

# RELiZORB<sup>®</sup>

(IMMOBILIZED LIPASE) CARTRIDGE

## Table of Contents

1.0	INDICATIONS FOR USE .....	2
2.0	DESCRIPTION .....	2
3.0	CONTRAINDICATIONS.....	2
4.0	WARNINGS.....	2
5.0	CAUTIONS AND PRECAUTIONS .....	2
6.0	PRODUCT USE .....	3
7.0	RELiZORB SETUP PROCEDURE AND USE .....	3
8.0	DISASSEMBLY AND DISPOSAL .....	12
9.0	MECHANISM OF ACTION.....	12
10.0	<i>IN VITRO</i> PERFORMANCE CHARACTERISTICS.....	13
11.0	PRE-CLINICAL STUDIES .....	16
12.0	CLINICAL STUDY SUMMARY .....	19
13.0	HOW SUPPLIED/STORAGE AND HANDLING .....	23
14.0	SPECIFICATIONS .....	23
15.0	TROUBLESHOOTING .....	24

**PLEASE READ AND FULLY UNDERSTAND THESE INSTRUCTIONS FOR USE BEFORE USING RELiZORB<sup>®</sup>.**

## 1.0 INDICATIONS FOR USE

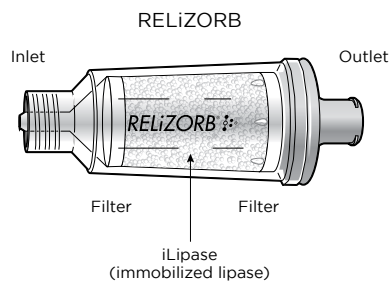
RELiZORB is indicated for use in pediatric (including neonates and infants) and adult patients to hydrolyze fats during enteral feeding.

## 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 nutrition, 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 nutrition, 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 nutrition is hydrolyzed as it comes in contact with iLipase as the enteral nutrition passes through the cartridge.

Figure 1: RELiZORB and its major components.



## 3.0 CONTRAINDICATIONS

None.

## 4.0 WARNINGS

- RELiZORB is for use with enteral tube 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 nutrition 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, leakage or risk of contamination.
- Do not use RELiZORB after the date marked on the pouch.
- Enteral nutrition administered through RELiZORB is for immediate consumption through an enteral feeding tube. RELiZORB should not be used to process enteral nutrition for later use. This has not been tested and may result in safety issues.

- RELiZORB is designed for use with enteral feeding pump systems with low flow/no flow alarms and enteral syringes for manual bolus by syringe (push or gravity). A detailed listing of enteral nutrition, pumps, and enteral feeding supplies compatible with RELiZORB can be found at [www.relizorb.com/compatibility](http://www.relizorb.com/compatibility).
- Patients less than 1 year old may be particularly vulnerable to unplanned interruptions of feeding.
- Do not use blenderized formulas with RELiZORB. A detailed listing of enteral nutrition compatible with RELiZORB can be found at [www.relizorb.com/compatibility](http://www.relizorb.com/compatibility).
- Powdered formulas should be mixed periodically during feedings.
- Do not use excessive force on the plunger 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.
- For neonates and infants 6 months of age or younger, 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.
- For infants greater than 6 months of age, pediatric and adult patients, 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 formula. For a single RELiZORB setup, RELiZORB has been evaluated with enteral pump flow rates of 10-400 mL/hr. 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 of formula, you can connect 2 RELiZORB cartridges together in a tandem configuration. For tandem configuration use, RELiZORB has been evaluated with enteral pump flow rates of 24-150 mL/hr.
- For continuous feeding, do not exceed use for more than 24 hours in either single or tandem configuration.
- For manual bolus by syringe (push or gravity), a single RELiZORB may be used for up to 250 mL of enteral nutrition.
- 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 nutrition used.
- RELiZORB has been evaluated for use with numerous commercially available formulas and pasteurized human milk and has been shown to efficiently hydrolyze (digest) fats into absorbable fatty acids and monoglycerides. A detailed listing of enteral nutrition evaluated for use and found to be compatible 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](http://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 4 different setup procedures depending on the feeding administration mode, enteral nutrition type, and feeding volume.

- Enteral feeding with pump for up to 500 mL using 1 single RELiZORB cartridge.
- Enteral feeding with pump for greater than 500 mL and up to 1000 mL using tandem RELiZORB configuration.
- Bolus feeding with RELiZORB by enteral syringe push for up to 250 mL using 1 single RELiZORB cartridge.
- Bolus feeding with RELiZORB by gravity using an enteral syringe for up to 250 mL using 1 single RELiZORB cartridge.

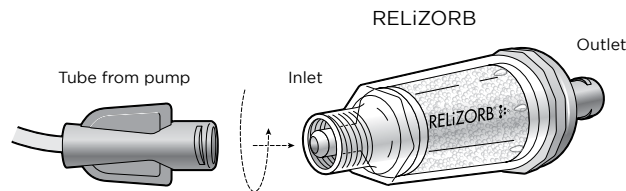
For information on specific enteral nutrition type and use conditions, refer to Table 1 located in the *In vitro* Performance Characteristics section and at [www.relizorb.com/compatibility](http://www.relizorb.com/compatibility).

**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 ENTERAL NUTRITION 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.*



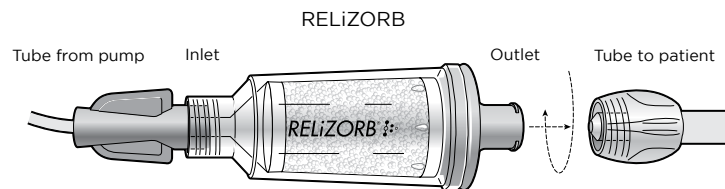
5. Prime the enteral feeding pump tubing per the manufacturer's instructions.
6. Manually prime the enteral nutrition through the RELiZORB, up to the outlet by holding the prime button on the enteral feeding pump.

**NOTE:** Ensure enteral nutrition does not come out of the RELiZORB outlet. If enteral nutrition drips out, wipe away excess enteral nutrition with a damp cloth or gauze and dry. Enteral nutrition residue in connections can harden causing difficulty disconnecting.

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.

**NOTE:** Ensure the extension set or enteral feeding tube is clean and dry. Enteral nutrition residue in connections can harden causing difficulty disconnecting.

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

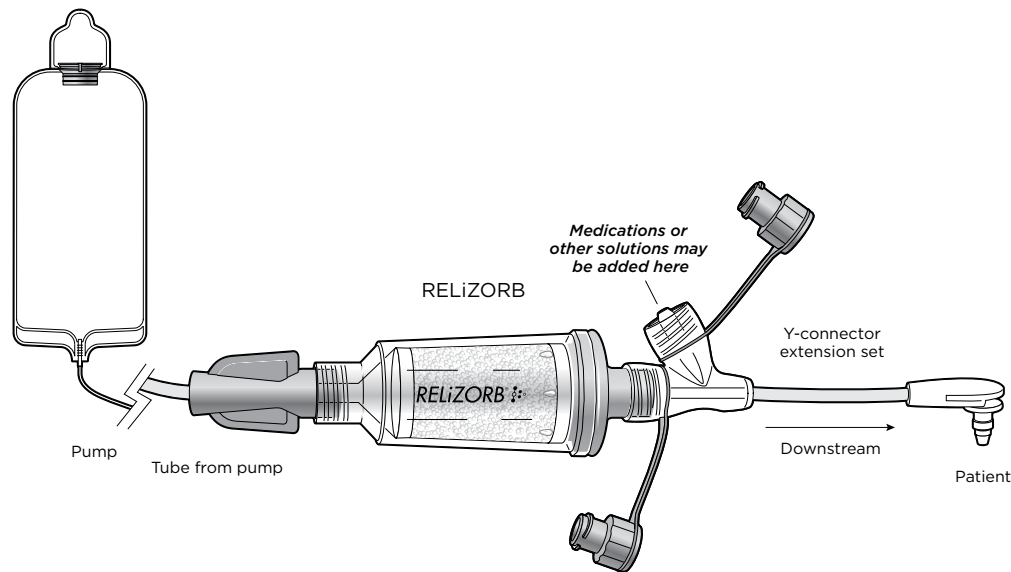


**NOTE:** Do not overtighten when connecting RELiZORB to enteral tubing. It usually needs just a quarter-turn to be secure.

8. If a patient extension set is being used, follow the pump manufacturer's instructions to prime the feeding enteral nutrition 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 nutrition materials are to be added, they must be introduced **AFTER** RELiZORB (i.e., between RELiZORB and the patient). Do not administer medication, flushes or other non-enteral nutrition materials through the same connector that connects directly to RELiZORB. 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) Disconnect the current RELiZORB from the enteral feeding pump tubing set and discard RELiZORB
- d) Clean any enteral nutrition or non-enteral nutrition residues from the enteral feeding pump tubing set connector with a damp cloth or gauze and dry
- e) Connect the new RELiZORB to the enteral feeding pump tubing set
- f) Prime the enteral nutrition 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 nutrition delivery

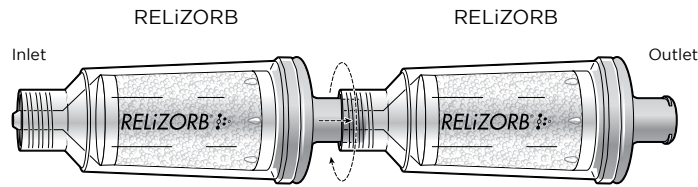
## B. SETUP PROCEDURE FOR ENTERAL FEEDING WITH PUMP FOR GREATER THAN 500 ML AND UP TO 1000 ML USING TANDEM RELiZORB CONFIGURATION.

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.**



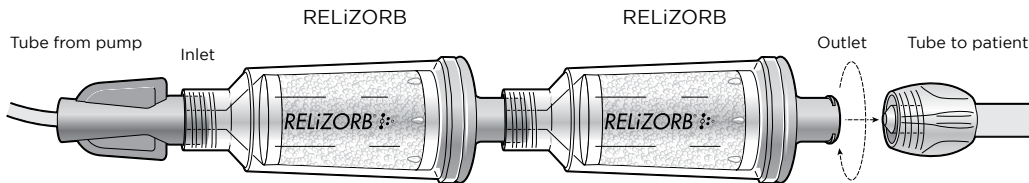
6. Prime the enteral feeding pump tubing per the manufacturer's instructions.
7. Manually prime the enteral nutrition through the RELiZORBs, up to the outlet by holding the prime button on the enteral feeding pump.

**NOTE:** Ensure enteral nutrition does not come out of the RELiZORB outlet. If enteral nutrition drips out, wipe away excess enteral nutrition with a damp cloth or gauze and dry. Enteral nutrition residue in connections can harden causing difficulty disconnecting.

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.

**NOTE:** Ensure the extension set or enteral feeding tube is clean and dry. Enteral nutrition residue in connections can harden causing difficulty disconnecting.

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

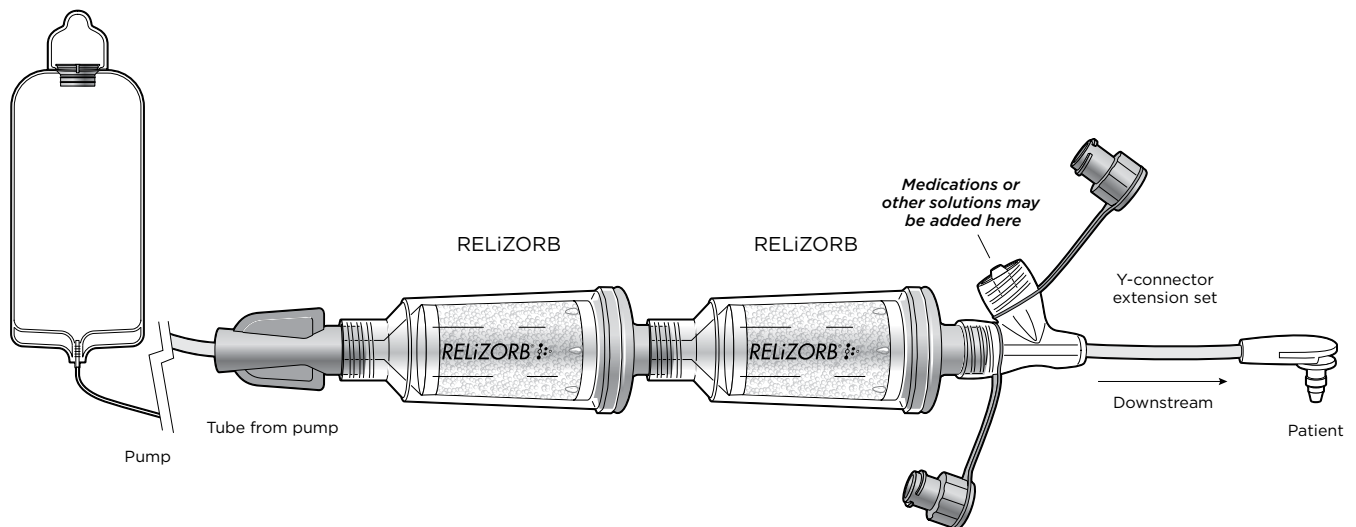


9. If a patient extension set is being used, follow the pump manufacturer's instructions to prime the feeding enteral nutrition to the end of the patient extension set.

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

**WARNING:** If medications, flushes or other non-enteral nutrition materials are to be added, they must be introduced **AFTER** the tandem RELiZORB (i.e., between tandem RELiZORB and the patient). Do not administer medication, flushes or other non-enteral nutrition materials through the same connector that connects directly to RELiZORB. 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.**



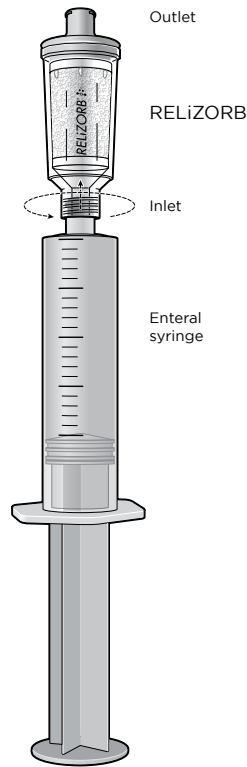
**NOTE:** If medications or flush solutions are added BEFORE the tandem RELiZORB, then both RELiZORBs must be discarded. You may re-start feeding using 2 new RELiZORBs. Please follow Steps 1-10 to re-start the process.

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

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

1. Draw the enteral nutrition up into the appropriately sized enteral syringe. Remove any air from the syringe and wipe the outlet of the enteral syringe of any excess enteral nutrition.
2. 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
3. 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
4. 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 enteral nutrition facing upward attached to RELIZORB.**

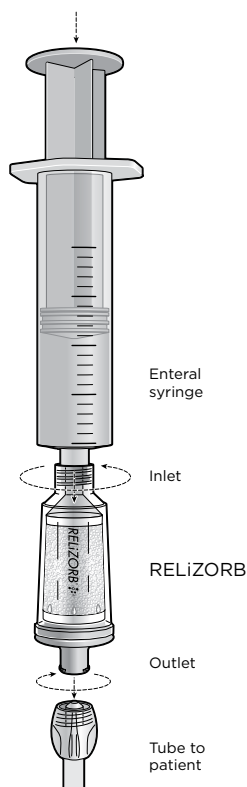


5. Position the syringe with the RELIZORB outlet facing up. Gently press the enteral syringe plunger to prime the enteral nutrition through the RELIZORB cartridge and expel excess air.

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

6. 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.**



7. If a patient extension set is being used, prime the feeding enteral nutrition to the end of the patient extension set.
8. Unclamp the feeding tube and gently push the enteral syringe plunger for the enteral nutrition 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.

**NOTE:** You may also use a syringe pump by inserting the enteral syringe and RELiZORB configuration into a syringe pump for feeding administration.

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

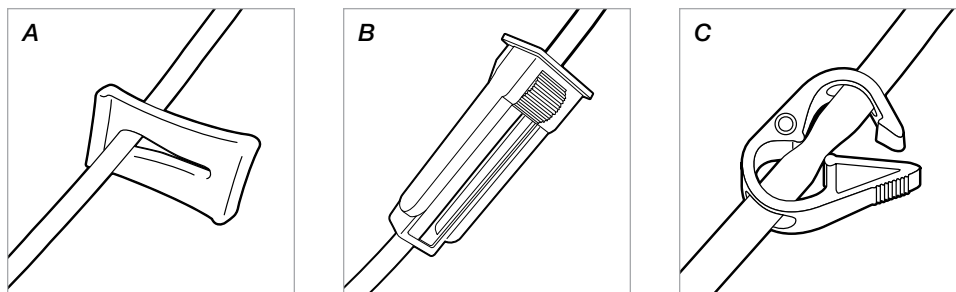
**NOTE:** If medications or flush solutions are added **BEFORE** the RELiZORB cartridge, then RELiZORB should be discarded. You may re-start feeding using a new RELiZORB. Please follow Steps 1-8 to re-start the process.

9. Once the syringe is empty, clamp the feeding tube. If more enteral nutrition 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 enteral nutrition.
10. Once the feeding is complete, remove the RELiZORB from the syringe and your feeding tube and discard.

#### D. BOLUS FEEDING WITH RELiZORB BY GRAVITY USING AN ENTERAL SYRINGE FOR UP TO 250 ML USING 1 SINGLE RELiZORB CARTRIDGE

**NOTE:** It is recommended that a patient extension set with an adjustable clamp, such as a sliding adjustable clamp or a rolling adjustable clamp, is used for this set up to help control the flow of enteral nutrition. If a patient extension set with an adjustable clamp is not available, a patient extension set with a standard clamp can be used. Examples of these extension set clamp types are shown in Figure 11.

*Figure 11: (A) Sliding adjustable clamp (B) Rolling adjustable clamp (C) Standard clamp*

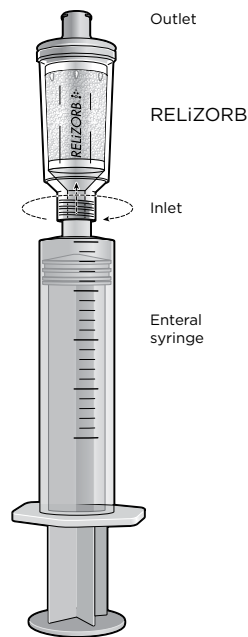


**Gravity feeding with RELiZORB starts with a syringe push to prime the RELiZORB and tubing with enteral nutrition.**

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

1. Using an enteral syringe, draw up enough enteral nutrition that will allow for priming through RELiZORB (approximately 5 mL) plus the additional volume needed to prime through the chosen extension set. Remove any air from the syringe and wipe the outlet of the enteral syringe of any excess enteral nutrition.
2. 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
3. Remove the RELiZORB from its pouch. Examine the RELiZORB. Do not use the RELiZORB cartridge if:
  - The RELiZORB is damaged or defective
  - The RELiZORB has been previously used
4. Turn the enteral syringe so the syringe tip is 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 twisting motion until secure (it usually needs just a quarter turn) as shown in Figure 12.

**Figure 12: Enteral syringe filled with enteral nutrition for priming, facing upward, attached to RELiZORB.**

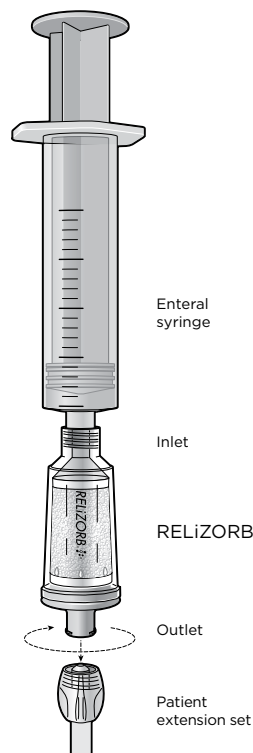


5. Position the syringe with the RELiZORB outlet facing up. Gently press the enteral syringe plunger to prime the enteral nutrition through the RELiZORB cartridge and expel excess air.

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

6. Secure the patient extension set to RELiZORB by inserting the outlet fitting from RELiZORB into the inlet fitting on the patient extension set with a gentle twisting motion until secure as shown in Figure 13.

**Figure 13: Connecting RELiZORB outlet to patient extension set that connects to enteral feeding tube.**

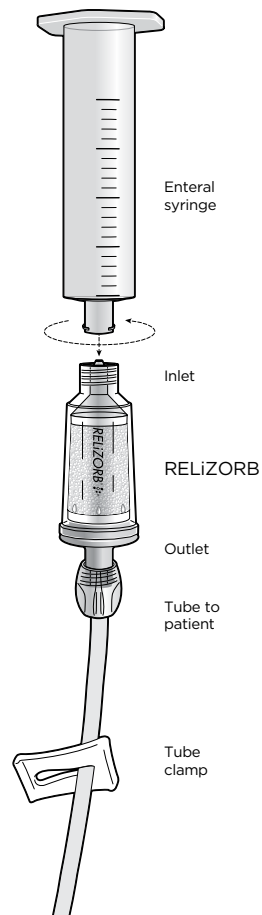


7. Gently push the enteral syringe plunger for the enteral nutrition to flow through the RELiZORB and through the extension set until the syringe is empty.
8. Close the clamp on the extension set, and then disconnect the enteral syringe from RELiZORB.

*Proceed with gravity feeding:*

9. Take the plunger out of the enteral syringe. Reattach the empty syringe to the RELiZORB and patient extension set assembly by inserting the outlet fitting of the enteral syringe into the inlet fitting from the RELiZORB with a gentle twisting motion until secure as shown in Figure 14.

*Figure 14: Reconnecting the empty syringe to RELiZORB and the extension set, with the clamp fully closed on the extension set.*



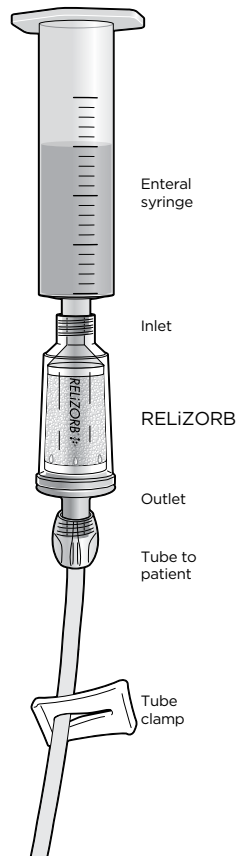
10. Slowly pour the required amount of enteral nutrition into the syringe.

11. Hold the syringe at a comfortable height and unclamp the feeding tube, allowing enteral nutrition to flow through as shown in Figure 15.

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

**NOTE:** If using a patient extension set with an adjustable clamp (Figure 11, A or B); the clamp may be adjusted to optimize the flow rate.

*Figure 15: enteral nutrition poured into enteral syringe and the patient extension set clamp open, allowing enteral nutrition to flow through RELiZORB and the tubing.*



12. Continue to refill the top of the syringe until you have reached the required amount.

**NOTE:** To maintain flow, ensure that there is enteral nutrition in the enteral syringe until the full feeding has been delivered. If the full volume of enteral nutrition in the syringe is delivered and the RELiZORB cartridge becomes dry, re-priming the device may be required if additional enteral nutrition needs to be delivered. Repeat steps 4-9 prior to resuming feeding.

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

**NOTE:** If medications or flush solutions are added BEFORE the RELiZORB cartridge, then the RELiZORB should be discarded. You may re-start feeding using a new RELiZORB. Please follow steps 1-12 to repeat the process.

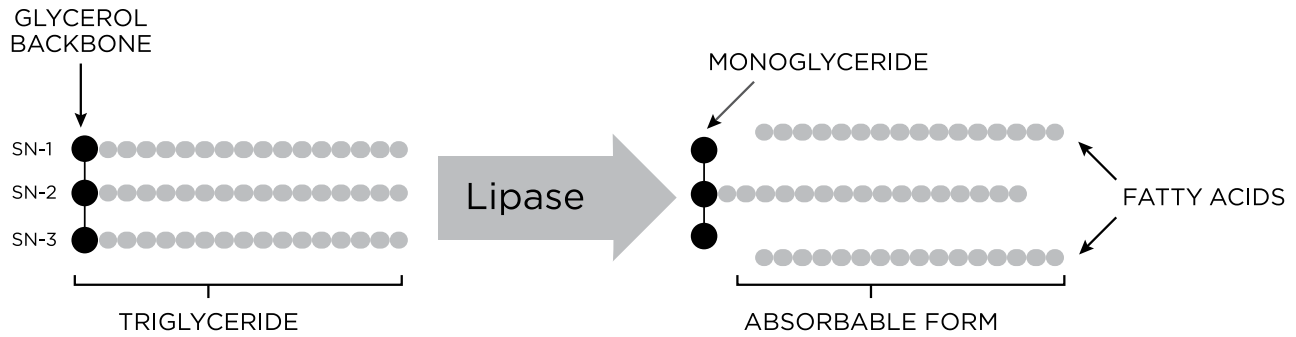
## 8.0 DISASSEMBLY AND DISPOSAL

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

## 9.0 MECHANISM OF ACTION

RELiZORB is designed to hydrolyze (digest) fats contained in enteral nutrition. RELiZORB contains the digestive enzyme lipase bound to beads (iLipase). By hydrolyzing fats from enteral nutrition, 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 16). When enteral nutrition 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 nutrition flows through RELiZORB.

Figure 16: 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 was tested and is compatible across a range of enteral feeding conditions. RELiZORB was tested with commercially available formulas with varying product characteristics and components (Table 1a and 1b, respectively), as well as pasteurized human milk (Table 1c). RELiZORB is not compatible with blenderized formulas.

**For a more detailed listing of compatible enteral nutrition tested with RELiZORB, along with a summary of the hydrolysis achieved, visit [www.relizorb.com/compatibility](http://www.relizorb.com/compatibility).**

### Representative Fat Hydrolysis Data Using RELiZORB

The following pediatric and adult enteral 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 1a: Enteral formulas evaluated with RELiZORB.

Enteral formulas evaluated with RELiZORB								
Formula Name	Per Serving						Fat Hydrolysis (%)*	
	Fat (g)	Calories (kcal)	Contains Pre-hydrolyzed Protein	Contains Insoluble Fiber	MCT:LCT Ratio	Omega-3 DHA & EPA (g)	Continuous Single and Tandem RELiZORB at 120 mL/hour with enteral pump (Condition 1)	Bolus** Single RELiZORB at ~400 mL/hour (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	30:70	-	>90	66
Kate Farms® Pediatric Standard 1.2	12	300	-	X	40:60	-	65	49
Neocate® Junior†	12.5	250	X	-	35:65	-	43	46
Neocate® Splash	12.1	237	X	-	-	-	34 <sup>‡</sup>	46 <sup>§</sup>
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 <sup>§§</sup>	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, manual bolus by syringe (push or gravity) of 250 mL with delivery of ~7 mL per min.

†Enteral powdered formula

‡Not recommended for use with tandem RELiZORB configuration.

§Not recommended for syringe gravity bolus feeding.

§§Fat hydrolysis rates are similar over the shelf life of RELiZORB.

NR—Not recommended

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

1. Continuous feeding with an enteral pump using single (~500 mL of formula) RELiZORB at 40 mL/hour
2. Continuous feeding with enteral pump using single (~500 mL of formula) and tandem (~1000 mL of formula) RELiZORB at 120 mL/hour
3. Bolus feeding with a single (~250 mL) RELiZORB at maximum feed rate of ~400 mL/hour

**Table 1b: Infant formulas evaluated with RELiZORB.**

Infant formulas evaluated with RELiZORB									
Formula Name	Per 250 mL Serving						Fat Hydrolysis (%)*		
	Fat (g)	Calories (kcal)	Caloric Density (kcal/oz)	Contains Pre-hydrolyzed Protein	MCT:LCT ratio	Contains DHA & ARA	Continuous		Bolus**
							Single RELiZORB at 40 mL/hour with enteral pump (Condition 1)	Single and Tandem RELiZORB at 120 mL/hour with enteral pump (Condition 2)	Single RELiZORB at 400 mL/hour (Condition 3)
Alfamino® Infant <sup>†</sup>	8.5	169	20	X	43:57	X	55	57	NR
EleCare® <sup>†</sup>	8.1	169	20	X	33:67	X	58	72	70
Enfamil® NeuroPro™	9.0	169	20	-	-	X	72	62	NR
Enfamil® NeuroPro™ EnfaCare®	9.9	186	22	-	20:80	X	70	63	48
Enfamil® NeuroPro™ Gentlease®	9.9	169	20	X	-	X	58	NR	NR
Enfamil® Premature 24 Cal	10.1	203	24	-	40:60	X	86	76	52
Enfamil® ProSobee®	9.0	169	20	-	-	X	62	65	54
Extensive HA® <sup>†</sup>	8.6	169	20	X	49:51	X	50	70	46
Fortini™	13.7	254	30	-	-	X	67	64	31
Good Start® Dr. Brown's™ GentlePro™ <sup>†</sup>	8.6	169	20	X	-	X	47	57 <sup>‡</sup>	NR
Good Start® Dr. Brown's™ SoothePro™ <sup>†</sup>	8.6	169	20	X	-	X	53	64 <sup>‡</sup>	47
Kendamil® Organic Infant <sup>†</sup>	9.0	169	20	-	-	X	61	48	NR
Neocate® Infant DHA/ARA <sup>†</sup>	8.6	169	20	X	33:67	X	NR	51 <sup>‡</sup>	47
Nutramigen®	9.0	169	20	X	-	X	52	67	58
Pregestimil® 20 Cal	9.5	169	20	X	55:45	X	NR	NR	42

Pregestimil® 24 Cal	11.4	203	24	X	55:45	X	NR	37 <sup>†</sup>	43
PurAmino™ <sup>‡</sup>	9.0	169	20	X	33:67	X	NR	42	51
Similac® Advance®	9.1	169	20	-	-	X	74	61	42
Similac® Alimentum®	9.4	169	20	X	-	X	NR	46 <sup>‡</sup>	NR
Similac® Neosure®	10.2	186	22	-	25:75	X	74	60	46
Similac® Neosure® <sup>‡</sup>	11.2	203	24	-	25:75	X	80	60	47
Similac® Special Care® 24 Cal Premature	11.0	203	24	-	-	X	84	76	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, manual bolus by syringe (push or gravity) of 250 mL with delivery of ~7 mL per min.

<sup>‡</sup>Infant powdered formula

<sup>†</sup>Not recommended for use with tandem RELiZORB configuration.

NR—Not recommended

Pasteurized human milk with and without human milk fortifiers has been evaluated for use with RELiZORB in the following use conditions:

1. Feeding with enteral syringe (~250 mL) with RELiZORB at 40 mL/hour
2. Feeding with enteral syringe (~250 mL) with RELiZORB at 120 mL/hour
3. Feeding with enteral syringe (~250 mL) with RELiZORB at 400 mL/hour

**Table 1c: Pasteurized human milk with and without human milk fortifiers evaluated with RELiZORB.**

PHM evaluated with RELiZORB						
PHM with or without Supplement	Caloric Density (kcal/oz)	Fat Content (grams per 250 mL)	Baseline Hydrolyzed Fat (%) <sup>*</sup>	Total Fat Hydrolysis (%) with RELiZORB <sup>††</sup>		
				40 mL/hr (Condition 1)	120 mL/hr (Condition 2)	400 mL/hr (Condition 3)
PHM only	20	9.3	28	45	43	NR
PHM + Enfamil® Human Milk Fortifier Standard Protein	24	12.5	13	62	63	54
PHM + Enfamil® Human Milk Fortifier High Protein	24	12.8	11	56	56	48
PHM + Similac® Human Milk Fortifier Extensively Hydrolyzed Protein	24	10.0	20	46	42	40
PHM + Enfamil® NeuroPro™ EnfaCare®	24	10.8	22	46	39	34
PHM + Similac® Neosure®	24	11.0	19	42	40	36

<sup>\*</sup>Baseline hydrolyzed fat refers to the percentage of hydrolyzed fat present in the tested human milk prior to the introduction of RELiZORB. The total fat hydrolysis percentage is inclusive of the baseline hydrolyzed fat and the fat hydrolyzed by RELiZORB.

<sup>†</sup>Composition of pasteurized human milk can vary and therefore, total fat hydrolysis may vary.

<sup>††</sup>All testing was performed using offset outlet syringes mounted on an enteral syringe pump to control flow rate. The pump was positioned at approximately a 45° angle with the syringe outlet facing upward.

NR—Not recommended

- The enteral nutrition included in Tables 1a, 1b and 1c has been evaluated for compatibility with RELiZORB. For a more complete list of enteral nutrition compatible with RELiZORB, please visit [www.relizorb.com/compatibility](http://www.relizorb.com/compatibility). RELiZORB has not been established in enteral nutrition not listed or at rates listed as not recommended per the compatibility guide.
- For most formulas tested, the free fatty acid content, as represented by percent hydrolysis, was lower at 400 mL/hour vs. 120 mL/hour when evaluated for compatibility.
- In Table 1a, enteral powdered formulas were tested at 30kcal/oz. In Table 1b, Infant powdered formulas were tested at 20 kcal/oz (except where noted at 24k cal/oz).
- Powdered formulas were mixed periodically when evaluated with continuous feedings with RELiZORB to prevent settling.
- The following formulas have been evaluated for use with RELiZORB and were shown to be incompatible: Liquid Hope, Nourish, Real Food Blends, Promote with Fiber, Compleat Pediatric, Compleat Organics, Compleat Pediatric Organics, Compleat Standard 1.4, Kate Farms Pediatric Blended Meals, Pediasure 1.5 with Fiber, Nutren Jr. with Fiber, Isosource 1.5, Replete with Fiber.
- Formula manufacturers may change the composition of their formulas, which may affect the operation of RELiZORB. Please refer to formula product websites for recent product descriptions, ingredients, and nutritional information.
- Consult with your healthcare provider regarding acceptable nutrition formulas for use with children.

## 11.0 PRE-CLINICAL STUDIES

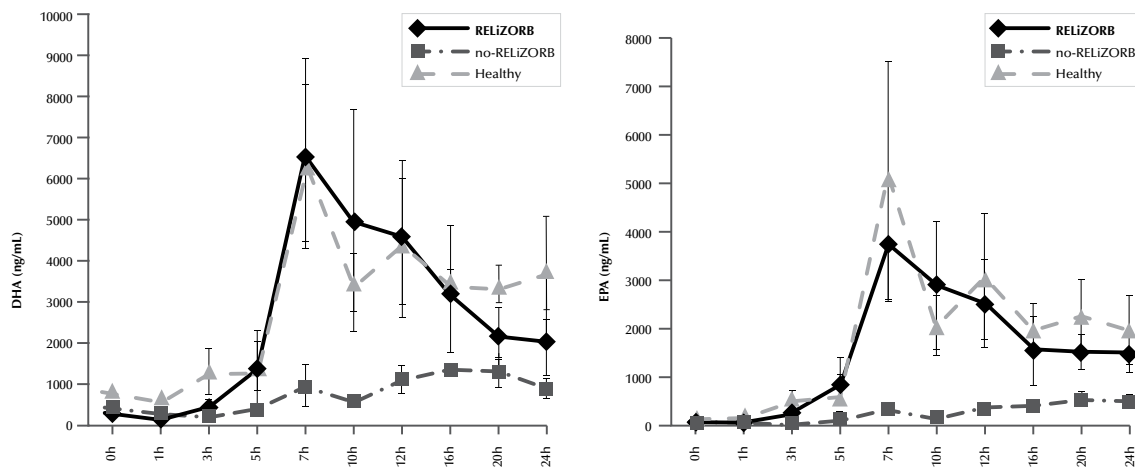
The efficacy, safety and intended use of RELiZORB was evaluated in porcine models of fat malabsorption: exocrine pancreatic insufficiency (EPI, 2 studies), and short bowel syndrome (SBS, 2 studies).

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 17). The clinical significance of these findings has not been determined.

**Figure 17: 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  $\pm$  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 $\pm$ 141.4	727.6 $\pm$ 164.9	513.4*	43.3 $\pm$ 23.5	512.6 $\pm$ 81.6	469.3**
NO RELiZORB	268.7 $\pm$ 129.2	442.8 $\pm$ 154.1	174.1	81.5 $\pm$ 84.0	190.8 $\pm$ 23.1	109.3

Results are shown as mean  $\pm$  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  $\pm$  102.2 ng/mL for DHA and 138.1  $\pm$  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)
<b>RELiZORB</b>	6.48 ± 2.8*	0.53 ± 0.3*
<b>NO RELiZORB</b>	3.82 ± 1.0	0.25 ± 0.1

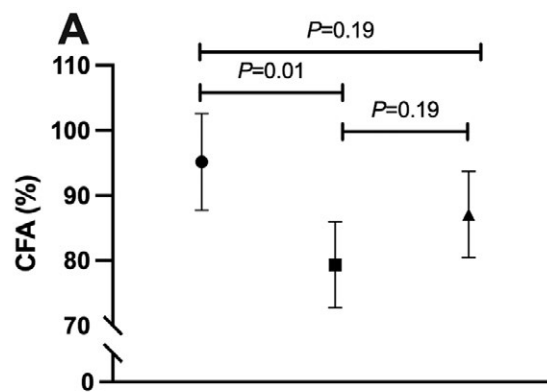
Results are shown as mean ± SD. \*p<0.05 for difference between RELiZORB vs. No RELiZORB for Vitamin D and Vitamin E.

### 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 18). 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 18: 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.

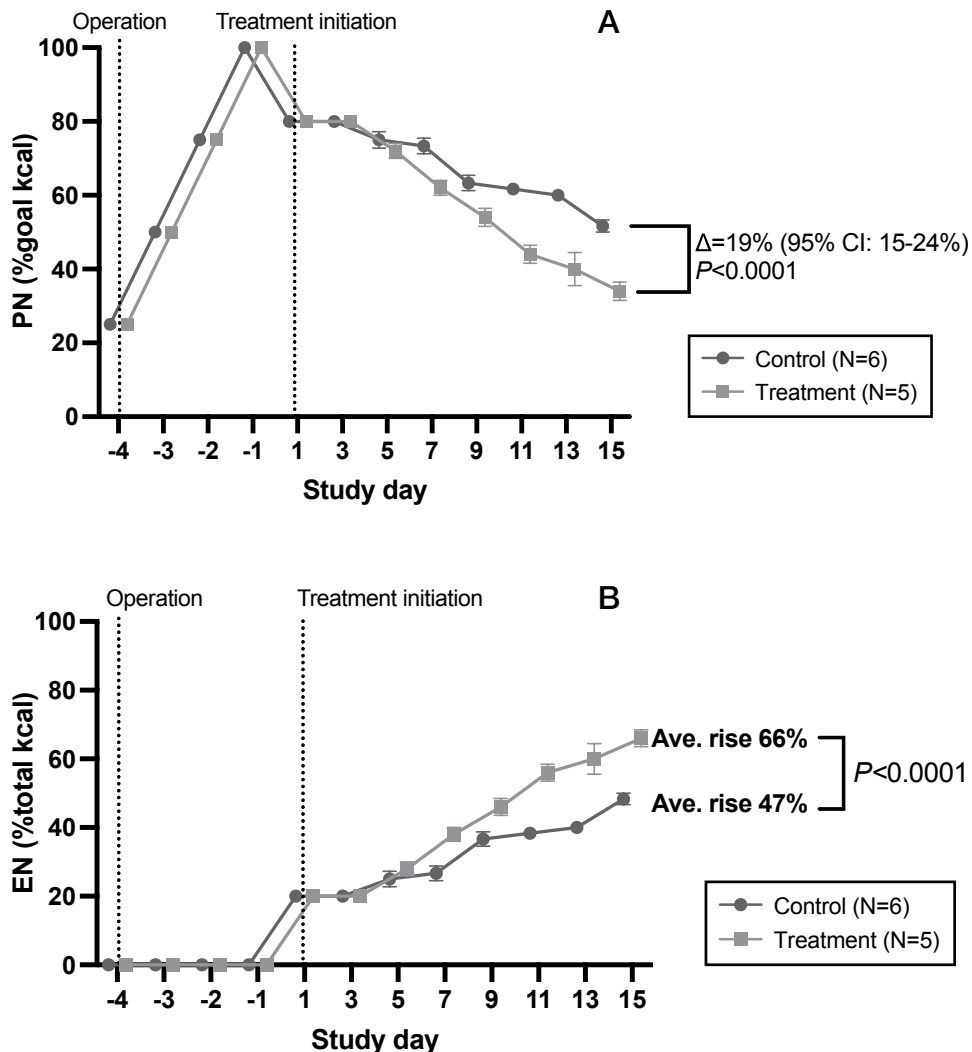
This was a parallel study with two groups: 75% intestinal resection (n=6) and 75% resection plus RELiZORB (n=5). Parenteral nutrition (PN) was initiated post-operatively and was decreased as enteral nutrition (EN) was advanced. EN was delivered daily via 6 bolus feedings with or without RELiZORB for 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 19). 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 ( $187\pm 10$  vs.  $121\pm 9$   $\mu\text{g/mL}$ ,  $p=0.0001$ ). The omega-3 fatty acid DHA was 1.4-fold higher in the RELiZORB group ( $41.9\pm 2.6$  vs.  $29.9\pm 2.3$   $\mu\text{g/mL}$ ,  $p=0.004$ ). Similarly, the plasma concentration of EPA was 1.9-fold higher in treatment animals compared to controls ( $89.1\pm 4.6$  vs.  $46.5\pm 4.2$   $\mu\text{g/mL}$ ,  $p<0.0001$ ). 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 19: 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  $\pm$  SEM. CI: confidence interval;  $\Delta$ : difference.**



## 12.0 CLINICAL STUDY SUMMARY

### STUDY 1

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<sup>®</sup> 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<sup>2</sup>) 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)
<b>TOTAL FREQUENCY</b>	<b>122</b>	<b>101</b>	<b>55</b>	<b>64</b>	<b>67</b>	<b>37</b>

\*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).

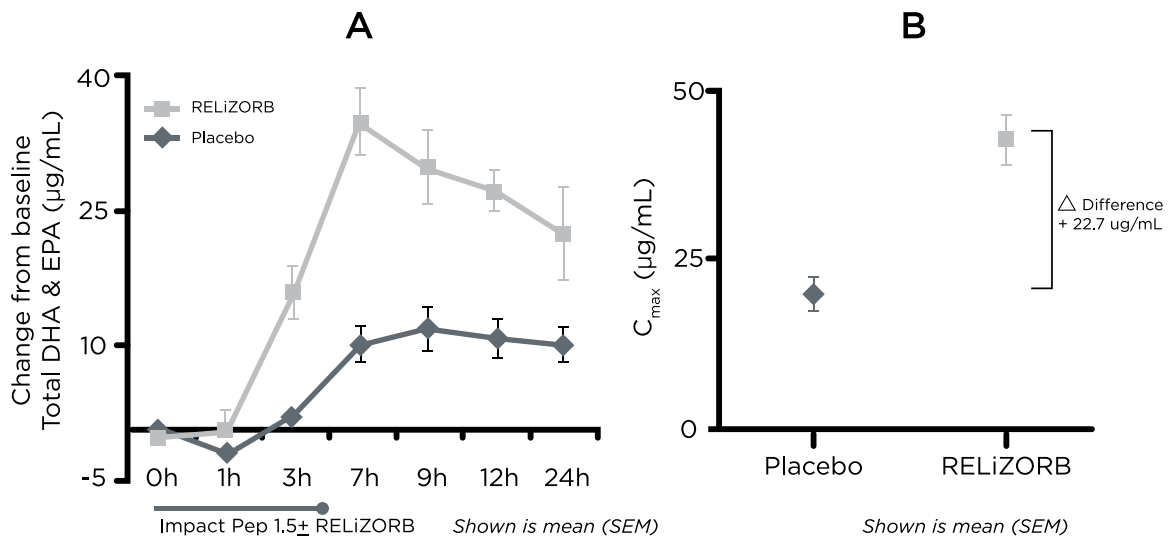
**EFFICACY: FAT ABSORPTION EVALUATION:** During the randomized double-blind, placebo controlled, crossover Period B, patients (n=33) received 500 mL of an enteral formula [Impact® Peptide 1.5; 32 (g) fat and 2.45 (g) DHA/EPA] with fixed quantities of DHA and EPA\* as well as total fat over 4 hours (120 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 ( $AUC_{0-24h}$ ) 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.  $AUC_{0-24h}$  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 20 and 21.

Baseline plasma concentrations of DHA and EPA were  $30.8 \pm 16.1$  for DHA and  $17.5 \pm 11.2$   $\mu\text{g/mL}$  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 20: 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.

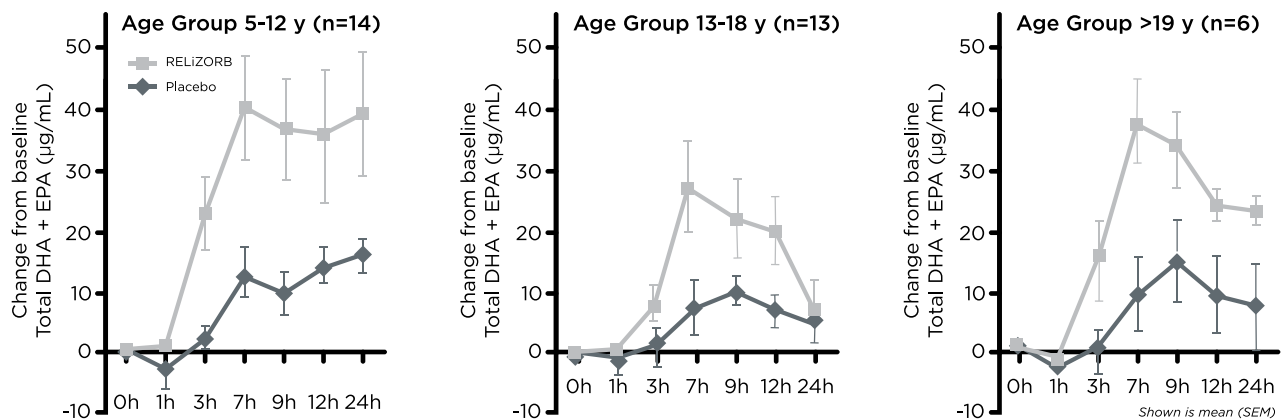
Mean plasma concentrations of total DHA and EPA (omega-3 fatty acids) significantly increased with administration of enteral formula through RELiZORB compared with administration through placebo. Calculated net  $AUC_{0-24h}$  for baseline adjusted changes for DHA and EPA was significantly increased ( $p < 0.001$ ) with formula administered through RELiZORB ( $537 \pm 400 \mu\text{g}^*\text{hr}/\text{mL}$ ) compared with formula administered through placebo ( $192 \pm 199 \mu\text{g}^*\text{hr}/\text{mL}$ ) 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 ( $42.8 \pm 22.9 \mu\text{g}/\text{mL}$ ) compared with formula administered through placebo ( $20.2 \pm 13.5 \mu\text{g}/\text{mL}$ ) resulting in a 2.1 fold change.

The increase from baseline to the mean  $C_{max}$  observed with RELiZORB use (Figure 20) 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 ( $AUC_{0-24h}$ ) was consistent across age groups,  $p < 0.001$  (Figure 21).

**Figure 21: 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  $AUC_{0-24h}$  for plasma concentrations of total DHA and EPA was of a similar magnitude in those patients with CFRD ( $n=12$ ) or without CFRD ( $n=21$ ).

## STUDY 2

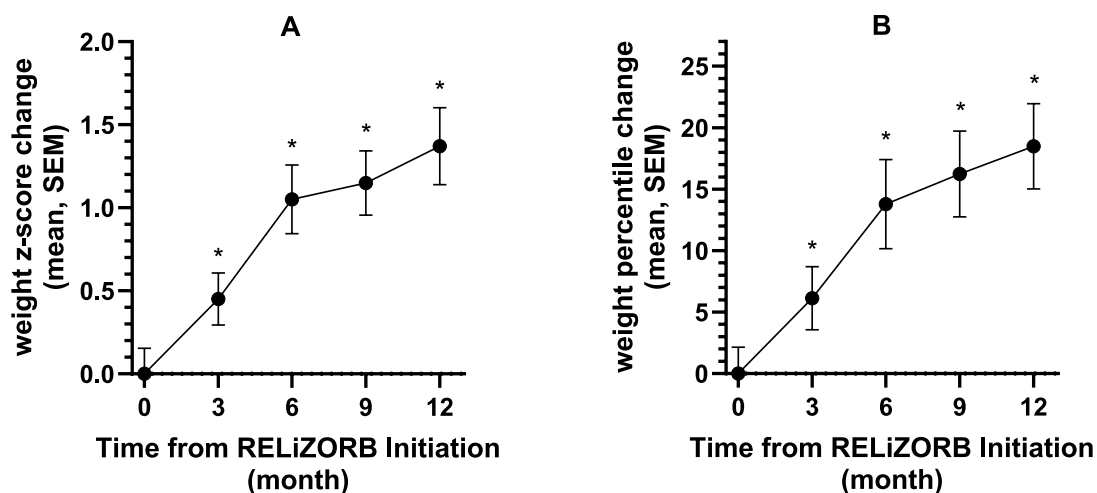
This study was a retrospective evaluation of real-world data extracted from Alcresta's insurance claims database in neonates and infants <1 year of age at the initiation of RELiZORB use as part of an enteral feeding regimen. The primary efficacy endpoint in 10 neonates and 47 infants was a change from baseline (prior to RELiZORB initiation) in World Health Organization (WHO) weight z-score at 12 months. A total of 96 patients initiated RELiZORB use between January 2020 and July 2024 at more than 60 centers in the United States (Intent to Treat [ITT] population).

The ITT population corrected gestational age, weight, and weight z-score mean (min, max) at the time of RELiZORB initiation was 5.0 (-2.2, 11.9) months, 5.36 (1.63, 10.93) kg, and -2.23 (-6.71, 1.39). Of the 96 ITT patients, 10 had RELiZORB use discontinued (6 for parent/clinician decision, 1 for "lack of efficacy," and 3 for "reason not provided/other"); yielding a 10% rate of discontinuation for potential intolerance.

Of the 96 patients, 57 had weight assessments at baseline and 3, 6, 9, or 12 months. The demographics and baseline characteristics for the ITT population are comparable to those for the population ( $n=57$ ) used to evaluate effectiveness. The 57 patients in the evaluable efficacy dataset were comprised of 49 patients on formula only, 4 patients on human milk and 4 patients on fortified human milk while using RELiZORB.

There was a statistically significant increase from baseline in weight z-scores and percentiles compared to an age- and sex-matched reference standard at 12 months following initiation of RELiZORB use with enteral feeding regimens. Improvements were shown as early as 3 months in the efficacy population (Figure 22).

Figure 22: Changes in Weight Z-scores and Percentiles from Baseline to 12 Months Following RELiZORB Initiation.



Mean (SEM) change in baseline-adjusted weight (A, WHO weight z-score; B, WHO weight percentile) with RELiZORB use. The baseline level prior to RELiZORB start is subtracted for each treatment period, so that each point on the graph represents the change from baseline. Numbers of patients at baseline: 57; 3 months: 47; 6 months: 36; 9 months: 36; and 12 months: 30. Statistically significant changes from baseline (one-sample two-sided t-test  $P < 0.05$ ) are indicated with an asterisk (\*).

No new safety concerns were identified in postmarket surveillance for neonates and infants <1-year of age that had not been reported in older patients.

### 13.0 HOW SUPPLIED/STORAGE AND HANDLING

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

### 14.0 SPECIFICATIONS

Cartridge use quantity:

	Maximum RELiZORB cartridge use per day
<b>FOR NEONATES AND INFANTS ≤6 MONTHS OF AGE:</b>	Up to 2 cartridges/day
<b>FOR INFANTS, PEDIATRIC AND ADULTS &gt;6 MONTHS OF AGE:</b>	Up to 6 cartridges/day

Product use set up specifications:

	Feeding with an enteral pump		Manual bolus by enteral syringe push or gravity
	SINGLE RELiZORB (continuous and bolus feeding)	TANDEM RELiZORB (continuous feeding only)	SINGLE RELiZORB
<b>ENTERAL NUTRITION VOLUME:</b>	Up to 500 mL	500-1000 mL	Up to 250 mL
<b>ENTERAL PUMP FLOW RATE:</b>	10-400 mL/hr	24-150 mL/hr	Not applicable
<b>OPERATING TEMPERATURE:</b>	Room temperature		

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

## 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 <sup>1</sup>
Incomplete priming during enteral pump feeding	Auto prime may not pump enteral nutrition completely through the cartridge	Use manual prime to completely prime the RELiZORB and patient extension set
Enteral nutrition is not flowing through the device during syringe gravity feeding	Extension set flow restrictor (tube feeding clamp) is engaged or device and extension set should be re-primed	Ensure flow restrictor is not engaged. Or follow steps to re-prime RELiZORB device and extension set
Enteral nutrition flow is too slow during syringe gravity feeding	Incompatible enteral nutrition type or incomplete priming	Check compatibility guide, use compatible enteral nutrition type. Or follow steps to re-prime RELiZORB device and extension set
Enteral nutrition flow is too slow during gravity syringe feeding	Height of syringe is too low	Raise the height of the syringe
Enteral nutrition flow is too fast during syringe gravity feeding	Height of syringe is too high	Lower height of syringe

**Reference 1.** ENFit® Cleaning Procedures. GEDSA; 2018. Accessed January 2, 2025. <https://stayconnected.org/enfit-cleaning-procedures-all-tubes/>

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