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Contribution of pancreatic enzyme replacement therapy to survival and quality of life in patients with pancreatic exocrine insufficiency

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SUPPLEMENTARY MATERIAL

Literature search details

This review focuses on the findings from prospective clinical trials assessing the effectiveness of PERT in increasing survival and/or improving quality of life in patients with PEI and CF, CP, or pancreatic cancer. Secondary objectives included effects of PERT on fat or protein absorption (measured by the coefficients of fat absorption [CFA] or nitrogen absorption [CNA], respectively); growth parameters, e.g. height, body weight, and body mass index (BMI); and GI symptoms, e.g. abdominal pain, stool consistency, and flatulence.

To identify relevant clinical trials, PubMed literature searches were performed (cut- off date 1 July 2018; clinical trial filter) using the following key words: (i) CF: (pancreas OR pancreatic) AND (cystic AND fibrosis) AND (enzyme OR replacement OR pancreatin OR pancrelipase OR liprotamase OR creon) [119 hits]; (ii) CP: (pancreas OR pancreatic) AND (chronic AND pancreatitis) AND (enzyme OR replacement OR pancreatin OR pancrelipase OR liprotamase OR creon) [112 hits]; (iii) Pancreatic cancer and/or pancreatic surgery: (pancreas OR pancreatic) AND (adenocarcinoma OR cancer OR surgery) AND (enzyme replacement OR pancreatin OR pancrelipase) [32 hits]. To identify clinical trials involving non-animal source PERT, a PubMed literature search was performed using the following key words: (novel microbial lipase OR burlulipase) [9 hits].

Articles were selected for inclusion in this review if they reported findings from trials assessing the effects of PERT on quality of life, survival, malabsorption, growth parameters, or GI symptoms. Prospective, randomized trials were selected if they compared PERT with placebo. Trials were excluded if they compared different doses of PERT with no comparison to a placebo group, or if the outcomes measured were not relevant to this review. Due to the short duration over which many of the randomized, placebo-controlled trials were conducted, open-label, single-arm trials of longer duration were included in this review in order to assess the long-term effects of PERT on quality of life, survival, and growth parameters.

Supplementary Table 1 Randomized, double-blind, placebo-controlled studies evaluating PERT in patients with CF and PEI

Study and duration	Age	*N*[1]	Treatment	Study outcomes	Safety/tolerability
Borowitz *et al.* 2011[19] 6 days[3]	≥7 years	70/ 68[2]	1. Liprotamase (5 x 32500 lipase units/capsule/day) 2. Placebo	• Fat and protein absorption were significantly greater in the PERT group compared with placebo (LSM differences between groups were 10.6% and 9.2% for CFA and CNA, respectively; both $P < 0.001$) • PERT significantly decreased stool weight compared with placebo ($P = 0.0005$)	PERT was well tolerated, with no clinically significantly different AEs reported in either group. Most AEs were GI or pulmonary in nature
Heubi *et al.* 2016[20] Two 7-day crossover periods	≥12 years	35	1. Placebo 2. Burlulipase (90 mg burlulipase protein/meal and 45 mg/snack dissolved in ~50 mL water) 1. Burlulipase (90 mg burlulipase	• CFA was significantly greater in the PERT group compared with placebo (72.7% *vs* 53.8%; $P < 0.001$) • Subjective assessment of stool fat and consistency also improved in the PERT group	Overall PERT was well tolerated. AEs were mostly GI in nature and were more common in the group receiving burlulipase

Study and duration	Age	*N*[1]	Treatment	Study outcomes	Safety/tolerability
			protein/meal and 45 mg/snack dissolved in ~50 mL water) 2. Placebo		
Graff *et al*. 2010[21] Two 5-day crossover periods	7–11 years	8	1. Delayed-release pancrelipase (12000 lipase units/capsule; target dose 4000 lipase units/g fat) 2. Placebo	• Fat and protein absorption were significantly greater in the PERT group compared with placebo (CFA 82.8% *vs* 47.4%; CNA 80.3% *vs* 45.0%; $P < 0.001$) • Significant improvements in stool fat, weight, nitrogen, and daily stool frequency were observed with PERT	PERT was well tolerated, with AEs predominantly GI in nature; no serious AEs were reported
		8	1. Placebo 2. Delayed-release pancrelipase (12000 lipase units/capsule; target dose 4000 lipase units/g fat)		
Trapnell *et al.* 2009[22]	≥12 years	15	1. Pancrelipase (24000 lipase units/capsule;		PERT was well tolerated, with fewer AEs reported

Study and duration	Age	*N*[1]	Treatment	Study outcomes	Safety/tolerability
Two 5-day crossover periods			target dose 4000 lipase units/g fat[4]) 2. Placebo	• Fat and protein absorption were significantly greater in the PERT group compared with placebo (CFA 88.6% *vs* 49.6%; CNA 85.1% *vs* 49.9%; $P < 0.001$) • Stool fat, nitrogen, and stool weight were significantly lower with PERT compared with placebo ($P < 0.001$)	in patients receiving PERT compared with placebo
		16	1. Placebo 2. Pancrelipase (24000 lipase units/capsule; 4000 lipase units/g fat[4])		
Stern *et al.* 2000[23] Two 5–7-day studies			1. Pancrelipase minimicrospheres 2. Placebo	• Following an open-label phase with PERT, patients in the placebo group had a significant decrease in fat and protein absorption (CFA −36.9% [adults], −34.9% [pediatrics/adolescents]; $P < 0.001$) compared with PERT (CFA −2.0% [adults], −3.3% [pediatrics/adolescents])	PERT was well tolerated, with fewer AEs reported in patients receiving PERT compared with placebo
Pediatrics/ adolescents	7–18 years	18/ 18[2]			
Adults	≥18 years	18/ 20[2]			

Study and duration	Age	*N*[1]	Treatment	Study outcomes	Safety/tolerability
				• There were also significant increases in fecal fat excretion ($P \leq 0.001$), stool frequency ($P \leq 0.001$ in adults; $P = 0.002$ in pediatrics/adolescents), and the proportion of soft stools ($P = 0.001$) in the placebo groups after the open-label phase	
Wooldridge *et al.* 2009[24] Two 7-day crossover periods	≥7 years	32	1. Pancrelipase (5000, 10000, 15000, or 20000 lipase units/capsule; starting dose 1000 lipase units/kg/meal; target maximum dose ≤2500 lipase units/kg/meal and ≤4000 lipase units/g fat/day)[5] 2. Placebo	• Fat and protein absorption were significantly greater in the PERT group compared with placebo (CFA 88.3% *vs* 62.8%; CNA 87.2% *vs* 65.7%; $P < 0.001$) • The incidence of malabsorption signs and PEI-related symptoms were reduced following PERT	PERT was well tolerated, with AEs mild or moderate in severity. Most AEs reported were GI in nature

Study and duration	Age	*N*[1]	Treatment	Study outcomes	Safety/tolerability
		31	1. Placebo 2. Pancrelipase (5000, 10000, 15000, or 20000 lipase units/capsule; starting dose 1000 lipase units/kg/meal; target maximum dose ≤2500 lipase units/kg/meal and ≤4000 lipase units/g fat/day)[5]		
Trapnell *et al*. 2011[25] ≤7 days[6]	7–60 years	20	1. Pancrelipase (10500 or 21000 lipase units/capsule; maximum 10000 units of lipase/kg/day) 2. Placebo	• Fat and protein absorption were significantly greater in the PERT group compared with placebo (CFA 86.8% *vs* 56.4%; CNA 82.4% *vs* 57.9%; both $P < 0.001$)	PERT was well tolerated, with commonly reported AEs GI in nature

Study and duration	Age	*N*[1]	Treatment	Study outcomes	Safety/tolerability
				• Stool consistency was improved in the PERT group compared with placebo	

[1]Number of subjects included in the analysis; [2]Study treatment/placebo; [3]Prior to the randomized withdrawal part of the study, patients received liprotamase in an open-label fashion for 21 to 31 days; [4]Based on the prescribed fat intake per meal or snack; [5]PERT was administered as 5000, 10000, 15000, or 20000 USP lipase units/capsules; [6]Prior to the randomized withdrawal part of the study, patients received pancrelipase for 3 days.

AE: Adverse event; CF: Cystic fibrosis; CFA: Coefficient of fat absorption; CNA: Coefficient of nitrogen absorption; GI: Gastrointestinal; LSM: Least squares mean; PEI: Pancreatic exocrine insufficiency; PERT: Pancreatic enzyme replacement therapy; USP: United States Pharmacopeia.

Supplementary Table 2 Open-label studies evaluating PERT in patients with CF and PEI

Study and duration	Age	*N*[1]	Treatment	Study outcomes	Safety/tolerability
Colombo *et al.* 2009[27] 8 weeks	<2 years	12	Pancreatin 5000 minimicrospheres (2000 lipase units/g of fat[2])	• CFA was significantly increased from 58.0% at baseline to 84.7% after 2 weeks of PERT (P = 0.0013) • Stool fat excretion decreased by 8 g/day (P = 0.0013) and stool weight decreased by 30 g/day (NS) after 2 weeks of PERT • After 8 weeks of PERT, body weight increased by 1.0 kg and body length increased by 3.7 cm. Analyses of age- adjusted z-scores for weight and length showed a significant increase from baseline to 8 weeks in weight-for-age z-score (P = 0.0269) and an increase in length-for-age z-score that did not reach statistical significance (P = 0.0883)	9 patients (75%) reported at least 1 TEAE. None of the TEAEs were serious, led to death, or required discontinuation of the treatment or study

Kashirskaya *et al.* 2015[28] 3 months	1 month to <4 years	40	Pancreatin gastro- resistant granules (5000 lipase units/120 mL formula or breastfeed or 1000 lipase units/kg body weight/meal; minimum dose 5000 lipase units/meal; maximum dose 2500 units/kg/feed or 4000 units/g fat or 10000 lipase units/kg/day)	• In the overall population, mean (±SD) increases in z-score from baseline after 3 months were: height/length-for-age (0.13 [0.48]), weight-for-age (0.20 [0.39]), and BMI-for-age (0.29 [0.65]). The increases in growth parameters were greatest for children <2 years of age • Treatment was rated 'easy to administer' by 95% of caregivers; acceptance was rated good/very good by 90%	PERT was well tolerated with a favorable safety profile. AEs occurred in 40% of children; none were serious or lead to discontinuation
Borowitz *et al.* 2012[29] 12 months	≥7 years	214	Pancrelipase (starting dose 2 x 32500 lipase units/capsule/meal and 1 x 32500 lipase units/capsule/snack;	• Age-appropriate gains in height and weight were observed. By Month 12, in the 7 to <12 years of age group, none of the children had lost >5% of body weight, while 67.5% had gained >5%.	PERT was well tolerated without any significant safety concerns

			3 meals per day and 2 snacks per day; option to increase to 8 x capsules per day[3])	In the 12 to <17 years of age group, none of the children had lost >5% of body weight, while 62.8% had gained >5%	
Munck *et al.* 2009[30] 14 days each in a cross- over design	6–36 months	40	1. Pancrelipase for children (1 x 5000 lipase units/1 spoon of granules) 2. Pancrelipase (1 x 10000 lipase units/capsule)	• 20 parents (51%) preferred pancrelipase for children, 9 (23%) preferred pancrelipase, and 10 (26%) had no preference • The applied doses led to a mean CFA with similar results for both treatments (77.8% *vs* 78.7% for pancrelipase for children and pancrelipase, respectively)	Both preparations were well tolerated. In total, 17 patients in each treatment group showed AEs. The most common AEs were respiratory tract infections and GI disorders

[1]Number of subjects included in the analysis; [2]Higher doses were administered in 2 patients who were taking higher doses of standard pancreatic enzyme before enrolment; [3]Based on specific criteria defined in the protocol (related to steatorrhea, weight loss, or lack of weight gain for pediatric patients).

AE: Adverse event; BMI: Body mass index; CF: Cystic fibrosis; CFA: Coefficient of fat absorption; GI: Gastrointestinal; NS: Not significant; PEI: Pancreatic exocrine insufficiency; PERT: Pancreatic enzyme replacement therapy; SD: Standard deviation; TEAE: Treatment-emergent adverse event.

Supplementary Table 3 Randomized, double-blind studies evaluating PERT in patients with CP and PEI

Study and duration	Age	*N*[1]	Treatment	Study outcomes	Safety/tolerability
Safdi *et al.* 2006[31] 2 weeks[2]	≥18 years	27	1. Pancrelipase (4 x 10000 lipase units/meal; 2 x 10000 lipase units/snack) 2. Placebo	• After 2 weeks, subjects treated with PERT showed a significant increase in fat absorption compared with placebo-treated subjects (CFA +36.7% *vs* +12.1%; *P* = 0.0185) • Compared with placebo, PERT resulted in significantly greater improvement in stool consistency (*P* = 0.0102), reduced stool frequency (*P* = 0.0015), and reduced mean fat excretion in stool (−56.5 g/day *vs* −11.4 g/day; *P* = 0.0181)	PERT was well tolerated. There were no serious AEs and no discontinuation of treatment any reason

Toskes *et al.* 2011[32] Cross over study: high-low and low-high dosing sequences with treatment periods of 9–11 days[3]	≥18 years	72	Delayed-release pancrelipase 1. High dose (7 x 20000 lipase units/capsule/day) 2. Low dose (7 x 5000 lipase units/capsule/day) Delayed-release pancrelipase 1. Low dose (7 x 5000 lipase units/capsule/day) 2. High dose (7 x 20000 lipase units/capsule/day)	• After 18–22 days of PERT, absorption of fat was significantly increased *vs* baseline ($P < 0.001$) with no difference between doses (CFA 88.9% and 89.9% for low- and high-dose PERT, respectively). Significant increases were also observed in protein absorption ($P < 0.001$) • Increases from baseline were observed in body weight (0.38 kg and 0.50 kg for low- and high-dose PERT, respectively; $P = 0.021$ and $P = 0.006$) and BMI (0.13 kg/m^2 and 0.16 kg/m^2 for low and high dose PERT, respectively; $P = 0.020$ and $P = 0.007$) • PERT also significantly increased levels of HDL-c ($P < 0.001$) compared with baseline, while LDL-c and fat- soluble vitamins (A, E, and K) remained unchanged	PERT was well tolerated at both doses

Thorat *et al.* 2012[33] 1 week[4]	>18 years	61	1. Pancreatin minimicrospheres (2 x 40000 lipase units/capsule/meal; 1 x 40000 lipase units/capsule/snack; 3 meals per day and 2–3 snacks per day; total of 6–9 capsules per day) 2. Placebo	• After 1 week, fat absorption was improved significantly more with PERT compared with placebo (LSM change in CFA from baseline 18.5% *vs* 4.1%, respectively; treatment difference 14.4%; $P = 0.001$) • Significantly greater increases in the absorption of protein ($P = 0.005$) and reductions in stool fat were also observed ($P = 0.001$) with PERT compared with placebo	TEAEs occurred in 35.3% patients in the pancreatin group and 25.0% in the placebo group. TEAEs were mainly GI in nature

Whitcomb *et al.* 2010[34] 1 week[5]	≥18 years	54	1. Pancrelipase (6 x 12000 lipase units/capsule/meal and 3 x 12000 units/capsule/snack) 2. Placebo	• After 1 week, the mean (±SD) change from baseline in CFA was significantly greater with pancrelipase compared with placebo (32.1±18.5% *vs* 8.8±12.5%; $P < 0.0001$) • The increase in CNA from baseline was also significantly greater with pancrelipase compared with placebo (CNA 97.7±82.3% *vs* 24.4±101.0%; $P = 0.0013$) • Greater improvements from baseline in stool frequency, stool consistency, abdominal pain, and flatulence were also observed with pancrelipase compared with placebo	A similarly low number of TEAEs were recorded in both groups. TEAEs mainly consisted of GI events and metabolism and nutritional disorders. No discontinuations owing to AEs or deaths occurred and there were no meaningful treatment group differences observed for any of the laboratory parameters tested or vital signs

[1]Number of subjects included in the analysis; [2]After a 2-week placebo run-in period (washout); [3]After a placebo run-in period of 7 to 9 days; [4]After a 2-week run-in period during which patients received no PERT for 5 days, followed by usual PERT for ~1 week; [5]After a 5-day placebo run-in period.

AE: Adverse event; BMI: Body mass index; CFA: Coefficient of fat absorption; CNA: Coefficient of nitrogen absorption; CP: Chronic pancreatitis; GI: Gastrointestinal; HDL-c: High-density lipoprotein cholesterol; LDL-c: Low-density lipoprotein cholesterol; LSM: Least squares mean; PEI: Pancreatic exocrine insufficiency; PERT: Pancreatic enzyme replacement therapy; SD: Standard deviation; TEAE: Treatment-emergent adverse event.

Supplementary Table 4 Open-label studies evaluating PERT in patients with CP and PEI

Study and duration	Age	*N*[1]	Treatment	Study outcomes	Safety/tolerability
Gubergrits *et al.* 2011[35] 24 weeks[2]	≥18 years	48	Pancrelipase (delayed- release) (24000 lipase units/capsule; mean dose 186960 lipase units/day)[3]	• A clinically meaningful and statistically significant mean (±SD) increase in body weight of 2.73 (±3.35) kg was observed from baseline to study end ($P < 0.0001$), while BMI increased by 0.9 (±1.2) kg/m^2 • Stool frequency significantly decreased from (mean [±SD]) 2.8 (±1.3) at baseline to 1.8 (±0.9) at study end ($P < 0.001$) • Clinical symptomatology (abdominal pain, stool consistency, and flatulence) improved. However, no clinically meaningful changes in quality of life assessed using the SF-36 were	Pancrelipase was well tolerated over 6 months with a good safety profile. No unexpected TEAEs were observed. The most common classes of TEAE were GI disorders and infections and infestations. Only 4 patients (7.8%) had TEAEs that were considered treatment related

				observed at the end of the 6- month treatment period	
Ramesh *et al.* 2013[36] 51 weeks[4]	>18 years	48	Pancreatin (minimicrospheres) (2 x 40000 lipase units/capsule/meal and 1 x 40000 lipase units/capsule/snack; 3 meals per day and up to 3 snacks per day)	• Significant improvements (mean [±SD]) from baseline to study end were observed in the absorption of fat (CFA 22.7 [±12.2]%; *P* = 0.001) and protein (CNA 6.5 [±7.9]%; *P* = 0.001) • Mean±SD body weight and BMI were also significantly improved (4.9 [±4.9] kg and 1.9 [±1.9] kg/m^2, respectively; both *P* = 0.001). An increase in body weight of ≥7% occurred in 61.7% of patients • There was a significant reduction in stool frequency, stool weight, and the content of fat and nitrogen in stools at study end *vs* baseline (all p≤0.001)	Pancreatin was well tolerated. TEAEs were reported in 63.9% of patients. Nine treatment-related TEAEs were reported: constipation (n=7), abdominal discomfort (n=1), and frequent bowel movements (n=1)

		• Improvements in clinical symptoms (abdominal pain, stool consistency, and flatulence), clinical global impression of disease symptoms and quality of life were also improved

[1]Number of subjects included in the analysis; [2]After a 7-day, double-blind, placebo-controlled study; [3]Administered at individualized doses as prescribed by the investigator/treating physician; [4]After a 1-week, double-blind, placebo-controlled study.

BMI: Body mass index; CFA: Coefficient of fat absorption; CNA: Coefficient of nitrogen absorption; CP: Chronic pancreatitis; GI: Gastrointestinal; PEI: Pancreatic exocrine insufficiency; PERT: Pancreatic enzyme replacement therapy; SD: Standard deviation; SF-36: 36-item Short Form Health Survey; TEAE: Treatment-emergent adverse event.

Supplementary Table 5 Randomized, double-blind studies evaluating PERT in patients with pancreatic cancer and PEI

Study and duration	Age	*N*[1]	Treatment	Study outcomes	Safety/tolerability
Bruno *et al.* 1998[37] 8 weeks	>18 years	21	1. Enteric-coated pancreatic enzyme preparation (2 x 25000 lipase units/capsule/meal; 1 x 25000 lipase units/capsule/snack) 2. Placebo	• Patients receiving PERT gained a mean (±SD) 0.7 kg (2.5 kg), whereas patients on placebo lost 2.2 kg (2.7 kg) (P = 0.02) • Fat absorption increased by 12% (25%) in patients receiving PERT, whereas in patients on placebo it decreased by 8% (25%) (P = 0.13) • The mean changes in the severity and occurrence of steatorrhea-associated complaints between groups were not significantly different	No AEs were observed that could be attributed to the use of the trial medication
Woo *et al.* 2016[38] 8 weeks	>18 years	67	1. Enteric-coated pancreatic enzyme preparation (2 x 25000 lipase units/capsule/meal; 1 x 25000 lipase units/capsule/snack;	• Patients receiving PERT and placebo lost 1.49% and 2.99% body weight, respectively (P = 0.614) • The daily total calorie intake (SD) was 1487.5 (655.2) with PERT and 1297.7 (552.8) with placebo (P = 0.29)	3 patients died during the study; 1 in the PERT group and 2 in the placebo group. Medication compliance was comparable

	3 meals per day and up to 3 snacks per day; total of 6–9 capsules per day) 2. Placebo	• There were no significant between- group differences in improvements in quality of life scores	between the two groups. No serious PERT-related AEs were reported

[1]Number of subjects included in the analysis.

AE: Adverse event; PEI: Pancreatic exocrine insufficiency; PERT: Pancreatic enzyme replacement therapy; SD: standard deviation.

Supplementary Table 6 Open-label extensions and observational studies evaluating PERT in patients with pancreatic cancer and PEI

Study and duration	Age	*N*[1]	Treatment	Study outcomes	Safety/tolerability
Bruno *et al.* 1998[37] 4 weeks[2]	>18 years	14	1. Patients previously receiving placebo were switched to enteric- coated pancreatin (2 x 25000 lipase units/capsule/meal; 1 x 25000 lipase units/capsule/snack; 3 meals per day and 3 snacks per day) 2. Patients previously receiving high-dose pancreatin received lower-dose pancreatin (1 x 25000 lipase units/capsule/meal;	• In patients who were switched from placebo to PERT, mean (±SD) body weight remained stable during the 4 weeks of treatment (0.1 kg [1.5 kg]), while in those receiving a lower dose of PERT, mean body weight showed a slight reduction (–0.8 kg [2.0 kg]) • Mean total daily energy intake did not change substantially in either group over the 4-week period • The occurrence and severity of steatorrhea-associated complaints showed a tendency towards improvement in patients switched from placebo to PERT, and tended	Not stated

			3 meals per day and 3 snacks per day)	to worsen in patients receiving a reduced dose of PERT	
Woo *et al.* 2016[38] 16 weeks[2]	>18 years	67	Patients were recommended to take PERT: enteric-coated pancreatic enzyme preparation (recommended dose not stated)	• Overall survival did not differ significantly between the PERT and placebo groups (5.84 months *vs* 8.13 months; $P = 0.744$)	Not stated

[1]Number of subjects included in the analysis; [2]After an 8-week, double-blind, placebo-controlled study.

PEI: Pancreatic exocrine insufficiency; PERT: Pancreatic enzyme replacement therapy; SD: Standard deviation.

Supplementary Table 7 Randomized, double-blind studies evaluating PERT in patients who had pancreatic surgery

Study and duration	Age	*N*[1]	Treatment	Study outcomes	Safety/tolerability
Seiler *et al.* 2013[39] 1 week[2]	≥18 years	58	1. Pancreatin (minimicrospheres) (3 x 25000 lipase units/capsule/meal; 2 x 25000 lipase units/capsule/snack; 3 meals per day and 2–3 snacks per day; total of 9–15 capsules per day) 2. Placebo	• Patients receiving PERT showed significant increases in fat and protein absorption from baseline (LSM CFA 21.4%; CNA 18.9%), while those receiving placebo showed decreases from baseline in CFA and CNA values (−4.2% and −10.3%, respectively) suggesting that excretion was greater than intake ($P < 0.001$ between groups) • Stool fat content reduced *vs* baseline in patients receiving PERT and increased in those receiving placebo (LSM treatment different 30.2 g/day; $P < 0.001$) • Modest improvements in clinical symptoms were observed from baseline to the end of the	The overall incidence of AEs was slightly higher in the pancreatin group (37.5%) than in the placebo group (26.9%) and the most common was flatulence. There were no AEs leading to study discontinuation, no serious AEs, and no deaths in the double-blind phase

	double- blind period in patients receiving PERT, but there was no change in CGI or quality of life scores in either group

[1]Number of subjects included in the analysis; [2]After a 2-week run-in period during which patients received no PERT for ~1 week, followed by usual PERT for ~1 week.

AE: Adverse event; CFA: Coefficient of fat absorption; CGI: Clinical Global Impression; CNA: Coefficient of nitrogen absorption; LSM: Least squares mean; PERT: Pancreatic enzyme replacement therapy.

Supplementary Table 8 Open-label extensions and observational studies evaluating PERT in patients who had pancreatic surgery

Study and duration	Age	*N*[1]	Treatment	Study outcomes	Safety/tolerability
Seiler *et al.* 2013[39] 51 weeks[2]	≥18 years	58	Pancreatin (minimicrospheres) (3 x 25000 lipase units/capsule/meal; 2 x 25000 lipase units/capsule/snack; 3 meals per day and 2–3 snacks per day; total of 9–15 capsules per day)	• After 1 year of open-label pancreatin treatment, statistically significant improvements from baseline were observed in CFA (24.8%), CNA (21.8%), stool fat (−27.6 g/day), and stool nitrogen (−3.5 g/day; all $P < 0.001$) • There was a significant reduction in daily stool frequency (−0.9 per day) and stool weight (−232 g/day; both $P < 0.001$), and a significant increase in body weight (2.3 kg) and BMI (0.9 kg/m^2; both $P < 0.05$) from baseline to end of OLE	2 subjects discontinued during the OLE due to AEs: 1 due to diarrhea (possible relationship to study treatment) and 1 due to metastases to the peritoneum, which resulted in death (unrelated to study treatment). In the OLE, 15 patients (26%) experienced 27 serious AEs, but all were considered unrelated or unlikely related to study drug by the Investigator
Braga *et al.* 1989[40]	23–73 years	9	Pancreatin powder (18000 lipase	• 2 years after surgery and while taking pancreatin powder as an enzyme	Not reported

2.5 years	units/meal) for 2 years, then pancrelipase enteric- coated microspheres (16050 lipase units/meal)[3,4] for 6 months	supplement, 33.3% of patients were malnourished. Modest weight gain after surgery occurred only in the first year and then plateaued • After 6 months on enteric-coated pancrelipase microspheres, all patients were well nourished having attained a mean of 93.4% of usual body weight • Fecal fat excretion reduced from 32.8 g/day when receiving no treatment to 16.7 g/day after 3 days of enteric-coated pancrelipase ($P < 0.001$); 6 months later, fecal fat excretion was 10.7 g/day

[1]Number of subjects included in the analysis; [2]After a 1-week, randomized, double-blind, placebo-controlled period; [3]Following 2 days on enzyme supplement discontinuation; [4]Increased over first 3 days as follows: 5350 lipase units on Day 1, 10700 lipase units on Day 2, and 16050 lipase units on Day 3.

AE: Adverse event; BMI: Body mass index; CFA: Coefficient of fat absorption; CNA: Coefficient of nitrogen absorption; OLE: Open-label extension; PERT: Pancreatic enzyme replacement therapy