Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Delhaye M. Comparative evaluation of a high lipase pancreatic enzyme preparation and a standard pancreatic supplement for treating exocrine pancreatic insufficiency in chronic pancreatitis. *European Journal of Gastroenterology & Hepatology.* 1996; 8(7):699-703. Ref ID:488	1+ randomized open crossover study	N=32 Completed study n=25 Drop out n=7	**Inclusion criteria**: patients with alcohol-related chronic pancreatitis. Diagnosis of exocrine pancreatic insufficiency was based on steatorrhoea defined as a fat balance of more than 10g/day on a 100g fat intake without enzyme supplementation. **Exclusion criteria**: patients allergic or hypersensitive to porcine protein, suffering from any other pathological condition, pregnant women, or patients continuously taking medications which could interfere with the study medications such as H^2 antagonist, antacids, anti-diarrhoeals, sucralfate, carbenoxolone, bismuth compounds or antispasmodics. **Patient Characteristics**: Men/women: 24/1 Mean age (SE; range): 52.4 (1.7; 40-69) years Weight: 63.6 ± 2.3 kg Height: 171.7 ± 1.3 cm Alcoholic pancreatitis: 23/25 (92%) Idiopathic pancreatitis: 2/25 (8%) Previous pancreatic surgery: 9/25 (36%) Diabetic patients: 16/25 (64%)	Pancrease HL 3 capsules/day (high dose enteric-coated enzyme supplement: 25 000 European Pharmacopoeia Units (EPU) lipase, 22 500 EPU amylase, 1250 EPU protease per capsule). *Study divided into 4 periods of 2 weeks, each one corresponding to a new treatment regimen: A. Pancrease HL 1 capsule/meal + omeprazole 20mg/day, 30 min before breakfast B. Creon 3 capsules/meal and omeprazole 20mg/day, 30 min before breakfast C. Pancrease HL 1 capsule/ meal. D. Creon 3 capsules/meal All patients were randomized to received the same 4 different treatment regimen but in varying orders: ABCD n=7 BCDA n=8 CDAB n=3 DABC n=7 At the end of each 2 week period patients received a standard diet for 5 days (fixed daily intake 100g fat) Stool collection was done	Creon 9 capsules/day (standard lipase dose enteric-coated enzyme supplement: 8000 EPU lipase, 9000 EPU amylase, 450 EPU protease per capsule.) See intervention for details*	56 days	Efficacy: 72 hrs faecal fat, Stool frequency, odour, colour, and consistency, general wellbeing, abdominal pain and appetite. Safety: blood samples for renal and liver function and haematological parameters at day 0, 14, 28, 42 and 56	Not reported

				at the last 3 days of the standard diet.				

Effect Size

Outcomes

1. Faecal Fat (g/100g):

- A. Pancrease HL + omeprazole: 9.52 ± 0.71
- B. Creon 3 + omeprazole: 9.14 ± 0.56
  - Significant reduction in faecal fat with the addition of an enzyme and omeprazole p=0.03
- C. Pancrease HL: 10.68 ± 0.66
- D. Creon 3: 10.26 ± 0.61
  - No significant reduction in faecal fat with the addition of an enzyme alone
- There is no significant difference between the 2 pancreatic enzyme treatment groups for the mean values of faecal fat.

2. Abdominal Pain:

- No significant change during the 4 treatment period (no results provided).

3. Weight:

- No significant change: Day 0: 63.6 ± 2.3 kg compared to 64.1 ± 2.2 kg at Day 56.

4. Wellbeing score:

- No significant change in wellbeing score during the 4 treatment periods (no data)

5. Absorption:

- **Fat (%)**
  - A: Pancrease + omperazole: 83.8 ± 2.4
  - B: Creon + omeprazole: 83.1 ± 3.3
  - C: Pancrease: 82.0 ± 2.0
  - D: Creon: 82.1 ± 2.3
  - No significant difference between different enzymes or with the addition of omeprazole.
- **Protein (%)**
  - A: Pancrease + omperazole: 80.2 ± 1.9
  - B: Creon + omeprazole: 77.5 ± 2.7
  - C: Pancrease: 80.9 ± 1.5
  - D: Creon: 81.1 ± 1.8
  - No significant difference between different enzymes or with the addition of omeprazole.

Authors Conclusion:

'The reduction in capsule number is cited in most cases as the main reason for preferring Pancreas HL.'

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Vecht J. Efficacy of lower than standard doses of pancreatic	1+ Cross over study	N=16	**Inclusion criteria:** patients with chronic pancreatitis and an exocrine insufficiency, defined	Treatment A: Omeprazole 60 mg + enteric-coated	Treatment B: Omeprazole 60 mg with enteric-coated	45 days	Faecal parameters Abdominal	Grant from Jansen Cilag.

enzyme supplementation therapy during acid inhibition in patients with pancreatic exocrine insufficiency. *Journal of Clinical Gastroenterology.* 2006; 40(8):721-725. Ref ID: 2018	.		as faecal fat excretion >10g/24hr. Pancreatic enzyme replacement had to be stopped at least 3 days before starting the study. **Exclusion criteria**: not reported **Patient Characteristics**: Men/women: 13/3 Age (range): 53 ± 3 yrs (27-74) Interval between diagnosis of chronic pancreatitis and entering study (range): 9 ± 2 yrs (4-20yrs) Alcohol related chronic pancreatitis: 9/16 (56 %) Pancreatic duct anomaly: 1/16 (6%) Idiopathic: 6/16 (38%) Previous pancreatic surgery: 4/16 (25%) All patients were on pancreatic enzyme replacement therapy, mean: 4± 1 yrs. Acid suppression use: H2 receptor blockers: 2/16 (13%) Proton pump inhibition: 6/16 (38%)	microspheres (Pancrease, 10,000 FIP lipase, tid) before meals Pancrease dose was given as 2 capsules, each consisting of 5000 FIP IU lipase, 2900 FIP IU amylase and 330 FIP IU protease. These were given with 2 pancrease-placebo capsules. Omeprazole 60 mg was ingested 30 mins before meals (3 capsules of 20 mg)	microspheres (Pancrease, 20,000 FIP lipase, tid) before meals. Pancrease dose was given as 4 capsules (each capsule containing 5000 FIP IU lipase, 2900 FIP IU amylase and 330 FIP IU protease) Omeprazole 60 mg was ingested 30 mins before meals (3 capsules of 20 mg)		symptoms	

Effect Size

Outcomes

1. **Faecal fat excretion:**

	Basal (before treatment)	Treatment A (omeprazole + lipase 10,000 IU tid)	Treatment B (omeprazole + lipase 20,000 IU tid)
Faecal fat excretion (g/24hrs)	36.5 ± 8.4	17.9 ± 6.5 *	18.3 ± 4.7 *

*p<0.01 compared with basal value

- Faecal fat excretion was not effected by whether a patient had previously been operated on or not.

2. **Abdominal symptoms:**

- Abdominal symptoms score included: abdominal pain, cramps, bloating and flatulence (0=no symptoms, 10= intolerable).
- The change in symptom scores did not differ between patients who had been operated on and those that had not.

	Basal (before treatment)	Treatment A (omeprazole + lipase 10,000 IU tid)	Treatment B (omeprazole + lipase 20,000 IU tid)
Abdominal symptoms	3.2 ± 0.5	1.3 ± 0.3*	1.2 ± 0.3 *

(0-10)			

*p<0.01 compared with basal value

3. Wellbeing score (0-10):

	Basal (before treatment)	Treatment A (omeprazole + lipase 10,000 IU tid)	Treatment B (omeprazole + lipase 20,000 IU tid)
Wellbeing score (0-10)	4.9 ± 0.2	6.1 ± 0.2*	6.2 ± 0.2*

*****p<0.05 compared basal

4. Fat absorption (%):

	Basal (before treatment)	Treatment A (omeprazole + lipase 10,000 IU tid)	Treatment B (omeprazole + lipase 20,000 IU tid)
Fat absorption (%)	49 ± 8	76 ± 7*	75 ± 5*

- Significant increase in fat absorption in both treatment groups compared to basal value, p<0.01*

Authors conclusion:

' During acid inhibition with 60 mg omeprazole, not only standard doses of 20,000 FIP IU lipase tid with meals but also lower doses of 10,000 FIP IU lipase significantly improve fat absorption by 50% and significantly and beneficially affect abdominal symptoms and general wellbeing.'

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Van Hoozen CM, Peeke PG, Taubeneck M et al. Efficacy of enzyme supplementation after surgery for chronic pancreatitis. *Pancreas.* 1997; 14(2):174-180. Ref ID: 2010	1+ randomized crossover trial	N=11	**Inclusion criteria:** patients with a clinical diagnosis of chronic pancreatitis who underwent elective surgery (local resection longitudinal pancreaticojejunostomy) for relief of recurrent abdominal pain. The diagnosis of chronic pancreatitis was based on a compatible history and abnormal endoscopic retrograde pancreatography and CT of the pancreas and was confirmed in each instance by surgical and histopathological findings. **Exclusion criteria:** subjects with a history of bowel resection, active cancer, chronic liver, or kidney disease or evidence of ongoing drug or alcohol abuse. **Patient characteristics:** Male/Female: 8/3 Age range: 33-62 yrs History of chronic alcohol abuse: 11/11 (100%)	3 different time points: **1. Initial baseline evaluations 3 weeks after surgery:** DIET MODIFICATION: Including 1 week of adaptation to oral feeding (patients withdrawn from parenteral nutritional support and adapted to rountine hospital diet providing 30 kcal/kg ideal body weight, containing 35% of kcal as fat, 15-20% protein, and 44-55% carbohydrate). **2. First 4 weeks after baseline measurements:** PANCREATIN (+H2 BLOCKER): All patients received pancreatin USP: each capsule containing 8,000 USP U of lipase, 13,000 USP U of protease, and	NA	8 weeks	Absorption Nitrogen Weight Vitamin and mineral levels Abdominal pain	Grants from Solvay Pharmaceuticals and the National Institutes of Health.

			Concurrent cholethiasis: 1/11 (9%) Concurrent haemochromatosis: 1/11 (%) Recurrent abdominal pain as the major indication for surgery: 11/11 (100%) Weight loss >10kg + diarrhoea +/or greasy stools prior to surgery: 6/11 (55%) Pancreatic calcifications prior to surgery: 9/11 (82%) Fasting hyperglycaemia prior to surgery: 5/11 (45%)	30,000 USP U of amylase in enteric-coated microspheres and minimicrospheres. The total daily dose of pancreatin was based on the initial daily faecal fat excretion and was divided among meals to provide 4, 7, 8, 11 or 12 capsules/day for patients whose daily faecal fat excretion exceeded 15 g and reached 30, 40, 50, 60 or 70g/day, respectively. Each patient also received an oral H2 blocker of gastric acid secretion in usual therapeutic dose range. **3. After 4 weeks (4-8 week period):** PANCREATIN OR PLACEBO**:** Tests of digestion and nutritional assessment were repeated in the outpatient clinic, and patients were then double-blind randomized to receive the same dose of pancreatin or placebo. At the end of the 8 weeks tests were repeated.				

Effect Size

Outcomes:

1. **Weight:**
   - **Week 4- 8:** those randomized to receive pancreatin gained 3.6-5.5kg in body weight over the 8 week period compared to no weight gain in those randomized to placebo.
2. **Abdominal Pain:**
   - All patients reported decreased abdominal pain following surgery.
   - Pain scores (0=no pain, 5=worst ever pain):
     - Pain scores were similar and minimal prior to starting the 4-8week period of the trial:
       - patients randomized to pancreatin: 1.55 ± 0.56
       - patients randomized to placebo: 1.59 ± 0.37

- No changes in pain scores were reported between or within the groups during the 8 week follow up.

3. Absorption (coefficient %):

- **Fat:**
  - Baseline: 62.2 ± 6.2
  - Week 4: 78.5 ± 3.6
  - P<0.02
- **Protein**
  - Baseline: 75.3 ± 4.5
  - Week 4: 80.1 ± 2.5
  - P<0.1 NS
- **Carbohydrate**
  - Baseline: 95.6 ± 1.8
  - Week 4: 93.9 ± 1.6
  - P<0.7 NS
- **Energy**
  - Baseline: 77.9 ± 3.9
  - Week 4: 85.1± 1.8
  - P<0.05

Patients randomized to placebo for weeks 4-8 had significantly worse fat and total energy absorption than patients who continued to receive pancreatin, p<0.02.

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Ramo OJ, Puolakkainen PA, Seppala K et al. Self-administration of enzyme substitution in the treatment of exocrine pancreatic insufficiency. *Scandinavian Journal of Gastroenterology.* 1989; 24(6):688-692. Ref ID: 428	1 + Randomized crossover trial	N=10	**Inclusion criteria:** 1) chronic pancreatitis verified by either histologically and/or with endoscopic retrograde pancreatography; 2) persistent upper abdominal pain: 3) continuous enzyme substitution necessary; 4) bicarbonate output <6 mmol/l/30 min in the secretin test by duodenal intubation (normal value >15 mmol/l/30min) 5) All patients stopped previous enzyme supplements 1 week befor entering the study. **Exclusion criteria:** not reported **Patient Characteristics:** Male/female: 3/7	'Regular dosage' -Pancrease- encapsulated enteric coated microspheric pancreatic enzyme (each capsule containing 4000 NFU lipase, 20,000 NFU amylase, 25,000 NF proteases) - dosage recommended by the manufacturer: 2 capsules at meals and 1 capsule with snacks. After 4 weeks patients were examined, weighed and laboratory tests were performed and then changed to the 'individual dosing/ self administration' dosing for 4 weeks.	'individual dosing/ self administration' - Pancrease - Dosage given in accordance with the symptoms experienced to obtain maximum relief of symptoms. After 4 weeks patients were examined, weighed and laboratory tests were performed and then changed to the 'regular dosing' for 4 weeks. All patients were told not to use any analgesics or alcohol during the study, but	8 weeks	Laboratory markers Weight Bowel movements Pain (0-3)	Sigrid Juselius Foundation (Star Oyy, Tampere, Finland and Cilag AB, Sollentuna, Sweden wh donated the pancrease)

			Mean age(range): 52.4 yrs (36-73 yrs) Aetiology: Chronic alcohol abuse: 9/10 (90%) Idiopathic: 1/10 (10%) Mean duration of disease: 8.2 ± 2.5 yrs Insulin-dependant diabetics:10/10 (100%) Previous resection of the caudal part of the pancreas: 9/10 (90%)- performed 5.0 ± 1.7yrs earlier.	All patients were told not to use any analgesics or alcohol during the study, but could follow a normal diet.	could follow a normal diet.			

Effect Size

Outcomes

The consumption of pancreatic enzyme (capsules/day) was significantly higher ($p<0.001$) during the self-administration of the pancrease:

- Regular dosage: 5.0 ± 1.3
- Individual dosing/ self administration: 11.4 ± 2.4

1. Weight:

- There was no significant change in weight (kg) between the 2 groups:
  - Regular dosage: 62.8 ± 13.2
  - Individual dosing/ self administration: 63.8 ± 13.2

2. Pain score (0-3):

- The pooled data on pain showed a significantly lower ($p<0.05$) pain score during the self-administration of pancrease:
  - Regular dosage: 2.2 ± 0.7
  - Individual dosing/ self administration: 1.1 ± 0.7
- The difference in pain scores did not reach significance in 3 of the patients in individual comparison, although there was a tendency towards a decrease of pain in these patients.

Authors' Conclusion:

'It might be useful to allow patients with chronic pancreatitis to try self-administration in the treatment of chronic pancreatitis to achieve optimal relief of symptoms.'

Reference	**Study type/ Evidence level**	**Number of patients**	**Patient characteristics**	**Intervention**	**Comparison**	**Length of follow-up**	**Outcome measures**	**Source of funding**
Gouerou H. Alipase versus nonenteric-coated enzymes in pancreatic insufficiency. A french multicenter crossover comparative study. *International*	1+ Open multi-centre crossover study (conducted in 16 centres in France.)	N=35 Drop Out= 8/35 (23%) Completed study: 27	**Inclusion criteria:** patients with pancreatic insufficiency and signs of chronic pancreatitis. The diagnosis of exocrine pancreatic insufficiency was based on steatorrhea >8g/24hrs without enzyme therapy, and chronic pancreatitis shown morphologically by pancreatic calcifications, abnormal cholangio-pancreato retrograde endoscopy or other	Group 1: (P then E) n=20 Pancrease- enteric coated microphere containing enzyme. 9 capsules/day Patients received	Group 2: (E then P) n=15 Eurobiol- non-enteric coated enzyme. 3 vials/day. Patients received eurobiol then	52 days (10 days washout, 2×21 dasfor each treatment)	Steatorrhoea Digestive symptoms: abdominal extension, pain Drug acceptance Adverse reactions	Not reported

<table>
<tr>
<td>Journal of Pancreatology. 1989; 5 Suppl:45-50. Ref ID: 498</td>
<td></td>
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<td>histological signs. Patients may have had previous pancreatic surgery.
Exclusion criteria: patients who had acute attacks of pancreatitis within the last 15 days, gastric or duodenal ulcer, disease of the small intestine, previous enterectomy, hepatic insufficiency, cholestasis, or plans for surgery.
Patient Characteristics:
<table>
<tr><td></td><td>Group 1</td><td>Group 2</td></tr>
<tr><td>Sex M/F</td><td>19/1</td><td>14/1</td></tr>
<tr><td>Age (yrs)</td><td>50.5 (±9.8)</td><td>47.2 (±11.4)</td></tr>
<tr><td>Weight (kg)</td><td>57.0 (±9.0)</td><td>57.9 (± 12.3)</td></tr>
<tr><td>Pancreatitis due to alcoholism</td><td>19/20 (95%)</td><td>14/15 (93%)</td></tr>
<tr><td>Abdominal pain</td><td>16/20 (80%)</td><td>13/15 (87%)</td></tr>
<tr><td>Diabetes</td><td>9/20 (56%)</td><td>7/15 (54%)</td></tr>
<tr><td>Surgical operations</td><td>85%</td><td>53%</td></tr>
<tr><td>Steatorrhoea g/d</td><td>25.8 (±31.8)</td><td>20.3 (±15.1)</td></tr>
</table>
There were no statistically significant differences in baseline characteristics across groups.</td>
<td>pancrease then Eurobiol for 21 days each.

Pancrease was started after a 10 day wash-out period.</td>
<td>pancrease for 21 days each.

Eurobiol was started after a 10 day wash-out period.</td>
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<tr>
<td colspan="9">Effect Size
Outcomes
• Faecal fat excretion:
- No significant difference in mean faecal fat between the 2 groups (mean ± SD) :
o Pancrease: 13.9 ± 12.96 (2.2-52.1)
o Eurobiol: 12.32 ± 9.48 (0-33.2)
- Data of individual patients showed a wide variation in both drug groups;
o After Pancrease: faecal fat excretion varied from2.2- 52.1 g/d
o After Eurobiol: faecal fat excretion varied from 0- 33.2 g/d
• Abdominal pain:
- No significant/borderline decrease in the number of patients (n=8) complaining of abdominal pain (p<0.10) (pancrease 14% vs. Eurobiol 86%)
Authors' Conclusion:
'Improvement in functional symptoms, improved taste, and ease of administration of Pancrease when compared to conventional enzymes leads to better patient compliance, which is the best guarantee of long-term drug efficacy.'</td>
</tr>
<tr>
<th>Reference</th><th>Study type/</th><th>Number of</th><th>Patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of</th><th>Outcome</th><th>Source</th>
</tr>
</table>

	Evidence level	**patients**				**follow-up**	**measures**	**of funding**
Lankisch PG, Lembcke B. Therapy of pancreatogenic steatorrhoea: does acid protection of pancreatic enzymes offer any advantage? *Zeitschrift für Gastroenterologie.* 1986; 24(12):753-757. Ref ID: 507	1+ Randomized crossover trial	N=8	**Inclusion criteria:** patients with chronic pancreatitis diagnosed by typical case histories, abnormal secretin-pancreozymin test and/or histological investigation of the pancreas at operation. Patients' daily fat intake was 100g and previous pancreatin supplementation was stopped 3 days prior to the study. **Exclusion criteria:** not reported. **Patient Characteristics:** Male/Female: 7/1 Faecal fat excretion: >15g/day Aetiology: Alcohol related pancreatitis: 7/8 (88%) Idiopathic: 1/8(13%)	Each patient received 1 of the following 3 regimens for 5 successive days: 1. Pankreon 700 (6.3g/day: 252,000 FIP lipase/day): 3×3 dragees daily 2. Pankreon 700 (6.3g/day: 252,000 FIP lipase/day): 3×3 dragees daily + cimetidine 300mg, 30 min prior to 3 main meals 3. Kreon (5.4g/day:180,000 FIP lipase/day): 3×6 capsules daily	NA	Faecal weight Faecal fat	8 days	Not reported

Effect Size

Outcomes:

- **Faecal Fat excretion(g/day):**
  - Pankreon 700: non-significant mean reduction of 44% (33.5g/day)
  - Pankreon 700 + cimetidine: significant mean reduction of 60% (23.6 g/day) $p<0.05$
  - Kreon: significant mean reduction of 79% (12.6 g/day) $p<0.05$
  - Despite the mean reduction of faecal fat excretion during Pankreon + cimetidine and Kreon treatment, the individual daily faecal fat excretion was only normalized in 2 patients (2/8; 25%) both of whom were on the Kreon regimen.

Authors' Conclusion:

' The new acid-protected pancreatin preparation Kreon has been shown to be an equally potent alternative for this therapeutic concept, and may possibly simplify treatment of excocrine pancreatic insufficiency n the presence of gastric hypersecretion.'

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Isaksson G, Ihse I. Pain reduction by an oral pancreatic enzyme preparation in chronic pancreatitis.	1++ Double-blind crossover	N=19	Patients with chronic pancreatitis Diagnosis was based on low pancreatic isomylase in serum 10/19 patients, pathological findings at Lundh test in 12/12, calcification on x-ray 6/19,	Pankreon	Placebo	One week per treatment	Pain (patient on o to 100 mm analog scale and physician blind to written records)	

Digestive Diseases & Sciences. 1983; 28(2):97-102. Ref ID: 2014			pathological ECRP findings in 14/14 investigated Patient population: female:male 8:11, mean age 43 and 47 respectively. 10/11 male patients had alcohol-related pancreatitis 0/8 in female patients suspected alcohol etiology					
Effect Pancreatic enzyme vs placebo Pain 15/19 had pain relief during the week on pancreatic enzyme treatment compared with placebo (no data; p<0.05) Examiner rated pain was significantly lower when patients were on pancreratic enzyme compared with placebo (p<0.05) The patient-rated mean pain score during the week was significantly lowers when patients were on enzyme supplementation compared with placebo (210 vs 120; p<0.01) The examiner-rated mean pain score was significantly lower on pancreatic enzyme compared with placebo (32 vs 20; p<0.05) The frequency of pain was significantly lower in patients on enzyme supplementation compared with placebo (score 1 to 4: 2.22±0.19 vs. 2.78± 0.2, P<0.05) There was no significant difference in the number of analgesic tablets consumed when patients were on enzyme supplementation compared with placebo (7.8 vs 8.9; ns) Side effects 'Several patients stopped taking enzyme supplementation because of side effects'. No further details given.								
Halgreen H, Thorsgaard P, Worning H. Symptomatic effect of pancreatic enzyme therapy in patients with chronic pancreatitis. *Scandinavian Journal of Gastroenterology.* 1986; 21(1):104-108. Ref ID: 339	1+ Double-blind, crossover	N=20	Patients with chronic painful pancreatitis Chronic pancreatits with steatorrhea Alcohol etiology N=4 Chronic pancreatitis without steatorrhoea Alcohol etiology N=7 Chronic pancreatitis was verified by a reduced exocrine function and at least one of the following criteria: pancreatic calcifications, previous acute attacks of pancreatitis and/or typical abnormalities by endoscopic retrograde pancreatography	Pancreatic enzyme Encapsulated enteric-coated microspheric enzymes Pancreas Lipase 4000 Nationak Forumulary Units Amylase 20 000 NFU 25 000 Proteases NFU 2 capsules at meals, 1 capsule at snacks Patients already on enzyme supplementation had it stopped two weeks prior to	Placebo	4 week trial duration 2 and 4th weeks daily records of pain	Postprandial pain score, pain between meals, No. of pain attacks, analgesic consumption, subjective pain score, general well-being	Cilag AB, Sollentuna, Sweden

			11 patients had severely reduced pancreatic function, with a meal-stimulated duodenal lipase concentration of less than 50 kU/l and a faecal fat excretion of more than 7 g/day. 9 patients had less severe reduction of the exocrine pancreatic function and a normal faecal fat excretion Chronic pancreatitis with steatorrhea: age range 29 to 58 yrs, disease duration range 4 to 20 yrs, diabetes mellitus present N=6 Chronic pancreatitis without steatorrhoes: age range 32 to 58 yrs, disease duration range 3 to 10 yrs, diabetes melititus present N=1 Patients population	entering the study				
Effect Enzyme supplementation vs placebo Pain For patients with or without steatorrhea there were no significant differences when patients were on enzyme supplementation compared with placebo for: Postprandial pain score: chronic pancreatitis with steatorrhoea (n=11) placebo 6.4, pancrease 4.6; chronic pancreatitis without steatorrhoea (n=9) placebo 2.5, pancrease 3.6 (ns; no p value) pain between meals: chronic pancreatitis with steatorrhoea (n=11) placebo 7.4, pancrease 6.1; chronic pancreatitis without steatorrhoea (n=9) placebo 5.3, pancrease 6.0 (ns; no p value) No. of pain attacks: chronic pancreatitis with steatorrhoea (n=11) placebo 20, pancrease 17; chronic pancreatitis without steatorrhoea (n=9) placebo 16, pancrease 19 (ns; no p value) analgesic consumption; chronic pancreatitis with steatorrhoea (n=11) placebo 58, pancrease 49; chronic pancreatitis without steatorrhoea (n=9) placebo 48, pancrease 57 (ns; no p value) subjective pain score: chronic pancreatitis with steatorrhoea (n=11) placebo 3.5, pancrease 2.6; chronic pancreatitis without steatorrhoea (n=9) placebo 1.5, pancrease 2.0 (ns; no p value) general well-being: chronic pancreatitis with steatorrhoea (n=11) placebo 2.3, pancrease 1.7; chronic pancreatitis without steatorrhoea (n=9) placebo 1.7, pancrease 2.0 (ns; no p value) Faecal fat g/day: 1. Chronic pancreatitis with steatorrhoea (n=11): Placebo: 24.2; Pancrease: 10.4; P<0.01 2.Chronic pancreatitis without steatorrhoea: Placebo: 2.3; Pancrease: 3.3; No significant difference (no data)								
Mossner J, Secknus J, Meyer J et al. Treatment of pain with pancreatic extracts in chronic pancreatitis: Results of a	1+ multi-centre double blind crossover trial	N=47 N=43 completers	Patients with chronic pancreatitis Inclusion criteria: acute or chronic abdominal pain most likely due to chronic pancreatits, parenteral nutrition or intensive therapy not	Pancreatic enzyme Acid-protected Given at higher dosage than commonly used treatment	Placebo	28 days	Pain (score 1 to 3) Analgesic use Symptoms	Nordmark Arzneimittel, Uetersen, FRG

prospective placebo-controlled multicenter trial. *Digestion.* 1992; 53(1-2):54-2. Ref ID: 2016			required, abnormlaties at ERCP or calcification or typical signs on CT/sonography, faecal fat below 30 g/day, duration not more than 30 months Exclusion criteria included: history of gastric resections or vagotomy, history of pancreatic resections, Patient population: 41 males, 6 females	Panzytrat 20 000 capsules with microtablets 5 x 2 capsules/day Lipase 20 000 Eur U Amylase 18 000 Ph Eur E Proteases 1 000 ph Eur U This dosage ensured the application of 10 000 Ph Eur U of proteases/day				
Effect Pancreatic enzyme vs placebo Faecal fat There was no significant difference in faecal fat when patients were on enzyme supplementation compared with placebo at 14 days (11 vs 10 g/day; ns) or 28 days (11 vs 9 g/d; ns) Pain There was no significant difference in mean daily pain score at 14 days when patients were on enzyme supplementation compared to placebo (mean score 1.08± 0.87 vs 1.26± 0.89; ns) There was no significant difference at 28 days for analgesic use when comparing patients on enzyme supplementation compared to placebo (no data; ns) Symptoms There was no significant difference for patients on enzyme supplementation compared with those on placebo for: Diarrhoea (ns) Nausea (ns) Vomiting (ns) Flatulence (ns)								
O'Keefe SJ, Cariem AK, Levy M. The exacerbation of pancreatic endocrine dysfunction by potent pancreatic exocrine supplements in patients with chronic pancreatitis. *Journal of Clinical Gastroenterology.* 2001; 32(4):319-323. Ref ID: 2007	1+ Randomised, parallel	N=29 intervention/treatment N=40 (run-in period)	Adults with pancreatic insufficiency defined as presence of suppressed cholecystokinin-stimulated enzyme secretition or steatorrhea and to have to have typical signs of chronic pancreatitis Alcohol etiology: 14/15 treatment 13/15 placebo Exclusion criteria included gastroparesis with nausea and vomiting after large meals, malignant disease, current alcohol	Pancreatic enzyme supplementation: Creon N=15 Mini-microspheres Lipase 10 000 USP U/capsule Amylase 33 200 U SP U/capsule Protease 37,5000 USP U/capsule	Placebo N=14	7 days per treatment	Symptoms steatorrhea	Kali-Chemie Pharma Germany

			use Patiebt population: Placebo Mean age 57.8*, Body weight 65.5 kg, decompression surgery 2/14, insulin diabetes 10/14*, oral diabetes 2/14, stool fat 44.3 g/d Supplement group: Mean age 49.1*, Body weight 57.2 kg, decompression surgery 7/15, insulin diabetes 5/15*, oral diabetes 1/15, stool fat 48/0 g/d * denotes significant difference	Four capsules were given with each main meal and two with snacks = 16 capsules per day for 7 days Run-in period consisting of a placebo, nonsupplemented, 7-day study to assess the degree of pancreatic malaborption followed by a 7-day observation period of standard pancreatic enzyme supplementation whilst awaiting the results of the absorption tests Patients were asked to adhere to a standard diet of 12.6 MJ of energy per day for men and 10.5 MK/d for women consisting of 31% fat, 54% carbohydrate and 15% protein throughout the study periods			
Effect Enzyme vs placebo Symptoms There was no significant difference between enzyme supplementation and placebo for: Abdominal pain (ns) Distention (ns) Flactulance (ns) Steatorrhea Stool fat was significantly lower when patients were taking enzyme supplementation compared with placebo (20.3 ± 4.3 vs 48 ± 10.6 g/d; p=0.003) Fat absorption: Creon: 80.8 ± 3.8% Placebo: 54.0 ± 9.7% P=0.002								
Slaff J, Jacobson D, Tillman CR. Protease-specific suppression of pancreatic exocrine	1+ Double-blind crossover	N=20	Patients with well-established chronic pancreatitis (alcohol-induced) or idiopathic	Pancreatic enzme Ilozyme 6 tablets q.i.d	Placebo	60 days trial duration (30 days per treatment)	Pain (score 1 to 4) Daily analgesic requirements	Adria Inc., Columbus and National

secretion. *Gastroenterology.* 1984; 87(1):44-52. Ref ID: 447			N=10 Alcohol-induced Each patients had an abnormal secretin test on at least two occasions (> 80 mEq/L normal) 12 patients had a normal fat excretion and a maximum bicarbonate on the secretin test of 63.67 mEq/L 8 patients had steatorrhea and a maximum bicarbonate of 42.75 mEq/L Age range 31 to 65 yrs Steatorrhea range 1.6 to 48.4 g/24 hr	Pancreatic extract was stopped 2 weeks prior to investigation				Institute of Health
Effect Pancreatic enzyme vs placebo Patients with mild to moderate impairments of exocrine function (maximum bicarbonate concentration in the secretin test between 50 and 80 mEq/L and normal faceal fat determination) had significantly more pain relief with enzyme supplementation than placebo ($p<0.05$, no data) 9/12 (75%) with mild to moderate disease experience pain relief with enzyme supplementation compared with 2/8 (205)% of patients with severe disease (steatorrhea) For patients with mild to moderate disease the average daily pain score was significantly lower on enzyme supplementation compared with placebo (1.02 ± 0.39 vs. 3.4 ± 0.35, $P<0.01$) In addition, the use of analgesics decreased by 40% in these 9 patients								
Delchier JC, Vidon N, Saint MGM et al. Fate of orally ingested enzymes in pancreatic insufficiency: comparison of two pancreatic enzyme preparations. *Alimentary Pharmacology & Therapeutics.* 1991; 5(4):365-378. Ref ID: 162	1+ Double blind, crossover	N=6	Patients with severe pancreatic insufficiency secondary to chronic pancreatitis N=5 history of chronic alcohol abuse before the onset of pancreatitis, N=1 familial chronic pancreatitis Pancreatic insufficiency defined as: abnormal faecal fat excretion (> 7.0 g/24 hr on 100 g/day fat intake); b) a normal d-xylose absorption test; and c) the presence of at least one of the following clinical criteria: a marked abnormal BT-PABA test, radiological evidence of pancreatic calcifications or multiple strictures	Eurobiol Freeze-dried pig pancreas (1 dose = 5 g) Eurobiol 25 000 Capsules containing 500 mg of pH-sensitive, enteric-coated pancreatin microtablets (1 dose = 2 capsules) The meal was 490kcal 50% carbohydrate, 30% fat and 20% protein	Placebo Powder of pork fillet (1 dose = 5 mg) and gelatine capsules containing 500 mg of enteric-coated microtablets of pork fillet	24 hr per treatment	Facecal fat	Laboratoires Euroga (France)

			in the main pancreatic duct, or histological evidence of chronic pancreatitis on surgically resected tissue. All three criteria were present in each patient Mean disease duration 19 yrs (range 2 to 38 yrs). Four patients presented mild cholestatis and one had histologically proven cirrhosis. Insulin-dependent and non-insulin dependent diabetes mellitus were presented in 3 and 1 patient respectively. At the time of the study all 6 patients had been taking pancreatic enzyme supplements for more than one year and were in stable metabolic condition					
Effect Eurobiol vs Eurobiol 25 000 vs placebo Faecal fat excretion There was a significant difference in mean faecal fat excretion in g/ 24 hr between the treatments (32 ± 7.8 vs. 24 ± 1.5 vs. 42 ± 4.5 g/ 24 hr; $p<0.05$) Eurobiol 25 000 was significantly different to placebo ($p<0.05$). Daily faecal fat output was not normalised in any patient, regardless of the preparation used.								
Schneider MU, Knoll RM, Domschke S et al. Pancreatic enzyme replacement therapy: comparative effects of conventional and enteric-coated microspheric pancreatin and acid-stable fungal enzyme preparations on steatorrhoea in chronic pancreatitis. *Hepato-Gastroenterology.* 1985; 32(2):97-102. Ref ID: 216	1- open label crossover trial	N=17	**Inclusion criteria:** patients with alcoholic pancreatitis insufficiency as shown by the secretin-pancreozymin test, and considerable steatorrhoea (>15g total faecal fat excretion per day) as a sign of pancreatogenic maldigestion, were examined. **Exclusion criteria**: patients with extra-pancreatic causes of steatorrhoea**.** **Patient Characteristics**: Previous Whipple's procedure with intraoperative pancreatic duct occlusion (performed 3-8 months prior to entering study): 9/17 (53%)	**Group A**: patients who had previously undergone Whipple's procedure. 3 separate enzyme preparations were taken for 2 weeks each: 1) Kreon-acid protected preparation. 10 capsules /day (100,000 U lipase, 100,000 U amylase, 6,500 U protease per capsule) 2) Pankreon- conventional porcine preparation. 10 teaspoonfuls or 30g/day (360,000 U lipase, 270,000	**Group B:** patients with intact upper digestive tract. See Group A info.	47 days	Stools/day Stool weight Weight Faecal fat concentrations	Not reported

			Chronic pancreatitis + intact upper digestive tract: 8/17 (47%)	U amylase, 24,000 U protease per capsule) 3) Nortase- acid-stable fungal preparation. 10 capsules/day (75,000 U lipase, 100,000 U protease, 7,000 U amylase per capsule). Prior to entering the study patients went for 5 days without pancreatic enzyme preparations, H2 antagonists or antacids. During the 3 treatment periods the diet of the patients was based on worked-out daily diet containing 100g fat/day and adequate carbohydrate and protein.				

Effect:

1. **Weight**
   - The mean increase in weight in response to 2 weeks of supplementation with Kreon was:
     - Group A: from 62.0 ± 9.9 to 64.3 ± 8.8 kg
     - Group B: from 60.1± 10.4 to 61.5 ± 10.5 kg
2. **Faecal Fat concentration**
   - Group A:
     - A significant ($p<0.01$) reduction in faecal fat concentrations was found when using the conventional porcine preparation (Pankreon).
     - The acid stable fungal preparation (Nortase) led to a statistically non-significant mean reduction in faecal fat concentration. Although 2/8 (25%) of patients the preparation led to mormalization of faecal fat concentrations.
   - Group B:
     - There was no significant reduction in faecal fat seen when using the conventional porcine preparation (Pankreon).
     - The acid stable fungal preparation (Nortase) led to a statistically non-significant mean reduction in faecal fat concentration.
   - In both treatment groups all pancreatic enzyme preparations led to a significant reduction in total faecal fat excretion/day:
     - Group A (average): Kreon:58% drop; Pankreon: 67% drop; Nortase: 54% drop
     - Group B (average): Kreon:58% drop; Pankreon: 52% drop; Nortase: 46% drop
   - In treatment Group A the total faecal fat excretion/day was lowered to below the 'indication threshold' for enzyme replacement (15g faecal fat excretion/day) in 1 patient by Nortase and the Pankreon preparations.
   - In treatment Group B the total faecal fat excretion/day was lowered to below the 'indication threshold' for enzyme replacement (15g faecal fat excretion/day) in 2 patients by the Kreon preparation.
   - The difference in the reduction of total faecal fat excretion/day produced by various enzyme preparations were not statistically significant , either within the therapy groups (A or B) or in a direct comparison of the enzyme preparations with one another.

Authors' Conclusion:

'..the virtually identical lipase activities of an acid-protected porcine pancreatic enzyme preparation (Kreon) and an acid-stable fungal enzyme preparation (Nortase) produced largely the same

effect as a conventional porcine pancreatic enzyme preparation (Pankreon) with four times as much lipase activity, in the treatment of severe pancreatogenic steatorrhoea.

Reference	Study type/ Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Source of funding
Dutta SK, Tilley DK. The pH-sensitive enteric-coated pancreatic enzyme preparations: an evaluation of therapeutic efficacy in adult patients with pancreatic insufficiency. *Journal of Clinical Gastroenterology* . 1983; 5(1):51-54. Ref ID: 2012	1- crossover trial	N=7	**Inclusion criteria:** patients with pancreatic insufficiency diagnosed by: 1) the presence of steatorrhoea (>7.0g/24 hrs faecal fat) 2) an abnormal secretin test 3) a normal d-xylose absorption test **Exclusion criteria:** not reported. **Patient Characteristics:** Men/female:7/0 Mean age (range):50 yrs (44-57) Pancreatic insufficiency secondary to chronic alcoholic pancreatitis: 7/7(100%) Previous pancreatic, biliary tract or gastrointestinal surgery: 0/7 (0%) Insulin dependant diabetes: 3/7 (43%)	Patients received each of the 3 different regimes for 72 hrs each: 1) Pancreatin: a conventional pancreatic enzyme preparation with low enzyme content (protease USP units 8743 ± 187; lipase USP units 684 ± 52) 10 tablets with each meal 3 times/day (3 tablets at beginning and end of meal and 4 tablets in the middle) 2) Pancrease: enzyme preparation with pH sensitive coating (protease USP units 28000 ± 335; lipase USP units 4933 ± 140) 4 capsules with each meal, 3 times/day (1 capsule at the beginning and end of meal and 2 in the middle). 3) Cotazym-S: enzyme preparation with pH sensitive coating with higher lipase concentration (protease USP units 28000 ± 298; lipase USP units 5712 ± 152) 4 capsules with each meal, 3 times/day (1 capsule at the beginning and end of meal and 2 in the middle). All patients were given a 100g/day fat diet for 3 days	NA	12 days	Faecal fat excretion Bowel movement	The Veterans Administration

				with 72 hour faecal collection prior to starting any treatment.				

Effect Size

Outcomes

- **Faecal fat excretion**, g/24 hrs (mean ± SEM):
  - Untreated: 31.0 ± 4.0
  - Pancreatin: 19.0 ± 4.0
  - Pancrease: 13.0 ± 5.0
  - Cotazym-S: 9.0 ± 2.0
  - A trend to greater reduction of faecal fat with pH sensitive enteric coated pancreatic enzymes (Cotazym-S + Pancrease) did not reach statistical significance.
  - There was no difference between the 2 pH sensitive enteric coated pancreatic enzymes (Cotazym-S + Pancrease).