb.com/compatibility.

- RELiZORB is designed for use with enteral feeding pump systems with low flow/no flow alarms and enteral syringes for bolus syringe push. A detailed listing of formulas, pumps, and enteral feeding supplies compatible with RELiZORB can be found at www.relizorb.com/compatibility.
- Do not use excessive force when using RELiZORB with bolus syringe feeding method.
- Do not rush bolus feeds. Follow guidance from your healthcare professional on how long it should take you to complete your tube feeding.
- Ensure all inlet and outlet connectors on RELiZORB and enteral feeding supplies are clean and dry prior to making connections.
- 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.
- Up to 6 RELiZORBs can be used in a day (24-hour period) and there are no requirements on the amount of time between using them.
- For continuous or bolus feedings with an enteral pump, 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 continuous feedings with an enteral pump, for volumes greater than 500 mL and up to 1000 mL, you can connect 2 RELiZORB cartridges together in a tandem configuration. RELiZORB has been evaluated with enteral pump flow rates listed in the table below:

	SINGLE RELiZORB* 6 cartridges/day	**TANDEM RELiZORB*** 3 tandem configurations (6 cartridges)/day
ENTERAL FORMULA VOLUME (per feeding)**:**	Up to 500 mL	500-1000 mL
ENTERAL PUMP FLOW RATE:	10-400 mL/hr	24-150 mL/hr

*For continuous feeding, do not exceed use for more than 24 hours in either single or tandem configuration.

- For bolus feedings using the enteral syringe push feeding method, a single RELiZORB may be used for up to 250 mL of enteral formula.
- 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 has 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/compatibility.
- RELiZORB has been tested for up to a 1-hour stop/pause in feeding with an enteral pump 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 3 different setup procedures depending on the feeding administration type and feeding formula volume:

(A) Enteral feeding with pump for up to 500 mL using 1 single RELiZORB cartridge.

(B) Enteral feeding with pump for greater than 500 mL and up to 1000 mL using tandem RELiZORB configuration.

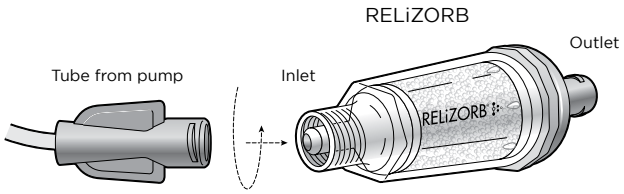
(C) Bolus feeding with RELiZORB by enteral syringe push for up to 250 mL using 1 single RELiZORB cartridge

IMPORTANT: WHEN CONNECTING RELIZORB TO ENTERAL FEEDING SUPPLIES OR ANOTHER RELiZORB, GENTLY TWIST, DO NOT OVERTIGHTEN. IT USUALLY NEEDS JUST A QUARTER-TURN TO BE SECURE. AVOID GETTING FORMULA IN THE ENFIT® CONNECTIONS.

A. SETUP PROCEDURE FOR ENTERAL FEEDING WITH PUMP FOR UP TO 500 ML USING 1 SINGLE RELIZORB CARTRIDGE.

1. Set up the pump and enteral feeding pump tubing set per the pump 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 gentle twisting motion until secure (it usually needs just a quarter turn) as shown in Figure 2.

Figure 2: Securing RELiZORB inlet to outlet fitting from pump tubing.

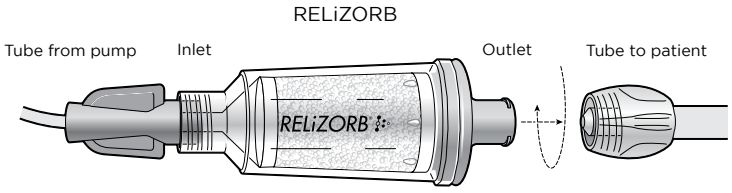


5. Prime the enteral feeding pump tubing per the manufacturer's instructions.
6. Manually prime the enteral formula through the RELiZORB, up to the outlet by holding the prime button on the enteral feeding pump.

NOTE: Ensure enteral formula does not come out of the RELIZORB outlet. If formula drips out, wipe away excess formula to keep connections clean and dry.

7. Connect the 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 3.

Figure 3: Connecting RELiZORB outlet to patient extension set or enteral feeding tube that connects to patient.

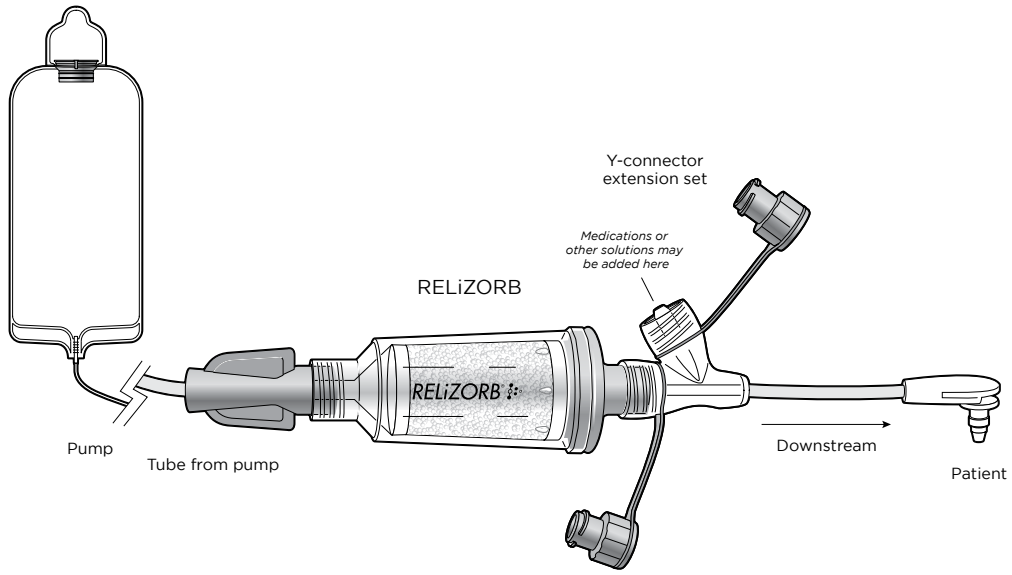


NOTE: Do not overtighten when connecting RELiZORB to enteral tubing. It usually needs just a quarter-turn to be secure.

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, flushes or other non-enteral formula liquids are to be added, they must be introduced ***AFTER*** RELiZORB (i.e., 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 4.

Figure 4: Medications may be added between RELiZORB and patient.



NOTE: If medications or flush solutions are added BEFORE the RELiZORB cartridge, then RELiZORB must be discarded. You may re-start feeding using a new RELiZORB. Please follow Steps 1-9 to re-start the process.

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

a) Pause the pump following the pump manufacturer's instructions

b) Disconnect the current RELiZORB from the patient extension set or enteral feeding tube

c) Remove the current RELiZORB from the enteral feeding pump tubing set

d) Connect the new RELiZORB to the enteral feeding pump tubing set following Step 4

e) Check your tube connector and clean any residue before connecting

f) Prime the enteral formula through to the end of the RELiZORB following Step 6

g) Connect the new RELiZORB to the patient extension set or enteral feeding tube following Step 7

h) Follow Step 8 if a patient extension set is being used

i) Follow Step 9 to re-start enteral formula delivery

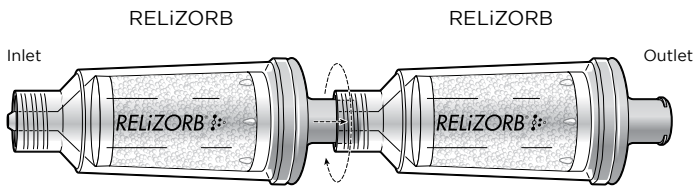
B. SETUP PROCEDURE FOR ENTERAL FEEDING WITH PUMP FOR GREATER THAN 500 ML AND UP TO 1000 ML USING TANDEM RELIZORB CONFIGURATION.

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 3 such uses 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.
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 or defective
   - 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 5.

Figure 5: Connecting RELiZORB cartridges together to form a tandem RELiZORB configuration.



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 gentle twisting motion until secure (it usually needs just a quarter turn) as shown in Figure 6.

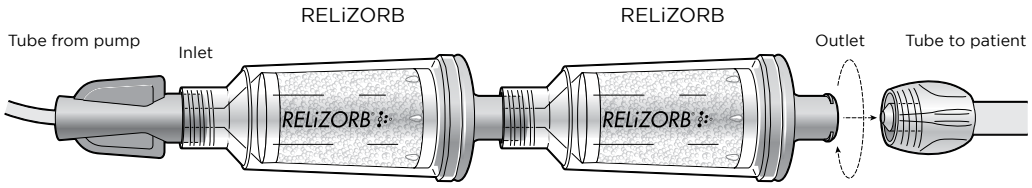
Figure 6: Securing tandem RELiZORB inlet to outlet fitting from pump tubing.

6. Prime the enteral feeding pump tubing per the manufacturer's instructions.
7. Manually prime the enteral formula through the RELiZORBs, up to the outlet by holding the prime button on the enteral feeding pump.

NOTE: Ensure enteral formula does not come out of the RELIZORB outlet. If formula drips out, wipe away excess formula to keep connections clean and dry.

8. 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 7.

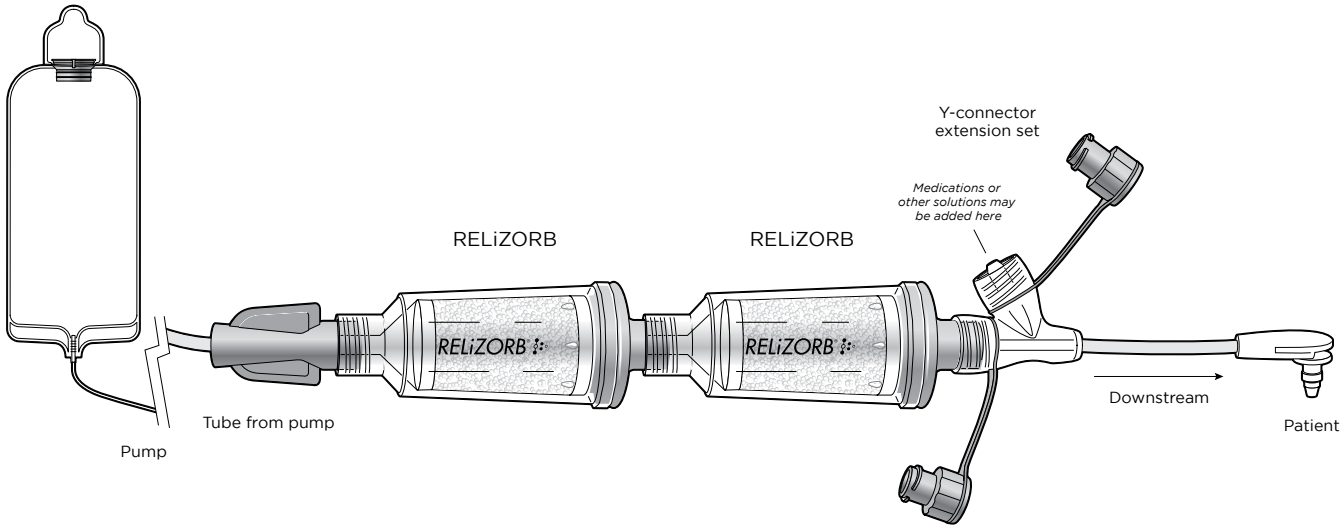
Figure 7: Connecting tandem RELiZORB outlet to patient extension set or enteral feeding tube that connects to patient.



9. 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.
10. Set the pump to the prescribed flow rate and proceed with feeding.

WARNING: If medications, flushes or other non-enteral formula materials are to be added, they must be introduced ***AFTER*** the tandem RELiZORB (i.e., 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 8.

Figure 8: Medications may be added between the tandem RELiZORB and patient.



NOTE: If medications or flush solutions are added BEFORE the tandem RELiZORB, then both RELiZORBs must be discarded. You may re-start feeding using 2 new RELiZORBs. Please follow Steps 1-10 to re-start the process.

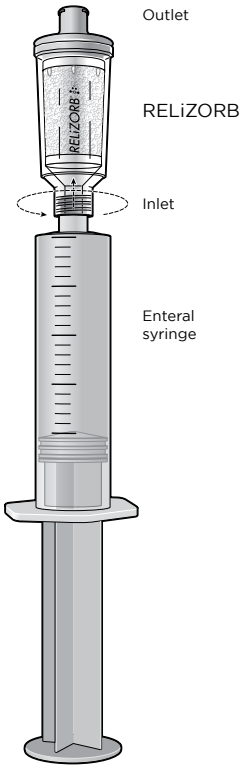
C. BOLUS FEEDING WITH RELiZORB BY SYRINGE PUSH FOR UP TO 250 ML USING 1 SINGLE RELiZORB CARTRIDGE.

1. Pour the required volume of formula into a clean container.

NOTE: Approximately 2 mL of enteral formula is retained in the RELiZORB cartridge during bolus feeding. Consult your healthcare provider on formula volume for bolus feeds.

2. Draw the formula up into the appropriately sized enteral syringe. Remove any air from the syringe and wipe the outlet of the enteral syringe of any excess formula.
3. Remove the RELiZORB pouch from its carton. Examine the RELiZORB pouch. Do not use RELiZORB if:
    - The pouch seal is broken
    - The current date is past the expiration date shown on the pouch
4. Remove the RELiZORB from its pouch. Examine the RELiZORB. Do not use RELiZORB cartridge if:
    - The RELiZORB is damaged or defective
    - The RELiZORB has previously been used
5. Turn the enteral syringe with the syringe tip facing upward. Secure the syringe to the RELiZORB by inserting the tip of the enteral syringe into the inlet fitting of RELiZORB with a gentle quarter turn twisting motion until secure as shown in Figure 9.

Figure 9: Enteral syringe filled with formula facing upward attached to RELiZORB.

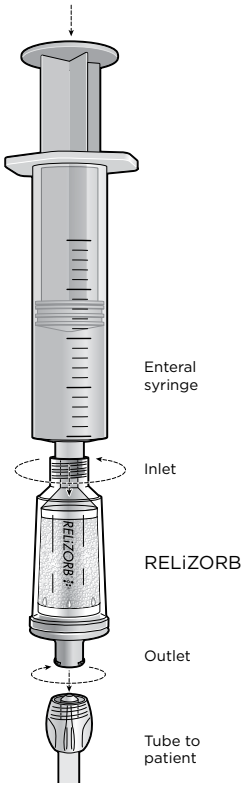


6. Position the syringe with the RELiZORB outlet facing up. Gently press the enteral syringe plunger to prime the enteral formula through the RELiZORB cartridge and expel excess air.

NOTE: Ensure enteral formula does not come out of the RELIZORB outlet. If formula drips out, wipe away excess formula to keep connections clean and dry.

7. Flip the enteral syringe and RELiZORB connection over. Secure the feeding tube that connects to the patient to RELiZORB by inserting the outlet fitting from RELiZORB into the inlet fitting of the patient feeding tube set with a twisting motion until secure as shown in Figure 10.

Figure 10: Connecting RELiZORB outlet to patient extension set or enteral feeding tube that connects to patient.



8. If a patient extension set is being used, prime the feeding formula to the end of the patient extension set.
9. Unclamp the feeding tube and gently push the enteral syringe plunger for the enteral formula to flow through the RELiZORB and through the feeding tube.

NOTE: Do not rush the feed. Consult with your healthcare provider on how long the bolus feeding should take.

WARNING: RELiZORB is for use with enteral formula only. Do not administer medications, flushes, or non-enteral formula materials through the RELiZORB device.

NOTE: If medications or flush solutions are added ***BEFORE*** the RELiZORB cartridge, then RELiZORB should be discarded. You may re-start feeding using a new RELiZORB. Please follow Steps 1-9 to re-start the process.

10. Once the syringe is empty, clamp the feeding tube. If more formula is required based on the volume prescribed by your healthcare provider, remove the syringe and repeat the process until you have reached your required amount of formula.
11. Once the feeding is complete, remove the RELiZORB from the syringe and your feeding tube and discard.

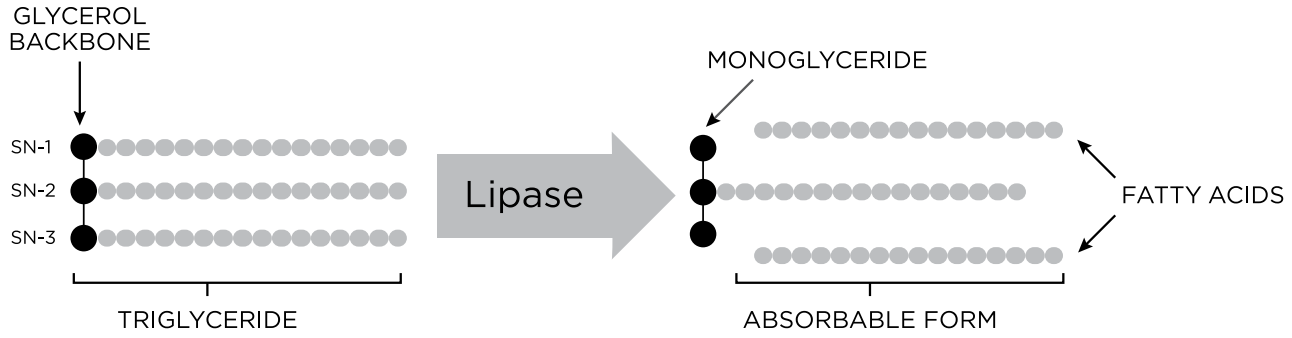
8.0 DISASSEMBLY AND DISPOSAL

When feeding is complete, disconnect the RELiZORB, and discard.

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 11). 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 11: 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, 10-400 mL/hr in single configuration and 24-150 mL/hr in tandem configuration, and commercially available enteral formulas with varying product characteristics and components (Table 1). RELiZORB is not compatible with blenderized formulas.

Representative Fat Hydrolysis Data Using RELiZORB

The following tube feeding formulas have been evaluated for use with RELiZORB in the following use conditions:

1. Continuous feeding with enteral pump using single (~500 mL of formula) and tandem (~1000 mL of formula) RELiZORB at 120 mL/hour
2. Bolus feeding with a single RELiZORB at maximum feed rate of ~400 mL/hour

Table 1: Enteral tube feed formulas evaluated with RELiZORB.

Enteral tube feed formulas evaluated with RELiZORB								
Formula Name	Per serving						Fat Hydrolysis (%)*	
							Continuous	Bolus**
	Fat (g)	Calories (kcal)	Contains pre-hydrolyzed protein	Contains Insoluble Fiber	MCT:LCT ratio	Omega-3 DHA & EPA (g)	Single and Tandem RELiZORB at 120 mL/hour with enteral pump (Condition 1)	Single RELiZORB at 400 mL/hour with enteral pump or syringe push (Condition 2)
Compleat® Pediatric Standard 1.4	16	350	-	X	20:80	-	36	32
EleCare® Junior†	12.3	254	X	-	-	-	47	48
Impact® Peptide 1.5	15.9	375	X	-	50:50	1.23	82	73
Kate Farms® Pediatric Peptide 1.5	17	375	X	X	40:60	-	62	53
Kate Farms® Pediatric Standard 1.2	12	300	-	X	40:60	-	44	40
Neocate® Junior†	12.5	250	X	-	35:65	-	43	46
Neocate® Splash	12.1	237	X	-	-	-	NR	46
Novasource® Renal	24	475	-	-	-	-	38	26
Nutren® 1.5	15	375	-	-	20:80	-	65	50
Nutren® 2.0	23	500	-	-	50:50	-	78	42
Osmolite® 1.0 Cal	8.2	250	-	-	-	-	60	52
Osmolite® 1.2 Cal	9.3	285	-	-	-	-	60	NR
Osmolite® 1.5 Cal	11.6	355	-	-	-	-	51	NR
PediaSure® 1.0	9	240	-	-	-	-	56	NR
PediaSure® 1.5	16	350	-	-	-	0.03	57	45
PediaSure® Peptide 1.0	9.6	237	X	-	-	-	56	55
PediaSure® Peptide 1.5	14.4	356	X	-	-	-	72	59
Peptamen®	10	250	X	-	70:30	-	68	72
Peptamen AF®	13.5	300	X	-	50:50	0.60	63	59
Peptamen® 1.5	14	375	X	-	70:30	-	74	68
Peptamen Junior®	9.5	250	X	-	60:40	-	63	54
Peptamen Junior® 1.5	17	375	X	-	60:40	0.15	75	48
Peptamen Junior® with Fiber	9.5	250	X	X	60:40	-	59	57
Pivot® 1.5 Cal	12	355	X	-	-	0.90	50	NR
TwoCal® HN§	21.5	475	-	-	-	-	36	20
Vital® 1.0	9	237	X	-	-	-	68	55
Vital® AF 1.2 Cal	12.8	284	X	-	-	0.90	61	57
Vital® 1.5 Cal	13.5	355	X	-	-	-	87	55

*Fat hydrolysis (%) is estimated based on label claim fat content.
**Representative hydrolysis for the following use conditions: Enteral pump for 500 mL at 400 mL/hr, Syringe push bolus of 250 mL with delivery of ~7 mL per min.
†Powdered formulas were tested at 30 kcal/oz.
§Fat hydrolysis rates are similar over the shelf life of RELiZORB.
NR—Not recommended

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

11.0 PRE-CLINICAL STUDIES

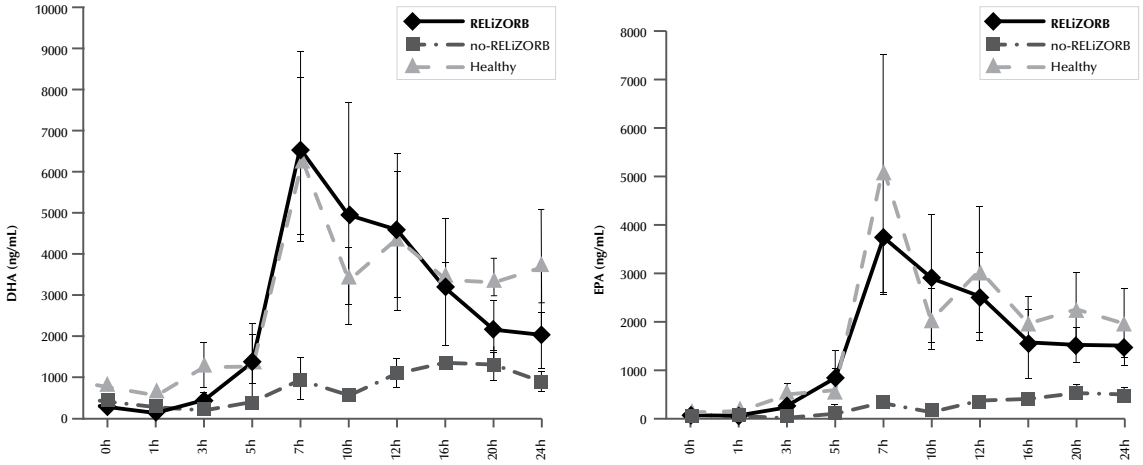
The efficacy, safety and intended use of RELiZORB was evaluated in porcine models of fat malabsorption: exocrine pancreatic insufficiency (EPI, 2 studies), and short bowel syndrome (SBS, 2 studies).

The well-established pre-clinical porcine model of exocrine pancreatic insufficiency (EPI) mimics the inability to digest and absorb fats. 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.

24-HOUR PLASMA FATTY ACID UPTAKE: SAFETY, TOLERABILITY AND FAT ABSORPTION WITH USE OF RELIZORB IN ENTERAL (TUBE) FEEDING.

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 plasma levels of omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) over 24 hours compared to animals receiving enteral formula that was not administered through RELiZORB ($p<0.05$) (Figure 12). The clinical significance of these findings has not been determined.

Figure 12: Plasma DHA and EPA concentration over 24-hour period after single administration of formula (500 mL) passed through 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 mean ± SD (n=3 to 5).



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

The safety, tolerability and fat absorption in plasma with repeated use of RELiZORB with supplemental nightly enteral feeding were evaluated in conditions consistent with the intended use in a second study conducted in the EPI porcine model. This was a parallel group study with (n=6) and without (n=5) 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).

There was enhanced fat absorption and caloric intake as demonstrated by improved plasma levels of DHA and EPA in animals receiving enteral formula administered through RELiZORB compared to control animals without RELiZORB (Table 2). 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 2: 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

Results are shown as mean ± 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.

Higher plasma levels of fat-soluble vitamins (Vitamin D, E) were observed with use of RELiZORB (Table 3). The clinical significance of this finding has not been determined.

Table 3: Fat-soluble vitamin plasma 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

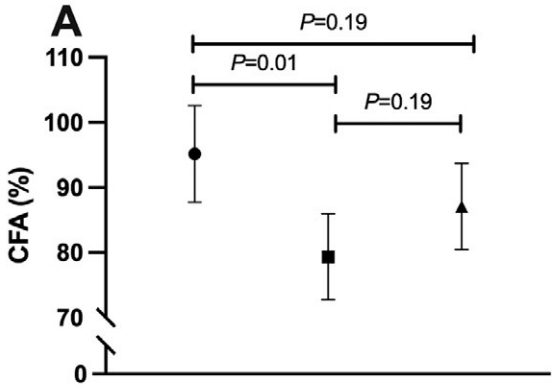
Results are shown as mean ± SD.*p<0.05 for difference between RELiZORB vs. No RELiZORB for Vitamin D and Vitamin E.

14-DAY SAFETY, TOLERABILITY AND FAT ABSORPTION WITH REPEATED USE OF RELiZORB IN A PORCINE MODEL OF SHORT BOWEL SYNDROME.

The ability of RELiZORB to improve fat and nutrient absorption was evaluated in a porcine model of short bowel syndrome (SBS) with preserved pancreatic function. SBS piglets with 75% bowel resection gain less weight, develop fat malabsorption, and demonstrate a decrease in fat-soluble vitamin concentrations, representing important clinical conditions in the pediatric and adult SBS populations. This was a parallel study with three groups: no intestinal resection (n=5), 75% resection (n=5), and 75% resection plus RELiZORB (n=5). After recovery, the animals were treated for 14 days. Piglets received 60% of calories from continuous enteral nutrition (EN) and 40% from chow.

Enteral feeding use with RELiZORB was associated with improved fat and fat-soluble vitamin absorption compared to resected animals. Animals receiving enteral formula administered through RELiZORB had similar weight gain compared to resected piglets. Animals in the 75% resection group had a significantly lower coefficient of fat absorption (CFA) compared to unresected controls (79.1% vs. 95.2%, p=0.01, Figure 13). There was no statistically significant difference in the CFA between resected animals that received EN through RELiZORB and unresected controls (87.1% vs. 95.2%, p=0.19). Although not reaching statistical significance, the mean CFA in animals receiving EN administered through RELiZORB was higher (87%) than that in untreated, resected animals (79%). Animals receiving EN administered through RELiZORB had increased plasma concentrations of HDL, vitamins D and E, and decreased serum triglyceride concentrations. There was no evidence of an increased frequency of adverse events in animals receiving EN with RELiZORB compared to the other groups (p=1.00).

Figure 13: Coefficient of Fat Absorption



Stool was collected for 72-h and was analyzed for fat content to determine the coefficient of fat absorption in animals with no resection (● circle, n=4), 75% resection (■ square, n=5), and 75% resection + RELiZORB (▲ triangle, n=5). Statistical analyses of the experimental groups were done using analysis of variance (ANOVA) with a Tukey-Kramer adjustment for multiple comparisons. Results are expressed as mean ± SE.

14-DAY SAFETY, TOLERABILITY AND FAT ABSORPTION WITH REPEATED USE OF RELiZORB IN A PORCINE MODEL OF SHORT BOWEL SYNDROME RECEIVING PARENTERAL NUTRITION.

The safety and efficacy of RELiZORB was evaluated when used in conjunction with bolus enteral feeding in weaning parenteral nutrition in a porcine model of short bowel syndrome (SBS) with intestinal failure.

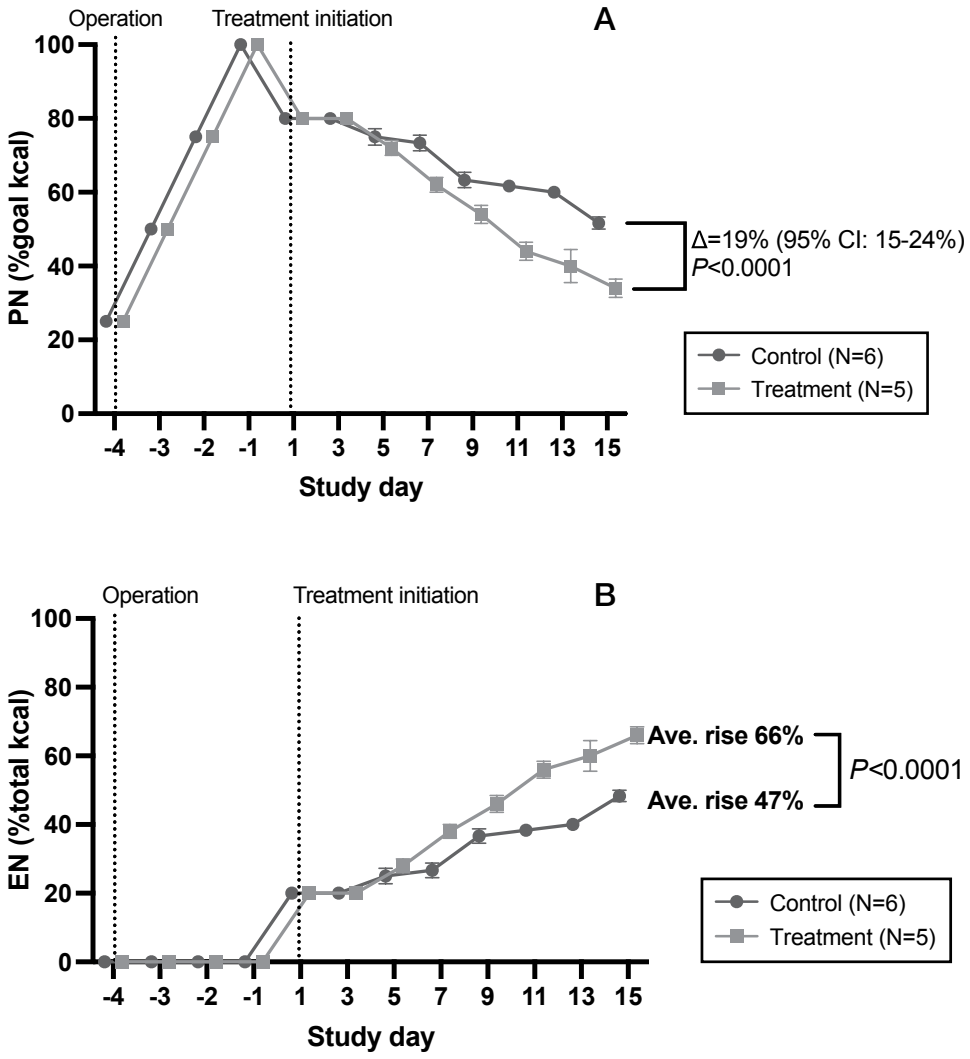
This was a parallel study with two groups: 75% intestinal resection (n=6) and 75% resection plus RELiZORB (n=5). Parenteral nutrition (PN) was initiated post-operatively and was decreased as enteral nutrition (EN) was advanced. EN was delivered daily via 6 bolus feedings with or without RELiZORB for 14 days.

When used with enteral feeding, RELiZORB reduced PN dependence, improved nutrient absorption, and increased bowel growth. All piglets received similar calories and had similar weight gain. Animals in the RELiZORB group had a 19% greater reduction in PN Calories (95% CI: 12-27%, p=0.0002, Figure 14). This coincided with a 66% increase in EN calories for treatment animals compared to 47% for control animals (p<0.0001).

Omega-3 fatty acids were elevated on Day 15 in treatment animals compared to controls (187±10 vs. 121±9 µg/mL, p=0.0001). The omega-3 fatty acid DHA was 1.4-fold higher in the RELiZORB group (41.9±2.6 vs. 29.9±2.3 µg/mL, p=0.004). Similarly, the plasma concentration of EPA was 1.9-fold higher in treatment animals compared to controls (89.1±4.6 vs. 46.5±4.2 µg/mL, p<0.0001). These results were consistent with the percent fatty acid composition of EN and indicate a superior fat absorption in the RELiZORB treated animals.

Intestinal crypt cell proliferation was 1.9-fold higher in the RELiZORB group compared to control (41.9 vs. 22.4 Ki67+ cells/crypt, p=0.02) which was accompanied by a significant increase in intestinal length (19.5% vs. 0.7%, p=0.03), and a significantly higher (p=0.02) plasma glucagon-like peptide-2 (GLP-2) concentration on Day 15. No device-specific adverse events or organ toxicity were observed.

Figure 14: Delivery of Parenteral (A) and Enteral (B) Nutrition. Statistical comparison of the groups at Day 15 was done using analysis of covariance (ANCOVA) adjusted for baseline (Day -1). Data are jittered left and right to prevent overlap. Results are expressed as mean ± SEM. CI: confidence interval; Δ: difference.



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 4). 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. 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 4.

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 4).

*Table 4: 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 4 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 5.

*Table 5: 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	1 (1)	1 (1)

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

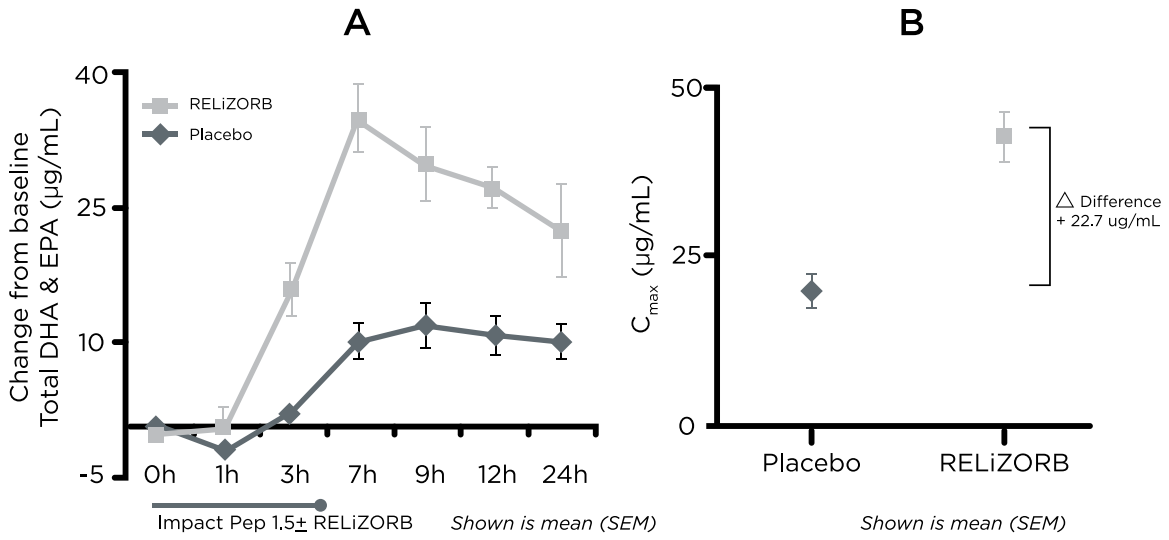
EFFICACY: FAT ABSORPTION EVALUATION: During the randomized double-blind, placebo controlled, crossover Period B, patients (n=33) received 500 mL of an enteral formula [Impact® Peptide 1.5; 32 (g) fat and 2.45 (g) DHA/EPA] with fixed quantities of DHA and EPA* as well as total fat over 4 hours (120 mL/h). 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 15 and 16.

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.

**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). 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.*

Figure 15: 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.

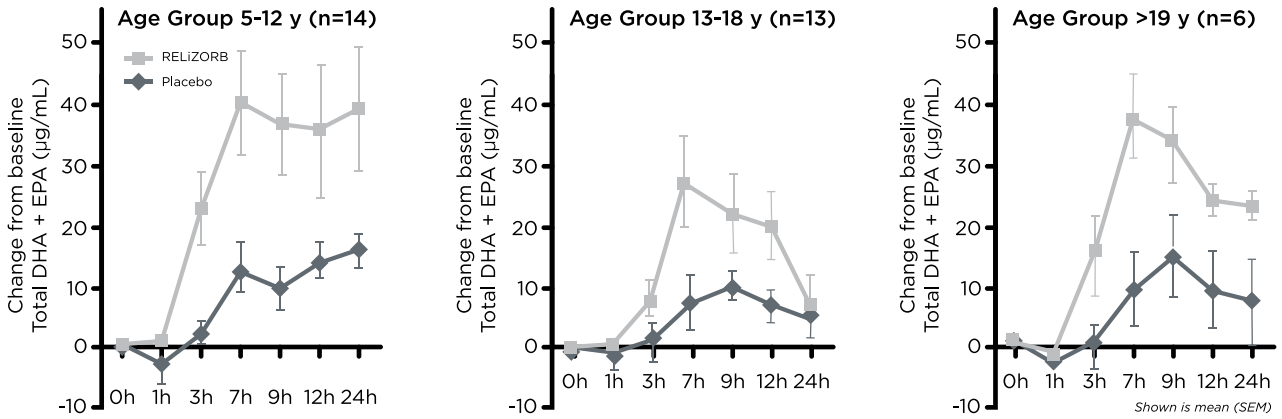
Mean plasma concentrations of total DHA and EPA (omega-3 fatty acids) significantly increased with administration of enteral formula through RELiZORB compared with administration through placebo. Calculated net $AUC_{0\text{-}24h}$ for baseline adjusted changes for DHA and EPA was significantly increased ($p<0.001$) 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 15) resulted in a plasma concentration that approximates plasma reference concentrations of DHA and EPA in the literature.

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 16).

Figure 16: 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

Feeding with an enteral pump*:

	SINGLE RELiZORB	TANDEM RELiZORB
USE:	Up to 6 cartridges/day	Up to 3 tandem configurations 6 cartridges/day
ENTERAL FORMULA VOLUME:	Up to 500 mL	500-1000 mL
ENTERAL PUMP FLOW RATE:	10-400 mL/hr	24-150 mL/hr
OPERATING TEMPERATURE:	Room temperature	

*For continuous feeding, do not exceed use for more than 24 hours in either single or tandem configuration.

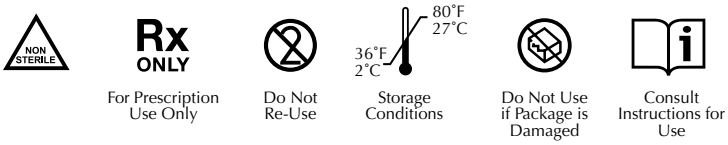
Feeding with an enteral syringe:

	SINGLE RELiZORB for Enteral Syringe Push
USE:	Up to 6 cartridges/day
ENTERAL FORMULA VOLUME:	Up to 250 mL
OPERATING TEMPERATURE:	Room temperature

15.0 TROUBLESHOOTING

SYMPTOM	PROBABLE CAUSE(S)	CORRECTION(S)
Flow Error Alarm during enteral pump feeding	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. Confirm that the syringe and patient extension set/tubing are clean and dry prior to connecting and that they are connected properly.
Incomplete priming during enteral pump feeding	Auto prime may not pump formula completely through the cartridge	Use manual prime to completely prime the RELiZORB and patient extension set.

CUSTOMER SERVICE NUMBER:
1-844-632-9271
WWW.RELIZORB.COM



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