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TABLE OF CONTENTS

ABSTRACT 1
PLAIN LANGUAGE SUMMARY 2
SUMMARY OF FINDINGS 4
BACKGROUND 17
OBJECTIVES 18
METHODS 18
RESULTS 20
Figure 1. 24
Figure 2. 25
Figure 3. 26
Figure 4. 27
DISCUSSION 27
AUTHORS' CONCLUSIONS 28
ACKNOWLEDGEMENTS 29
REFERENCES 30
CHARACTERISTICS OF STUDIES 40
DATA AND ANALYSES 64
Analysis 1.1. Comparison 1: ECM versus NECT + adjuvant cimetidine, Outcome 1: Change in weight 64
Analysis 1.2. Comparison 1: ECM versus NECT + adjuvant cimetidine, Outcome 2: Stool frequency 65
Analysis 1.3. Comparison 1: ECM versus NECT + adjuvant cimetidine, Outcome 3: Abdominal pain 65
Analysis 1.4. Comparison 1: ECM versus NECT + adjuvant cimetidine, Outcome 4: FFE 65
Analysis 2.1. Comparison 2: ECM versus ECT, Outcome 1: Change in weight 66
Analysis 2.2. Comparison 2: ECM versus ECT, Outcome 2: Stool frequency 66
Analysis 2.3. Comparison 2: ECM versus ECT, Outcome 3: Abdominal pain 66
Analysis 2.4. Comparison 2: ECM versus ECT, Outcome 4: FFE 66
Analysis 3.1. Comparison 3: ECM versus ECMM, Outcome 1: FFE 67
Analysis 4.1. Comparison 4: ECM (Creon®) versus another ECM, Outcome 1: Change in body weight [kg] 68
Analysis 4.2. Comparison 4: ECM (Creon®) versus another ECM, Outcome 2: Stool frequency (number/day) 68
Analysis 4.3. Comparison 4: ECM (Creon®) versus another ECM, Outcome 3: Proportion of days with abdominal pain 68
Analysis 4.4. Comparison 4: ECM (Creon®) versus another ECM, Outcome 4: Proportion of days with flatulence 68
Analysis 4.5. Comparison 4: ECM (Creon®) versus another ECM, Outcome 5: Coefficient of fat absorption [%] 69
Analysis 5.1. Comparison 5: ECM versus TPE, Outcome 1: FFE 69
Analysis 6.1. Comparison 6: Liprotamase versus porcine PERT, Outcome 1: Pulmonary exacerbation 70
ADDITIONAL TABLES 70
APPENDICES 71
WHAT'S NEW 71
HISTORY 71
CONTRIBUTIONS OF AUTHORS 72
DECLARATIONS OF INTEREST 72
SOURCES OF SUPPORT 72
DIFFERENCES BETWEEN PROTOCOL AND REVIEW 73
INDEX TERMS 73

[Intervention Review]

Pancreatic enzyme replacement therapy for people with cystic fibrosis

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ABSTRACT

Background

Most people with cystic fibrosis (CF) (80% to 90%) need pancreatic enzyme replacement therapy (PERT) to prevent malnutrition. Enzyme preparations need to be taken whenever food is taken, and the dose needs to be adjusted according to the food consumed. A systematic review on the efficacy and safety of PERT is needed to guide clinical practice, as there is variability between centres with respect to assessment of pancreatic function, time of commencing treatment, dose and choice of supplements. This is an updated version of a published review.

Objectives

To evaluate the efficacy and safety of PERT in children and adults with CF and to compare the efficacy and safety of different formulations of PERT and their appropriateness in different age groups. Also, to compare the effects of PERT in CF according to different diagnostic subgroups (e.g. different ages at introduction of therapy and different categories of pancreatic function).

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Trials Register comprising references identified from comprehensive electronic database searches and handsearches of relevant journals and abstract books of conference proceedings. Most recent search: 07 November 2019.

We also searched an ongoing trials website and the websites of the pharmaceutical companies who manufacture pancreatic enzyme replacements for any additional trials. Most recent search: 26 December 2019.

Selection criteria

Randomised and quasi-randomised controlled trials in people of any age, with CF and receiving PERT, at any dosage and in any formulation, for a period of not less than four weeks, compared to placebo or other PERT preparations.

Data collection and analysis

Two authors independently assessed trials and extracted outcome data. They also assessed the risk of bias and quality of the evidence (GRADE) of the trials included in the review.

Main results

14 trials were included in the review (641 children and adults with CF), two of these were parallel trials and 12 were cross-over trials. Interventions included different enteric and non-enteric-coated preparations of varying formulations in comparison to each other. The number of participants in each trial varied between 14 and 129. 13 trials were for a duration of four weeks and one trial lasted seven weeks. The majority of the trials had an unclear risk of bias from the randomisation process as the details of this were not given; they also had a high risk of attrition bias and reporting bias. The quality of the evidence ranged from moderate to very low.

We mostly could not combine data from the trials as they compared different formulations and the findings from individual trials provided insufficient evidence to determine the size and precision of the effects of different formulations.

Authors' conclusions

There is limited evidence of benefit from enteric-coated microspheres when compared to non-enteric coated pancreatic enzyme preparations up to one month. In the only comparison where we could combine any data, the fact that these were cross-over trials is likely to underestimate the level of inconsistency between the results of the trials due to over-inflation of CIs from the individual trials.There is no evidence on the long-term effectiveness and risks associated with PERT. There is also no evidence on the relative dosages of enzymes needed for people with different levels of severity of pancreatic insufficiency, optimum time to start treatment and variations based on differences in meals and meal sizes. There is a need for a properly designed trial that can answer these questions.

PLAIN LANGUAGE SUMMARY

Pancreatic enzyme supplements for people with cystic fibrosis

Review question

We reviewed the evidence about how good pancreatic enzyme replacement therapy (PERT) is in overcoming the enzyme deficiency in people with cystic fibrosis (CF) and if there are any side effects.

Background

Between 80% and 90% of people with CF take PERT because their pancreas can not make the enzymes needed to digest food. As a result, children may fail to gain weight and thrive; while adults may lose weight and become malnourished as they do not absorb vitamins properly. In people with CF, malnutrition is linked to poorer general health, more severe lung disease and shorter life expectancy. If their pancreas is not making enough enzymes, people with CF can also experience painful, frequent, bulky, offensive bowel movements. PERT is needed to help gain weight, prevent malnutrition and avoid some vitamin deficiencies, as well as to control bowel symptoms. This is an updated version of the review.

Search date

We last searched for evidence: 26 December 2019.

Study characteristics

We assessed 14 trials (641 adults and children with CF); 13 trials gave treatment for four weeks and one for seven weeks. Trials compared different formulations of PERT, some were treated to delay the release of the medication until they passed from the stomach into the intestine, while others were not. In 12 trials participants took both types of supplement for four weeks each, although the order in which they took them was random. These factors made it difficult to analyse trial results. Most of the trials were old; the most recent was from 2017, but the oldest was from 1986.

Key results

We are uncertain whether any PERT formulation is better than another for improving any of our most important outcomes (weight, height or body mass index). In two trials (41 participants) those taking delayed-release microspheres (miniature drug capsules) had less fat in their poo than those taking delayed-release tablets (normal size); they also had less abdominal pain and did not need to go to the toilet as often. In a different trial (12 participants), those taking the delayed-release microspheres also had less fat in their poo than those taking delayed-release supplements. We also found that in a large trial (128 participants), people taking PERT not made from animal enzymes had less fat in their poo than those taking PERT made from pigs' enzymes. We found no difference between any of the different PERT formulations for any other bowel symptoms (e.g. abdominal pain, flatulence, constipation), quality of life, side effects or for any measure of lung disease. None of the trials reported the number of days in hospital or the incidence of vitamin deficiency.

We did not find any evidence on different dose levels of PERT needed for people who produce different levels of pancreatic enzymes, on the best time to start treatment or for the amounts of supplements based on differences in type of food eaten and meal sizes. A properly designed trial is needed to answer these questions.

Quality of the evidence

We found the quality of the evidence for the different outcomes to be moderate at best, but mostly very low. We are not sure that the participants had equal chances of being put into the different treatment groups as the trials gave no details about how the decisions were made. In several trials large numbers of participants dropped out and reasons for this were often not given. In most trials, people took one treatment for four weeks and then swapped to the alternative treatment. This design means that the results may appear more consistent than they really are when we analyse them. The only results we could combine were from two such trials. Finally, several trials did not

completely report their findings in a way we could analyse in this review. We are not sure how these factors affect our confidence in the results we found.

SUMMARY OF FINDINGS

Summary of findings 1. Summary of findings: ECM compared with NECT plus cimetidine

ECM compared with NECT plus cimetidine for cystic fibrosis

Patient or population: adults with cystic fibrosis

Settings: outpatients

Intervention: ECM (Creon®) with food

Comparison: NECT (Pancrex V) with food and adjuvant cimetidine 40 minutes before meals

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	NECT plus cimetidine	ECM				
Change in weight (kg) Follow-up: 1 month	The mean change in weight in the control group was 0.1 kg lower.	The mean change in weight in the intervention groups was 0.4 kg higher (0.1 kg lower to 0.9 kg higher).	MD 0.40 (-0.10 to 0.90)	12 (1)	⊕⊝⊝⊝ **very low** [a,b]	The overall difference was not significant (P = 0.12), although the results favour ECM. This is a cross-over trial but the results have been analysed as a parallel trial (Stead 1987).
Change in height	This outcome was not measured.					
Change in BMI	This outcome was not measured.					
Frequency in bowel symptoms: abdominal pain (% of days affected) Follow-up: 1 month	The mean percentage of days with abdominal pain was 16% in the control group.	The mean percentage of days with abdominal pain in the intervention group was 10.5% lower (21% lower to 0.4% higher).	MD -10.50 (-21.40 to 0.40)	12 (1)	⊕⊝⊝⊝ **very low** [b,c]	P = 0.06 The trial also reported on stool frequency and the analysis showed that stool frequency was less in the ECM group (MD -0.70 (95% CI 0.90 to -0.50) P = 0.00001), but caution should be taken due to the risk of bias within the trial (particularly from blinding) and very small sample size.
CFA: change in FFE (g/day)	The mean change in FFE in the con-	The mean change in FFE in the intervention group	MD -6.70 (-14.70 to 1.30)	12 (1)	⊕⊕⊝⊝	

Follow-up: 1 month	trol group was 27.3 g/day.	was 6.7 g/day lower (14.7 g/day lower to 1.3 g/day higher).		**low** [b,d]
Adverse events	This outcome was not measured.			
Pulmonary exacerbations	This outcome was not measured.			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
BMI: body mass index; **CFA**: co-efficient of fat absorption; **CI**: confidence interval; **ECM**: enteric-coated microspheres; **FFE**: fecal fat excretion; **MD**: mean difference; **NECT**: non-enteric-coated tablets.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

a. Downgraded twice due to a high or unclear risk of bias across most domains and particularly around randomisation and allocation concealment. The trial was open-label and although weight is an objective measure, it is possible that knowledge of the treatment may have affected other factors influencing weight. The trial also had a cross-over design, but the data were anlaysed as if the trial were parallel, which may have affected the true result.
b. Downgraded once due to imprecision due to a very small sample size.
c. Downgraded twice due to a high or unclear risk of bias across most domains and particularly around randomisation and allocation concealment. The trial was open-label and it is possible that knowledge of the treatment may have affected subjective reporting of abdominal pain. The trial also had a cross-over design, but the data were anlaysed as if the trial were parallel, which may have affected the true result.
d. Downgraded once due to a high risk of bias across most domains including randomisation and allocation concealment. The trial was open-label but for this outcome we do not feel that this would have affected FFA results as FFA is an objective measure.

Summary of findings 2. Summary of findings: ECM compared with ECT

ECM compared with ECT for cystic fibrosis

Patient or population: children and adults with cystic fibrosis

Settings: outpatients

Intervention: ECM (Creon®) with food

Comparison: ECT with food (Pancrex V Forte (Stead 1986); not stated (Vyas 1990))

Outcomes	Illustrative comparative risks* (95% CI)	Relative effect (95% CI)	No of participants	Quality of the evidence	Comments

	Assumed risk	Corresponding risk		(trials)	(GRADE)	
	ECT	ECM				
Change in weight (kg) Follow-up: 1 month	The mean change in weight ranged across control groups from 0.01 kg to 0.42 kg.	The mean change in weight in the intervention groups was 0.3 kg higher (0.03 kg lower to 0.7 kg higher).	MD 0.32 (-0.03 to 0.67)	41 (2)	⊕⊖⊖⊖ **very low** [a,b]	The results favour ECM but this was not statistically significant (P = 0.07). Both trials included in this outcome were cross-over trials that were analysed as parallel trials.
Change in height	This outcome was not measured.					
Change in BMI	This outcome was not measured.					
Frequency of bowel symptoms: abdominal pain (% of days affected) Follow-up: 1 month	The mean percentage of days with abdominal pain ranged across control groups from 12.6% to 23.4%.	The mean percentage of days with abdominal pain in the intervention groups was 7.96% lower (13% lower to 3% lower).	MD -7.96 (-12.97 to -2.94)	41 (2)	⊕⊖⊖⊖ **very low** [a,b]	P = 0.002 Stool frequency (number/day) was also reported by the same two trials and was found to be significantly lower for the ECM group than the ECT group, MD -0.58 (95% CI -0.85 to -0.30), P = 0.0001 (Stead 1986; Vyas 1990).
CFA: change in FFE (g/day) Follow-up: 1 month	The mean change in FFE (g/day) ranged across control groups from 23.2 g/day to 27.1 g/day.	The mean change in FFE (g/day) in the intervention groups was12 g/day lower (17 g/day lower to 6 g/day lower).	MD -11.79 (-17.42 to -6.15)	41 (2)	⊕⊕⊖⊖ **low** [b,c]	The results should be viewed with caution as both trials were cross-over trials which were analysed as parallel trials.
Adverse events	This outcome was not measured.					
Pulmonary exacerbations	This outcome was not measured.					

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
BMI: body mass index; **CFA**: co-efficient of fat absorption; **CI**: confidence interval; **ECM**: enteric-coated microspheres; **ECT**: enteric-coated tablets; **FFE**: fecal fat excretion; **MD**: mean difference.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

a. Downgraded twice due to risk of bias across several domains of both included trials, particularly the domains of randomisation, allocation concealment and blinding. Both trials are cross-over trials which have been analysed as parallel trials.
b. Downgraded once due to imprecision caused by small number of participants.
c. Downgraded once for risk of bias as both trials were at high or unclear risk of bias across several domains including randomisation, allocation concealment and blinding. For this outcome, however, blinding is less of a concern as the measure is objective and less likely to be influenced by knowledge of the allocation.

Summary of findings 3. Summary of findings: ECM compared with ECMM

ECM compared with ECMM for cystic fibrosis

Patient or population: children with cystic fibrosis and proven pancreatic insufficiency

Settings: hospital patients in 3 centres

Intervention: ECM (Creon 8000 MS®)

Comparison: ECMM (Creon 10000 MMS®)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (trials)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	ECMM	ECM				
Change in weight	This outcome was not measured.					
Change in height	This outcome was not measured.					
Change in BMI	This outcome was not measured.					
Frequency of bowel symptoms Follow-up: 1 month	Stool frequency There was no difference between treatment groups with a median stool frequency of 2 stools per day in both treatment groups. Abdominal pain There was no significant difference between the groups and the participants reported that abdominal pain was mainly absent or mild throughout the trial. Flatulence There was no treatment difference between the groups and flatulence was stated to be absent or mild throughout the trial.		N/A	54 (1)	⊕⊖⊖⊖ **very low** a,b,c	No data were provided and results were reported narratively in the paper.

CFA: change in FFE (g/day) Follow-up: 1 month	The mean change in FFE (g/day) in the control group was 8.4 g/day.	The mean change in FFE (g/day) in the intervention groups was 2 g/day lower (7 g/day lower to 3 g/day higher.	MD -1.70 (-6.57 to 3.17)	22 (1)	⊕⊖⊖⊖ **very low** b,c,d	P = 0.49
Adverse events	This outcome was not measured.					
Pulmonary exacerbations	This outcome was not measured.					

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
BMI: body mass index; **CFA**: co-efficient of fat absorption; **CI**: confidence interval; **ECM**: enteric-coated microspheres; **ECMM:** enteric-coated mini-microspheres; **FFE**: fecal fat excretion; **MD**: mean difference.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

a. Downgraded twice for risk of bias in the trial design of the single included trial for this outcome. The trial was at high or unclear risk of bias across 6 of the 8 domains due to a lack of information on the randomisation and allocation concealment, no blinding and selective reporting of data. This was also a cross-over trial analysed as a parallel trial with no description of a washout period.
b. Downgraded once due to imprecision caused by a small sample size.
c. Downgraded once due to indirectness - the trial included only children and therefore may not be applicable to an adult population.
d. Downgraded once due to risk of bias within the trial design of the single included trial. The trial was at high or unclear risk of bias across 6 of the 8 domains due to a lack of information on the randomisation and allocation concealment, no blinding and selective reporting of data. We have only downgraded the evidence once for this particular outcome as the lack of blinding is not likely to be an issue. The measurement of FFA is an objective measure which is unlikely to be influenced by knowledge of the allocation.

Summary of findings 4. Summary of findings: ECM (Creon®) compared with a different ECM

ECM (Creon®) compared with another ECM for cystic fibrosis

Patient or population: children and adults with cystic fibrosis

Settings: outpatients

Intervention: ECM (Creon®)

Comparison: a different ECM (Pancrease® (Elliott 1992; Williams 1990), Nutrizyme® (Lacy 1992), Zenpep® (Taylor 2015)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (trials)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Another ECM	Creon®				
Change in weight (kg) Follow-up: 1 month	The mean change in weight in the control group was 0.5 kg.	The mean change in weight in the intervention group was 0.5 kg (the same as that in the control group).	MD 0 (-0.28 to 0.28)	83 (1)	⊕⊕⊕⊖ **moderate** [a]	P = 1.0 The control preparation in this trial was Zenpep® (Taylor 2015). 3 further trials measured this outcome, but did not provide data for analysis.The 3 trials all reported no statistically significant change in weight (Elliott 1992; Lacy 1992; Williams 1990).
Change in height	This outcome was not measured.					
Change in BMI	This outcome was not measured.					
Frequency of bowel symptoms: proportion of days with abdominal pain Follow-up: 1 month	The mean proportion of days with abdominal pain in the control group was 0.1.	The mean proportion of days with abdominal pain in the intervention group was 0.1 (the same as that of the control group).	MD 0 (-0.06 to 0.06)	83 (1)	⊕⊕⊖⊖ **low** [a,b]	P = 1.0 Only 1 trial provided data for analysis (Taylor 2015). A further 2 trials reported no significant difference in the proportion of days with abdominal pain although didn't provide data for analysis (Elliott 1992; Williams 1990) The same 3 trials reported on stool frequency, but showed no statistically significant difference between groups. Only 1 trial provided data for analysis, MD 0 (95% CI -0.28 to 0.28) P = 1.0 (Taylor 2015). Flatulence was measured in one trial (Taylor 2015) but no significant difference was found between groups MD 0 (-0.12 to 0.12) P = 1.0
CFA: CFA (%) Follow-up: 1 month	The mean CFA ranged across control groups from 83.97% to 84.1%.	The mean CFA in the intervention groups was 1.4% higher (1.4% lower to 4.13% higher).	MD 1.35 (-1.43 to 4.13)	110 (2)	⊕⊕⊕⊖ **moderate** [a]	A further trial comparing 2 preparations of ECM (Elliott 1992) and another comparing 3 preparations of ECM (Lacy 1992) found no significant difference for this outcome (no data available for analysis).

Adverse events Follow-up: 1 month	1 trial reported mostly mild adverse events, with abdominal pain, diarrhoea and flatulence being most common, and found the number of participants reporting adverse events was lower for the control ECM (Zenpep®) (19.6%) than Creon® (25.6%) (Taylor 2015).	NA	1 (83)	⊕⊕⊝⊝ **low** [a,b]	
Pulmonary exacerbations	This outcome was not measured.				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
BMI: body mass index; **CFA**: co-efficient of fat absorption; **CI**: confidence interval; **ECM**: enteric-coated microspheres; **MD:** mean difference.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

a. Downgraded once due to the risk of bias within the included trial due to concerns around the randomisation process and allocation concealment.
b. Downgraded once due to imprecision caused by low event rates.

Summary of findings 5. Summary of findings: ECM compared with TPE

ECM compared with TPE for cystic fibrosis

Patient or population: children with cystic fibrosis

Settings: home setting

Intervention: ECM (Creon®) (1.2 - 2.4 g/day)

Comparison: lyophilized TPE (4 - 8 g/day)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (trials)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	TPE	ECM				

Change in weight (kg) Follow-up: 1 month	One trial comparing ECM to TPE did not report any significant difference in change in body weight.		N/A	17 (1)	⊕⊖⊖⊖ **very low** a,b,c	No data available for analysis (Vidailhet 1987).
Change in height	This outcome was not measured.					
Change in BMI	This outcome was not measured.					
Frequency of bowel symptoms	This outcome was not measured					
CFA: change in FFE (g/day) Follow-up: 1 month	The mean FFA ranged in the control group was 6.6 g/day.	The mean FFe in the intervention groups was 1.6 g/day lower (3.3 g/day lower to 0.1 g/day higher).	MD -1.60 (-3.31 to 0.11)	17 (1)	⊕⊖⊖⊖ **very low** a,b,c	P = 0.07 (Vidailhet 1987)
Adverse events	This outcome was not measured					
Pulmonary exacerbations	This outcome was not measured.					

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
BMI: body mass index; **CFA**: co-efficient of fat absorption; **CI**: confidence interval; **ECM**: enteric-coated microspheres; **FFE**: fecal fat excretion; **MD:** mean difference; **TPE**: total pancreatic extracts.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

a. Downgraded twice due to unclear or high risk of bias across all domains and lack of information. There was also incomplete reporting of some outcomes.
b. Downgraded once due to imprecision as the trial included a very small number of participants (n = 17).
c. Downgraded once due to indirectness as the trial included only children and therefore may not be applicable to an adult population.

Summary of findings 6. Summary of findings: ECM compared with other enteric-coated preparations

ECM compared with other enteric-coated preparations for cystic fibrosis

Patient or population: children with cystic fibrosis

Settings: outpatients

Intervention: ECM Creon®

Comparison: another enteric-coated preparation (Pancreon forte (conventional) (Henker 1987); Pancrex V® (Petersen 1984))

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (trials)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Other enteric-coated preparation	ECM				
Change in weight (kg) Follow-up: 1 month	1 trial did not report any significant difference in change in body weight. 1 trial reported that weight gain was significantly better with ECM.		N/A	56 (2)	⊕⊖⊖⊖ **very low** a,b,c	No data were available for analysis and so results have been reported narratively from the 2 papers (Henker 1987); Petersen 1984).
Change in height Follow-up: 1 month	1 trial reported no difference between the ECM and another enteric-coated preparation (Pancreon forte)		.N/A	45 (1)	⊕⊖⊖⊖ **very low** a,b,c	No data were available for analysis and so results have been reported narratively from the paper (Henker 1987).
Change in BMI Follow-up: 1 month	This outcome was not reported.					1 trial measured the height and weight of participants, but did not report BMI and we were unable to calculate BMI ourselves since investigators did not report the actual data (Henker 1987).
Frequency of bowel symptoms: stool frequency Follow-up: 1 month	2 trials reported significantly decreased stool frequency with ECM compared to other enteric-coated preparations.		N / A	56 (2)	⊕⊖⊖⊖ **very low** a,b,c	No data were available for analysis and so results have been reported narratively from the papers (Henker 1987; Petersen 1984).
CFA: fat absorption Follow-up: 1 month	1 trial comparing ECM to conventional pancreatin reported finding no difference between the 2 treatment arms. 1 trial comparing ECM to enteric-coated granules found improved fat absorption on ECM, but the results were not statistically significant.		N / A	56 (2)	⊕⊖⊖⊖ **very low** a,b,c	No data were available for analysis and so results have been reported narratively from the papers (Henker 1987; Petersen 1984).
Adverse events	This outcome was not measured.					
Pulmonary exacerbations	This outcome was not measured.					

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
BMI: body mass index; **CFA**: co-efficient of fat absorption; **CI**: confidence interval; **ECM**: enteric-coated microspheres; **FFE**: fecal fat excretion.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

a. Downgraded twice due to risk of bias within the included trials, particularly around the domains of randomisation, allocation concealment and blinding. Neither trial reported data for analysis, therefore we have reported narratively directly from the paper.
b. Downgraded once due to imprecision as the trial included a very small number of participants (n = 45; n = 11).
c. Downgraded once due to indirectness as the trial included only children and therefore may not be applicable to an adult population.

Summary of findings 7. Summary of findings: low-dose compared with high-dose PERT

Low-dose compared with high-dose PERT for cystic fibrosis

Patient or population: children and adults with cystic fibrosis

Settings: home setting

Intervention: high-dose PERT (Nutrizyme 22 (22,000 BP units of lipase) (Assoufi 1994); Altu-135 25,000 units of lipase; Altu-135 100,000 units of lipase Borowitz 2005))

Comparison: low-dose PERT (Nutrizyme GR (10,000 BP units of lipase) (Assoufi 1994); Altu-135 5000 units of lipase (Borowitz 2005))

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (trials)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Low dose PERT	High dose PERT				
Change in weight (kg)	1 trial compared a high dose of enzymes to a low dose, maintaining lipase intake equal, but halving the number of capsules of high-dose preparation, and reported finding no significant difference in weight gain.		N/A	17 (1)	⊕⊖⊖⊖ **very low** a,b,c	No data available for analysis so results have been presented narratively (Assoufi 1994).
Change in height	This outcome was not measured.					
Change in BMI	This outcome was not measured.					

Frequency of bowel symptoms: stool frequency Follow-up: 1 month	The trial comparing a high dose of enzymes to a low dose, while maintaining lipase intake as equal but halving the number of capsules of high-dose preparation, found no significant difference in stool frequency.	N/A	17 (1)	⊕⊖⊖⊖ **very low** a,b,c	No data available for analysis so results have been presented narratively (Assoufi 1994). A further trial looking at ALTU-135 reported there was a single episode of DIOS requiring hospitalisation in 1 participant in the low-dose group (Borowitz 2005).
CFA: FFE (g/day) Follow-up: 1 month	1 trial that compared a high dose of enzymes to a low dose reported an FFE of 15.4 g/day on the high-dose enzyme and an FFE of 18.7 g/day on the low-dose enzyme. However, the difference was not statistically significant.	N/A	17 (1)	⊕⊖⊖⊖ **very low** a,b,c	No data available for analysis so results have been presented narratively (Assoufi 1994). A further trial reported this outcome but only at 14 days which does not fit our inclusion criteria (Borowitz 2005).
Adverse events	There were no noted side effects in 1 trial (Assoufi 1994). 1 trial did not find any serious adverse events or deaths (Borowitz 2005).	N/A	146 (2)	⊕⊖⊖⊖ **very low** a,c,d	
Pulmonary exacerbations	See comments.				1 trial reported pulmonary exacerbations, but the distribution of events across the groups was not reported (Borowitz 2005).

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
BMI: body mass index; **CFA**: co-efficient of fat absorption; **CI**: confidence interval; **FFE**: fecal fat excretion; **PERT**: pancreatic enzyme therapy.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

a. Downgraded twice due to risk of bias across several domains but particularly there was a lack of clarity around the randomisation process and allocation concealment and blinding of trial personnel and outcome assessors.
b. Downgraded once due to imprecision caused by very small participant numbers (n = 17).
c. Downgraded once due to indirectness as the study included only adults and the results may not be applicable to children.
d. Downgraded once due to imprecision from low event rates.

Summary of findings 8. Summary of findings: liprotamase compared with porcine PERT

Liprotamase compared with porcine PERT for cystic fibrosis

Patient or population: children aged 7 years or over and adults with cystic fibrosis

Settings: outpatients

Intervention: liprotamase (oral, soluble, non-enterically-coated, non-porcine PERT)

Comparison: porcine PERT (oral, enterically-coated PERT prepared from a porcine source)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (trials)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Porcine PERT	Liprotamase				
Change in weight (kg) Follow-up: 7 weeks	There was a weight loss of 1.2 kg (57.8 kg at baseline and 56.6 kg at week 7) in the liprotamase group and a weight gain of 0.2 kg in the pancrelipase group.		N/A	128 (1)	⊕⊕⊝⊝ **low** [a]	Mean body weight was reported at baseline and after 7 weeks in both groups, but no SDs were given (Konstan 2018a).
Change in height Follow-up: 7 weeks	This outcome was not reported.					Although height was measured at 7 weeks, no results were reported only the statement that height was stable through the trial period for both treatment arms.
Change in BMI Follow-up: 7 weeks	This outcome was not reported.					Although BMI was measured at 7 weeks, no results were reported only the statement that BMI was stable through the extension period for both treatment arms..
Frequency of bowel symptoms: abdominal pain Follow-up: 7 weeks	The trial observed that symptom scores were worse for abdominal pain in the liprotamase group than the porcine PERT.			128 (1)	⊕⊕⊝⊝ **low** [a]	No data were provided for inclusion in the analysis (Konstan 2018a).
CFA: change from baseline (%)	See notes.			128 (1)	⊕⊕⊝⊝ **low** [a]	The Konstan trial reported a significant decrease in CFA from baseline at seven weeks in the lipromatase group compared to the pan-

Follow-up: 7 weeks						crelipase group, MD (SE) -11.85 (2.12). This trial was a non-inferiority trial and the investigators stated that lipromatase missed the non-inferiority criterion.
Adverse events Follow-up: 7 weeks	No serious adverse events were identified thought to be due to the trial drug; treatment-emergent adverse events and serious adverse events were found to be similar between the 2 groups.			128 (1)	⊕⊕⊖⊖ **low** [a]	No data were provided and so results are reported narratively.
Pulmonary exacerbations: number of exacerbations Follow-up: 7 weeks	**79 per 1000**	**44 per 1000** (10 to 194)	OR 0.56 (0.13 to 2.45)	128 (1)	⊕⊕⊖⊖ **low** [a]	No significant difference was observed between groups, P = 0.44

.*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
BMI: body mass index; **CFA**: co-efficient of fat absorption; **CI**: confidence interval; **FFE**: fecal fat excretion; **MD**: mean difference; **OR**: odds ratio; **PERT**: pancreatic enzyme therapy; **SD**: standard deviation.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

a. Downgraded twice due to risk of bias within the trial. The process of randomisation and allocation concealment was unclear and the trial was open-label. The trial was at high risk of bias due to selective reporting of outcome data for weight, height and BMI.

BACKGROUND

A glossary of terms and abbreviations can be found in the additional tables (Table 1).

Description of the condition

Cystic fibrosis (CF) is a genetic disorder that affects approximately 80,000 individuals worldwide. The disease can involve many different organs and systems in the body. Between 80% and 90% of people with CF exhibit exocrine pancreatic insufficiency which is caused by decreased production of pancreatic enzymes (Fieker 2011). Pancreatic insufficiency (PI) leads to impaired digestion and absorption from the diet of fat, protein and the fat soluble vitamins A, D, E and K (Dodge 2006); it also predisposes to the development of a distal intestinal obstruction syndrome (DIOS) which is a condition unique to CF and is defined as an acute complete or incomplete fecal obstruction in the ileocecum. This occurs in about 10% to 20% of individuals, mainly in adolescents and adults, and is the result of the absence of CFTR function in the intestine which compromises chloride secretion and increased water absorption. Significant energy (calories) can be lost as fat in the stools (steatorrhea) resulting in a failure to gain weight and a failure to thrive in children and a loss in body weight in adults, with accompanying malnutrition from poor absorption of vitamins. In both children and adults with CF, malnutrition is associated with poorer general health, more severe pulmonary disease and shorter life expectancy (Corey 1988; Stallings 2008). Exocrine PI can result in unpleasant bowel symptoms such as pain and frequent, bulky, offensive stools. Pancreatic enzyme replacement therapy (PERT) is therefore required to promote weight gain, to prevent malnutrition, to avoid deficiency of fat-soluble vitamins and essential fatty acids, as well as to control abdominal symptoms of steatorrhea and maldigestion (Dodge 2006).

It is known that exocrine pancreatic function declines over the first months of life in infants with CF (Greer 1991; Waters 1990); and that this occurs earlier in those individuals who have "severe mutations" (Class 1 or Class 2, where the CFTR is absent) (Walkowiak 2005). Measurement of pancreatic elastase (a pancreatic enzyme) in the feces is one recognised technique for assessing PI and a fecal pancreatic elastase-1 concentration below 100 mcg per g of stool is diagnostic of PI. As steatorrhea is one of the most prominent clinical manifestations of PI and stool fat content can be reliably measured, fat-balance determination is a measure often used to assess this pathology and steatorrhea is assessed by measurement of fat excretion in the stool and by calculation of the co-efficient of fat absorption (CFA).

Description of the intervention

Pancreatic enzymes mainly of porcine origin (i.e. from pigs), have been used in treating pancreatic insufficiency since the 1930s. Currently all available preparations of PERT are porcine in origin but several non-porcine formulations are under various stages of research. First preparations were obtained by freeze drying hog pancreas, then extracting and purifying the enzymes which were subsequently administered as lyophilised total pancreatic extracts (TPE). These extracts reduced lipid malabsorption, but most of the enzyme was inactivated in the acidic environment of the stomach; to prevent this, bicarbonate or medication that suppressed acid was co-administered. Later, enteric-coated enzymes that were resistant to acid were developed, but these preparations did not completely prevent malabsorption as they did not empty into the duodenum as quickly as the smaller food particles. To overcome this problem, enteric-coated microspheres (ECM) were developed. They allow for a smaller size of the preparations and stable delivery. The microsphere technology also allows a more uniform mixture of the enzymes with chyme (partly digested food); however, trials of labelled capsules suggest that even with varying sizes of microspheres, the entry of the enzyme into duodenum maybe later than that of food particles. At present the main formulations in use are immediate-release enteric-coated microspheres and mini-microspheres, enteric-coated microtablets and enteric-coated microspheres with a bicarbonate buffer (Baker 2008; Fieker 2011). The activity and concentration of the enzymes present in porcine-derived PERT vary and are dependent on several factors like the age and sex of the animal and the husbandry practices (Ianiro 2017). They also carry the risk of zoonotic infections. Moreover, they may not be acceptable to all patient populations due to religious restrictions. To overcome some of these limitations newer sources for pancreatic enzymes from bacteria and fungi are being explored in combination with biotechnology. Burlulipase (derived from bacterium *Burkholderia plantarii* and *Burkholderia glumae*) was one such source which underwent phase 2 trials, but further development of the drug was stopped. Similarly, another biotechnology-derived drug that has been examined in clinical trials is liprotamase (Borowitz 2005; Konstan 2018a). A yeast-derived lipase formulation (MS1819 – derived from *Yarrowia lipolytca*) is currently being investigated in a clinical trial (NCT03746483).

Although PERT is generally considered to be safe, there are potential significant side effects including abdominal cramps, nausea, vomiting, constipation, diarrhoea, bloating and, in people taking high doses of enzymes, fibrosing colonopathy. One case-control study identified that fibrosing colonopathy could be due to the presence of methacrylic acid copolymer in the capsule and not due to the high doses of enzymes. Since the discontinuation of the use of polymer there have been no reports of fibrosing colonopathy (Bakowski 1997; Imrie 2010). Even though PERT has been used for a many years, not all enzymes are equally effective at correcting maldigestion and sustaining normal growth and nutrition on a normal diet. A number of factors contribute to this, including those related to the preparations, such as the delivery of the enzymes in the correct strength and at the correct location; and disease-related factors such as abnormal bile acid secretion, more acidic intestinal pH.

Some CF centres routinely administer pancreatic enzyme supplements from diagnosis. In countries that have neonatal screening programs, this is commonly in the first few weeks of life. Other centres administer PERT once growth falters in children or malabsorption and weight loss is evident clinically in older children and adults. Yet other centres conduct formal assessment of pancreatic function such as pancreatic-stimulation tests or by measuring pancreatic enzyme levels in the stool, most commonly fecal pancreatic elastase-1 or chymotrypsin or by measurement of fecal fat excretion such as the 72-hour (3-day) fat balance or the CFA. Other indicators of excess fecal fat excretion include stool microscopy or acid steatocrit (Leus 2000; Schibli 2002).

Pancreatic enzyme preparations currently available are given to individuals with CF orally 10 to 20 minutes before meals and snacks, either as tablets, enteric-coated or non-enteric-coated

capsules (for those individuals able to swallow a capsule) or as granules (for infants and young children). The number of enzyme capsules a person needs to take varies depending on the type of food being eaten, the degree of malabsorption, etc. Currently marketed pancreatic enzyme preparations differ in their composition, enzymatic activities, formulation, stability, and bioavailability.

How the intervention might work

The normal pancreas secretes digestive enzymes and bicarbonate into the duodenum to effect the breakdown of dietary protein, fats and starch. Pancreatic enzyme supplements contain all three main groups of digestive enzymes, namely lipase, amylase and protease, that respectively digest fats, carbohydrates and proteins into their basic components so that they can be absorbed and utilised by the body for growth and development. Thus PERT should facilitate sufficient digestion and absorption of food to support weight gain and growth and improve the bowel symptoms that arise from maldigestion and malabsorption.

Pancreatic enzymes normally act in the alkaline environment of the duodenum. They are denatured by pepsin and gastric acid, so PERT is usually administered as enteric-coated preparations to prevent inactivation by stomach acid. The coating is designed to dissolve only when the pH exceeds 5.5 within the duodenum. However, non-enteric-coated enzyme preparations are also available.

Clinical practice may differ between CF centres around the world depending on several factors such as: the level of expertise in certain centres in dealing with CF; the number of individuals with CF and PI as well as the diet and type of food that these people actually have access to; the different brands of ECM enzymes available in different countries, etc.

Why it is important to do this review

The most important reason to optimise PERT is to promote normal growth and to improve the nutritional status in people with CF and PI. This review aims to compare different preparations of PERT for their efficacy and safety in people with CF.

People with CF have a heavy burden of treatment and PERT significantly adds to that burden since enzymes in the form of capsules are taken whenever food is eaten in large numbers and doses need to be constantly adjusted according to what is being eaten, the level of malabsorption and weight gain. This can impact their social activities and well-being and may lead to non-compliance with the treatment. It can also be challenging for parents to administer these supplements to babies and young children since liquid preparations are not available. Also, excessive doses of pancreatic enzymes in infants have been associated with side effects such as abdominal pain, peri-anal irritation, constipation, hyperuricaemia and hyperuricosuria (BNF for Children 2014) and very occasionally with serious complications of the gastrointestinal system such as fibrosing colonopathy in both children and adults (CSM 1995).

A systematic review on the efficacy of PERT in people with CF may help to guide clinical practice. Currently the approach to the assessment of pancreatic function, the commencement of pancreatic enzyme supplements, the dose and choice of enzyme supplement for infants and young children with CF is variable between centres. Optimising fat absorption and avoiding malnutrition are important for children with CF to achieve the best possible growth, improve their respiratory disease, their general health and ultimately their life expectancy. It is therefore very important to establish the evidence for benefit and risk with PERT; to compare different formulations; to determine the optimum treatment for different age groups; and to clarify the role of tests of pancreatic function in therapy. This is an update of previously published reviews (Somaraju 2014; Somaraju 2016).

OBJECTIVES

1. To evaluate the efficacy and safety of PERT in children and adults with CF associated with PI.
2. To compare the efficacy and safety of different formulations of PERT and their appropriateness in different age groups.
3. To compare the effects of PERT in CF according to different diagnostic subgroups (e.g. different ages at introduction of therapy and different categories of pancreatic function).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and quasi-RCTs (using allocation methods such as alternate allocation to treatment and control groups).

Types of participants

People of any age with CF, either diagnosed clinically and confirmed with sweat test, or by genetic testing or by newborn screening.

Types of interventions

Any dose of PERT and in any formulation, in either a home or hospital setting, for a period of not less than four weeks, compared either to placebo or other PERT preparations, commenced either at diagnosis of CF, at the onset of symptoms or at confirmation of abnormal pancreatic function.

We have selected this minimum treatment period for the following reasons. While clinicians and patients would expect to see the effect of treatment in terms of content of fat in stools and bowel motion, etc., within a week after changes have been made, in order to properly assess any impact on weight gain, it is necessary to follow the participants for at least two to four weeks. However, this may also depend on the individual's age, as newborn babies and infants gain weight faster than older children and adolescents. Furthermore, longer periods may be necessary for the assessment of body mass index (BMI) and the evaluation of quality of life (QoL).

Types of outcome measures

Primary outcomes

1. Changes in nutritional status (absolute or relative change)
   a. weight
   b. height
   c. BMI

Where weight has been adjusted for age or a z score used, we will request data (either individual patient data or aggregate data) from

the trial authors. If this is not available, then we will report z scores and centiles and include in a meta-analysis where possible.

Secondary outcomes

1. Bowel symptoms
   a. stool frequency
   b. abdominal pain
   c. flatulence
   d. constipation
   e. distal intestinal obstruction syndrome (DIOS)
2. Days in hospital (for any reason during the trial period)
3. QoL (as assessed by a validated questionnaire to families)
4. Number of times vitamin deficiency diagnosed
5. Adverse events attributed to pancreatic enzyme replacement therapy
   a. fibrosing colonopathy
   b. any other adverse events
6. Fecal fat excretion (FFE) or CFA
7. Lung disease
   a. number of exacerbations (as defined by trial authors) requiring oral or intravenous antibiotics
   b. rate of decline (absolute or relative change) in lung function as measured by:
      i. forced expiratory volume at one second (FEV_1) (either in L or % predicted)
      ii. forced vital capacity (FVC) (either in L or % predicted)

Search methods for identification of studies

Studies are eligible for inclusion irrespective of publication status (e.g. abstract or online report) or language.

Electronic searches

We identified relevant trials from the Group's Cystic Fibrosis Trials Register using the term: pancreatic enzymes.

The Cystic Fibrosis Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of the Cochrane Library), weekly searches of MEDLINE, a search of Embase to 1995 and the prospective handsearching of two journals - *Pediatric Pulmonology* and the *Journal of Cystic Fibrosis*. Unpublished work is identified by searching the abstract books of three major cystic fibrosis conferences: the International Cystic Fibrosis Conference; the European Cystic Fibrosis Conference and the North American Cystic Fibrosis Conference. For full details of all searching activities for the register, please see the relevant section of the Cochrane Cystic Fibrosis and Genetic Disorders Group's website.

Date of last search: 07 November 2019.

We have searched the ClinicalTrials.gov website (clinicaltrials.gov), the WHO International Clinica Trials Registry Platform (ICTRP) database (www.who.int/ictrp/search/en/) and EU clinical trials database (www.clinicaltrialsregister.eu/ctr-search/search) using the terms 'pancreatic enzyme replacement therapy' and 'cystic fibrosis'. Date searched: 26 December 2019.

Searching other resources

We contacted the companies for further information in our previous update (2016). For this update (2020) we searched the websites of the pharmaceutical companies that manufacture the pancreatic enzyme replacements and also contacted them for further information. If we receive any further information we will include them in future updates of the review.

Data collection and analysis

Selection of studies

Two authors independently selected the trials to be included in the review. We resolved any disagreements through discussion.

Data extraction and management

Two authors independently extracted data from the included trials using standard data acquisition forms to ensure consistency. We resolved any disagreements through discussion. Since all the trials included in the review had a treatment period of four weeks, we were only able to report data in the graphs at the time-point of 'at one month'. In future updates, if data reported at any other time periods are available, we will report these as well.

Assessment of risk of bias in included studies

We independently assessed the risk of bias for each included trial using the established criteria as set out in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Criteria that we assessed included: how allocation sequence was generated; how the treatment allocation schedule was concealed; whether the trial was blinded; whether intention-to-treat analyses were possible from the data and if the number of participants who did not complete the trial or who were excluded for some reason was recorded; as well as selective reporting and any other potential risk of bias. We resolved any disagreements through discussion.

Measures of treatment effect

The authors did not record any dichotomous data; however, if in future we report such data, we plan to report the odds ratio and calculate the odds of an outcome among treated participants to the corresponding odds in the control group and their 95% confidence intervals (CIs).

For the continuous outcomes, we recorded mean post-treatment values or the mean change from baseline for each group with corresponding standard deviations (SDs). We entered the data into RevMan to produce a pooled estimate of treatment effect showing the mean difference (MD) between groups and the corresponding 95% CIs (RevMan 2012). Where papers provided the standard errors (SEs) instead of SDs, we converted SEs to SDs so that we were able to enter the data into RevMan.

Unit of analysis issues

We treated cross-over trials as if they were parallel trials. We are aware that by doing so, we are assuming a correlation of zero and that this may produce conservative results which ignore any within-patient correlation there may be; and furthermore the two groups will not be independent as each participant will appear in both treatment and control groups (Elbourne 2002).

Where the available data did not allow any analysis to be carried out and so incorporated within the review, we described the results individually.

Dealing with missing data

For an intention-to-treat analysis, we tried to obtain data for all participants who were later excluded from either treatment or follow up, for whatever reason, including poor compliance with treatment. We contacted the primary authors for any missing data.

Assessment of heterogeneity

In future updates, if we are able to combine more trials in the review, we will assess the trials for heterogeneity using the Chi^2 test and the I^2 statistic (Higgins 2003). We will assess heterogeneity such that we will consider values of under 40% as relatively unimportant; values between 40% and 60% as indicating moderate heterogeneity; and values above 60% as indicating substantial heterogeneity.

Assessment of reporting biases

Where possible we compared the original trial protocols, obtained from clinicaltrials.gov, with the final publications to identify any outcomes that were measured but not reported. We also tried to identify any instances of multiple publications of positive results and single publication of negative or neutral results.

We also made note of any language biases and assessed whether papers were published in multiple languages.

Data synthesis

We analysed the extracted data using a fixed-effect model. In future updates, if we are able to add more trials, where the between-trial variability is not statistically significant, we will use a fixed-effect model and if the between-trial variability is statistically significant, we will use a random-effects model.

Subgroup analysis and investigation of heterogeneity

In future updates, if we are able to add and combine more trials (n = 10) and we identify substantial heterogeneity between them, we will perform a subgroup analysis looking at the different formulations and dosages, the presence of symptoms and if possible look at effects at different ages.

Sensitivity analysis

In future updates, if we are able to include sufficient trials in the review (n = 10), we will assess results when including and excluding quasi-RCTs in addition to RCTs. We will also assess any differences from using a fixed-effect or a random-effects model.

In future updates, if we have sufficient data, we will undertake a meta-analysis including only the first-arm or last-arm data and present this as a sensitivity analysis. In the present review, none of the included cross-over trials presented first-arm or last-arm data separately, so we could not undertake this analysis.

Summary of findings tables

We will prepare summary of findings tables for each comparison included in the review. We will list population, setting, intervention and comparison and report an illustrative risk for the experimental and control intervention (Schünemann 2011). We will grade of overall quality of the body of evidence as high, moderate, low or very low using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) (Schünemann 2006). We will base our judgements on the risk of bias within the trials, their relevance to our population of interest (indirectness), unexplained heterogeneity or inconsistency, imprecision of the results or high risk of publication bias. We will downgrade the evidence once if the risk was serious and twice if the risk was deemed to be very serious and will describe the rationale for each judgement in footnotes to each table.

For each comparison we will report the following outcomes at the end of the trial:

- change in weight;
- change in height;
- change in BMI;
- frequency of bowel symptoms;
- CFA;
- adverse events; and
- pulmonary exacerbations.

RESULTS

Description of studies

Please see the tables for further details (Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies).

Results of the search

The literature searches identified 132 trials, 15 of which were immediately rejected. This left 107 trials for closer inspection. Of these we have included 14 trials (one of which was listed as ongoing in the 2016 version of the review (Konstan 2018a)); 83 trials were excluded; nine trials are listed as awaiting classification; and one trial is still ongoing (estimated primary completion date in February 2021).

Included studies

Trial characteristics

All 14 included trials were RCTs. Two trials were of parallel design (Borowitz 2005; Konstan 2018a) and the remaining 12 trials were of cross-over design (Assoufi 1994; Elliott 1992; Henker 1987; Lacy 1992; Patchell 1999; Petersen 1984; Stead 1986; Stead 1987; Taylor 2015; Vidailhet 1987; Vyas 1990; Williams 1990). The duration of treatment was 28 days in one parallel trial (Borowitz 2005) and seven weeks for the second parallel trial (with a 20-week extension period) (Konstan 2018a). For all cross-over trials, each arm lasted for a period of 28 days (Assoufi 1994; Elliott 1992; Henker 1987; Lacy 1992; Patchell 1999; Petersen 1984; Stead 1986; Stead 1987; Vidailhet 1987; Vyas 1990; Williams 1990; Taylor 2015). Three trials were multicentre (Borowitz 2005; Patchell 1999; Taylor 2015). Borowitz recruited participants from 26 Cystic Fibrosis Foundation centres in the USA (Borowitz 2005) and Patchell recruited from three hospitals in the UK (Patchell 1999). Taylor recruited participants from 34 sites in seven European countries including Belgium, Bulgaria, Germany, Hungary, Italy, Poland, and the UK (Taylor 2015). For two trials, one based in Denmark (Petersen 1984) and one in the UK (Williams 1990), we could not ascertain whether they were single or multicentre trials from published

reports. The remaining eight trials were single-centre; five of these were run in the UK (Assoufi 1994; Lacy 1992; Stead 1986; Stead 1987; Vyas 1990) and one each in New Zealand (Elliott 1992), in the former East Germany (Henker 1987) and in France (Vidailhet 1987). All the trials included in the review were based in a home setting.

Participants

Eight trials included children with CF and the age of children varied from one to 17 years (Elliott 1992; Henker 1987; Lacy 1992; Patchell 1999; Petersen 1984; Vidailhet 1987; Vyas 1990; Williams 1990). The participants in four trials were adults with mean ages varying between 21.4 and 24.8 years (Assoufi 1994; Borowitz 2005; Stead 1986; Stead 1987). Two trials included children and adults; one with participants aged 12 years and older (Taylor 2015) and the second with participants aged seven years and older (Konstan 2018a). The number of participants in the trials varied and ranged between 11 (Petersen 1984) and 129 participants (Borowitz 2005; Konstan 2018a). The total number of participants in all included trials was 641.

Interventions

The interventions used were heterogenous between the trials; 11 trials compared enteric-coated microspheres (ECM) with other preparations of PERT including other ECM.

ECM versus other enteric-coated preparations

Seven trials compared ECM to other enteric-coated preparations. Two trials compared ECM (Creon®) with enteric-coated tablets (ECT) (Pancrex®) (Stead 1986; Vyas 1990). One trial compared ECM (Creon 8000®) with enteric-coated mini-microspheres (ECMM) (Creon 10000®) (Patchell 1999). Petersen compared ECM (Pancrease®) with enteric-coated granules (Pancreatin®) (Petersen 1984). Two trials compared ECM with non-enteric-coated tablets (Henker 1987; Stead 1987). One of these trials compared ECM (Creon®) with pancreatin (Pankreon Forte®) (Henker 1987); while the second compared ECM (Creon®) with non-enteric-coated pancreatin (Pancrex V®) in combination with cimetidine (Stead 1987). Another trial compared ECM (Creon®) with lyophilised TPEs (Vidailhet 1987).

ECM versus another ECM

Four trials compared different preparations of ECM; three of these compared two preparations (Creon® versus Pancrease®; Kreon versus Zenpep®) (Elliott 1992; Williams 1990; Taylor 2015) and one trial compared three preparations of ECM (Nutrizyme GR® versus Nutrizyme MP® versus Creon®) (Lacy 1992).

Note: Kreon is the trade name for Creon® used in German-speaking regions, for clarity we will use Creon® in this review.

Different doses of PERT

Two trials compared PERT in different doses; one compared high-dose enzyme replacement therapy (Nutrizyme 22®) with low-dose therapy (Nutrizyme GR®) (Assoufi 1994) and the remaining trial assessed different doses of a novel microbial preparation (Altu-135) (Borowitz 2005).

Biotechnology-derived PERT versus porcine PERT

One trial compared PERT synthesised from biotechnology derived processes (liprotamase) with enteric-coated pancrelipase microtablets (Pancreaze®) in comparable doses (the dose was not allowed to exceed 10,000 units lipase/kg/day or 2,500 units lipase/kg/meal) (Konstan 2018a).

Outcomes

None of the trials included measured all of the outcomes of interest to the review, and we looked at both relative and absolute changes in the outcomes.

12 trials measured the change in weight from baseline (Assoufi 1994; Elliott 1992; Henker 1987; Konstan 2018a; Lacy 1992; Petersen 1984; Stead 1986; Stead 1987; Taylor 2015; Vidailhet 1987; Vyas 1990; Williams 1990). Five trials gave details on what they reported (absolute change in weight) (Stead 1986; Stead 1987; Taylor 2015; Vyas 1990; Konstan 2018a); the remaining trials provided insufficient details to know exactly which type of change was considered. Stool frequency was also reported in 11 trials (Assoufi 1994; Borowitz 2005; Elliott 1992; Henker 1987; Patchell 1999; Petersen 1984; Stead 1986; Stead 1987; Taylor 2015; Vyas 1990; Williams 1990) and one trial reported stool weight (Konstan 2018a)., Eight trials reported measuring abdominal pain (Elliott 1992; Konstan 2018a; Patchell 1999; Stead 1986; Stead 1987; Taylor 2015; Vyas 1990; Williams 1990). Constipation was reported in one trial (Elliott 1992) and DIOS was reported in one trial (Borowitz 2005). Only four trials reported on adverse events (Assoufi 1994; Borowitz 2005; Konstan 2018a; Taylor 2015). All included trials reported FFE or CFA; but one trial only measured it at 14 days and hence we did not include those data in our analysis (Borowitz 2005). Only two trials measured QoL (Borowitz 2005; Taylor 2015) and one trial measured lung disease (Borowitz 2005).

Excluded studies

We excluded a total of 84 trials identified in the searches. Six trials were excluded as they were neither an RCT or quasi-RCT (Araujo 2011; Katona 2000; Morrison 1992; NCT00449904; NCT01652157; NCT01858519). 12 trials were excluded as they did not employ a relevant intervention (Breuel 1996; Butt 2001; Colombo 2001; Eiel 2018; Geyer 2019; Hubbard 1984; Lubin 1979; NCT01851694; Ritz 2004; Stapleton 2001; van der Haak 2016; Vitti 1975) and two trials were excluded as they did not measure any outcomes relevant to this review (Hill 1993; Mack 1991). One trial was excluded as the participants were not relevant to the review (EUCTR 2007-004004-12) and one trial was deemed eligible, but data were not in a usable form and will not be available at any time in the future (Dalzell 1992). In the remaining 62 trials, the intervention was given for less than 28 days leading to exclusion.

Studies awaiting classification

Eight trials are currently listed as 'awaiting classification' for a number of reasons and we have contacted the investigators for further information (Brekke 2019; Dalzell 1992a; Holsclaw 1980; Lenoir 2008; Knill 1973; Konstan 2018b; Regele 1996; Stern 1988; Taylor 1993). The methodology with regards to randomisation was unclear in four trials (Holsclaw 1980; Lenoir 2008; Stern 1988; Taylor 1993). One trial presented data combined for 11 participants with CF and one with pancreatic insufficiency, but data were not available for just those participants with CF (Knill 1973). One cross-over trial presented data for each participant at the end of each treatment period, but did not make clear which treatment group the participant was part of in each period (Regele 1996). For two trials the results are not yet available, although they have been completed (Brekke 2019; Konstan 2018b).

Ongoing trials

One ongoing multicentre trial by Abbvie Pharmaceuticals is potentially eligible for inclusion (NCT03924947). It is a phase 4, quadruple-blind, cross-over RCT evaluating pancrelipase capsules manufactured in a modernised process compared to currently marketed pancrelipase capsules. Males and females with CF aged 12 years and above are eligible to participate in the trial. The estimated enrolment is 28 participants. The outcome measures of the trial are CFA (baseline up to eight weeks) and safety as measured by number of participants with adverse events or laboratory abnormalities (baseline up to 6 months). The expected date of completion of the trial is February 2021. Once results for this trial are published we will fully assess it for inclusion in a future update of this review.

Risk of bias in included studies

Allocation

Generation of sequence

All 14 trials included in the review were described as RCTs. Since the details of randomisation were not given for any of the trials, we have graded them all as having an unclear risk of bias. One trial did describe randomising participants in blocks of four, stratified by age at enrolment and gastric acid suppression use, but the method for generating the random sequence was not given (Konstan 2018a).

Allocation concealment

LIkewise, we graded all trials as having an unclear risk for allocation concealment as again no details were provided.

Blinding

Five of the included trials were open trials with no blinding and we graded them as having a high risk of bias (Henker 1987; Konstan 2018a; Patchell 1999; Stead 1986; Stead 1987). One trial had a single-blind, cross-over design (Williams 1990). The trial medication was issued by pharmacist and the order of treatment was not known to the doctor; but since the participants were not blinded, we also graded this trial as having a high risk of bias.

For one trial the details of blinding were not given; we therefore judged it to have an unclear risk of bias (Vidailhet 1987).

The remaining seven trials were described as double blind and in each of these trials all the participants received equal number of ungraded capsules (Assoufi 1994; Borowitz 2005; Elliott 1992; Lacy 1992; Petersen 1984; Taylor 2015; Vyas 1990). We judged these trials to have a low risk of bias.

Incomplete outcome data

We judged four trials to have a high risk of bias (Assoufi 1994; Lacy 1992; Vyas 1990; Williams 1990). For two trials, the reasons for withdrawals were not described (Assoufi 1994; Lacy 1992). In a further trial, there were 20 participants, but only 12 paired stool samples were analysed for fecal fat excretion; the reason for the exclusion of the other participants was not given (Vyas 1990). A fourth trial enrolled 39 participants and 12 of these withdrew for various reasons (Williams 1990). Although withdrawals were described clearly, because the proportion of participants withdrawing was 31%, we graded the trial as having a high risk of bias.

We judged two trials to have an unclear risk of bias due to incomplete outcome data (Henker 1987; Vidailhet 1987). The first of these did not give any details about whether there were any withdrawals (Henker 1987). The second trial appears to have included all the participants in the analysis, but the details were not given (Vidailhet 1987).

We graded eight included trials as having a low risk of bias due to incomplete outcome data (Borowitz 2005; Elliott 1992; Konstan 2018a; Patchell 1999; Petersen 1984; Stead 1986; Stead 1987; Taylor 2015). In the Borowitz trial, 12 of the 129 enrolled participants withdrew early; Borowitz described the withdrawals and 117 participants were included in a modified intention-to-treat analysis (mITT) (Borowitz 2005). Elliott described three withdrawals out of 30 children; two withdrew consent prior to randomisation and one withdrew from the trial due to respiratory exacerbations during the run-in period (Elliott 1992). Konstan reported 23 withdrawals (18 of which were from the liprotamase group) and all were described; to avoid the potential for bias all the randomised participants who received at least one dose of the study drug were included in the mITT analyses (Konstan 2018a). In one multicentre trial, 54 out of 59 randomised participants completed the trial; stool collection data were analysed in one centre on an ITT basis (Patchell 1999). In one trial, there were no withdrawals, with all 11 participants completing (Petersen 1984). In the two remaining trials by Stead reasons for withdrawal were described fully; in the earlier trial, two out of 23 participants withdrew (Stead 1986) and in the later trial one out of 14 participants withdrew (Stead 1987). There were 10 withdrawals from the Taylor trial and the reasons were described (Taylor 2015).

Selective reporting

We graded nine trials as having a high risk of bias since some of the outcomes were reported in a way that could not be included in the analysis (Assoufi 1994; Elliott 1992; Henker 1987; Konstan 2018a; Lacy 1992; Patchell 1999; Petersen 1984; Vidailhet 1987; Williams 1990). For four of these, the results were reported in a narrative fashion only (Assoufi 1994; Elliott 1992; Henker 1987; Lacy 1992). Another of these trials measured stool frequency, wind and abdominal pain, but full details were not given (Patchell 1999). A further trial presented the results as medians, which could not be included in analysis (Petersen 1984). Two trials measured change in body weight but reported this incompletely so it could not be analysed in the review (Vidailhet 1987; Konstan 2018a); Konstan also measured height and BMI, but again insufficient details were given to allow us to include the results in the analysis (Konstan 2018a). The remaining trial measured change in body weight, stool frequency and abdominal pain, again without sufficient detail to allow analysis in the review (Williams 1990).

For five trials the outcomes were reported adequately and we graded them as having a low risk of bias (Borowitz 2005; Stead 1986; Stead 1987; Taylor 2015; Vyas 1990).

Other potential sources of bias

We judged eight trials as having a high risk of bias as they were funded or supported by pharmaceutical companies (Borowitz 2005; Elliott 1992; Konstan 2018a; Stead 1986; Stead 1987; Taylor 2015; Vyas 1990; Williams 1990). For three of these the intervention drug (Creon®) was supplied by Duphar laboratories (Stead 1986; Stead 1987; Vyas 1990). One trial was sponsored and actively supported by Altus pharmaceuticals (Borowitz 2005) and the primary author of another trial was financially supported by Cilag Limited (Williams

1990). For one trial, Boehringer Ingelheim (NZ) Ltd Kali Chemie provided funding and materials (Elliott 1992). The Konstan trial was partially supported by Anthera Pharmaceuticals (Konstan 2018a). For the final trial, the corresponding author is a consultant to Aptalis and Profile Pharma and the trial was funded by Aptalis Pharma (Taylor 2015).

For three trials there was no information and we judged them to have an unclear risk of bias (Assoufi 1994; Henker 1987; Lacy 1992).

For three trials we could not identify any other potential source of bias and judged them to have a low risk of bias (Patchell 1999; Petersen 1984; Vidailhet 1987).

Although with cross-over trials there is a potential source of bias due to a lack of a washout period, since these enzymes are given orally and act locally within the gastro-intestinal tract (no systemic absorption), we do not believe a washout period is necessary (Law 2014). Further to these cross-over trials, none of them presented the first-arm data and last-arm data individually, so that they could be included in sensitivity analysis. In the only comparison where we could combine data, the fact that these were cross-over trials is likely to underestimate the level of inconsistency between the results of the trials due to over-inflation of confidence intervals from the individual trials. This could potentially be a risk of bias.

Effects of interventions

See: **Summary of findings 1** Summary of findings: ECM compared with NECT plus cimetidine; **Summary of findings 2** Summary of findings: ECM compared with ECT; **Summary of findings 3** Summary of findings: ECM compared with ECMM; **Summary of findings 4** Summary of findings: ECM (Creon®) compared with a different ECM; **Summary of findings 5** Summary of findings: ECM compared with TPE; **Summary of findings 6** Summary of findings: ECM compared with other enteric-coated preparations; **Summary of findings 7** Summary of findings: low-dose compared with high-dose PERT; **Summary of findings 8** Summary of findings: liprotamase compared with porcine PERT

We have included 14 trials in the review, but were only able to include seven of these in the analysis within the review (Patchell 1999; Stead 1986; Stead 1987; Taylor 2015; Vidailhet 1987; Vyas 1990; Williams 1990). We have presented summary statistics for both significant and non-significant results below.

We did not have sufficient information to include the remaining seven trials in the analysis at this time and have contacted the primary authors for further information. For these trials we have described the results, and we will update the review with information if we receive any at a later date (Assoufi 1994; Borowitz 2005; Elliott 1992; Henker 1987; Konstan 2018a; Lacy 1992; Petersen 1984).

Many of the outcomes of interest to our review were not reported in any of the included trials. In the summary of findings tables, we have graded the quality of the evidence for pre-defined outcomes (see above) and have provided the definitions of these gradings (Summary of findings 1; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6; Summary of findings 7; Summary of findings 8).

Primary outcomes

1. Changes in nutritional status

a. weight

This outcome was reported in 12 trials with 447 participants (Assoufi 1994; Elliott 1992; Henker 1987; Konstan 2018a; Lacy 1992; Petersen 1984; Stead 1986; Stead 1987; Taylor 2015; Vidailhet 1987; Vyas 1990; Williams 1990); but of these 12 trials, only five (n = 264) provided limited data for the analysis (Konstan 2018a; Stead 1986; Stead 1987; Taylor 2015; Vyas 1990).

ECM versus non-enteric-coated tablets (NECT) with adjuvant cimetidine

One trial with 12 participants compared ECM to non-enteric-coated tablets (NECT) with adjuvant cimetidine (Stead 1987). The change in weight in favour of ECM when compared to NECT with adjuvant cimetidine at one month was not statistically significant, MD 0.40 kg (95% CI -0.10 to 0.90) (Analysis 1.1) (very low-quality evidence).

ECM versus ECT

Two trials with data from 41 participants compared ECM to ECT (Stead 1986; Vyas 1990). At one month, there was a higher increase in body weight in participants receiving ECM than those receiving ECT, but this was not statistically significant, MD 0.32 kg (95% CI -0.03 to 0.67) and heterogeneity was substantial (I^2 = 73%) (Analysis 2.1) (very low-quality evidence). The heterogeneity between the trials may be due to the difference in the participant population; one trial recruited adults only with mean age of 24.8 years (Stead 1986), while the second trial recruited only children (Vyas 1990). The difference is unlikely to be due to dose differences as trial design would normally ensure that the lipase units are matched.

ECM (Creon®) versus another ECM

There were three trials comparing two different forms of ECM (Elliott 1992; Taylor 2015; Williams 1990) and one trial comparing three different forms of ECM (Lacy 1992); only one trial provided data for analysis (Taylor 2015). There was no difference in treatment effect between Creon® and Zenpep®, MD 0.00 kg (95% CI -0.28 to 0.28) (Analysis 4.1) (moderate-quality evidence). The remaining trials did not report any significant difference in change in body weight (Elliott 1992; Lacy 1992; Williams 1990).

ECM versus TPE

One trial comparing ECM to TPE did not report any significant difference in change in body weight (no data available for analysis) (Vidailhet 1987)

ECM versus other enteric-coated preparations

One trial compared ECM to a conventional pancreatin preparation and did not report any significant difference in change in body weight (Henker 1987). One trial compared ECM to enteric-coated granules and reported that weight gain was significantly better with ECM (Petersen 1984). Neither trial provided data for analysis; we judged the quality of the evidence as very low.

Different doses of PERT

One trial compared a high dose of enzymes to a low dose, maintaining lipase intake equal, but halving the number of capsules of high-dose preparation, and reported finding no significant difference in weight gain (Assoufi 1994) (very low-quality evidence).

Liprotamase versus porcine PERT

Konstan reported that there was a decline in weight of 0.84 kg in the liprotamase arm compared to the pancrelipase group at Week 7, which was statistically significant (P < 0.001) (low-quality evidence). The table in the paper shows a mean weight loss in the liprotamase arm of 1.2 kg compared to a small gain in mean weight in the pancrelipase arm of 0.2 kg (Konstan 2018a). The paper further reports that weight was stable in the follow-up period up to Week 20.

b. height

ECM versus other enteric-coated preparations

This outcome was measured in only one of the included trials in this comparison (45 participants) comparing ECM to conventional pancreatin preparation (Henker 1987). The trial did not give any details, but the investigators reported no difference between the two preparations (very low-quality evidence).

Liprotamase versus porcine PERT

One trial (129 participants) compared liprotamase with pancrelipase and reported that the height was stable through the trial period for both treatment arms (Konstan 2018a).

c. BMI

ECM versus other enteric-coated preparations

Only one trial in this comparison measured the height of participants, but did not report BMI and we ere unable to calculate BMI ourselves since investigators did not report the actual data (Henker 1987).

Liprotamase versus porcine PERT

The Konstan trial did not give data we could analyse in the review, but reported that the BMI remained stable in both the arms during the extension period (Konstan 2018a).

Secondary outcomes

1. Bowel symptoms

ECM (Creon®) versus another ECM

One trial described measuring symptom scores, but did not give any details as to which symptoms were measured or the results (Lacy 1992).

Different doses of PERT

In one trial of 117 participants comparing different doses of ALTU-135, 106 participants reported gastrointestinal adverse events which were mostly mild in intensity and were not significantly different between the three treatment arms; further details were not given (Borowitz 2005). However, four participants did withdraw due to gastrointestinal events.

a. stool frequency

This outcome was reported in 10 trials with 326 participants (Assoufi 1994; Elliott 1992; Henker 1987; Patchell 1999; Petersen 1984; Stead 1986; Stead 1987; Taylor 2015; Vyas 1990; Williams 1990). Of the these, only four trials (n = 136) have provided sufficient data for inclusion in our analysis (Stead 1986; Stead 1987; Taylor 2015; Vyas 1990).

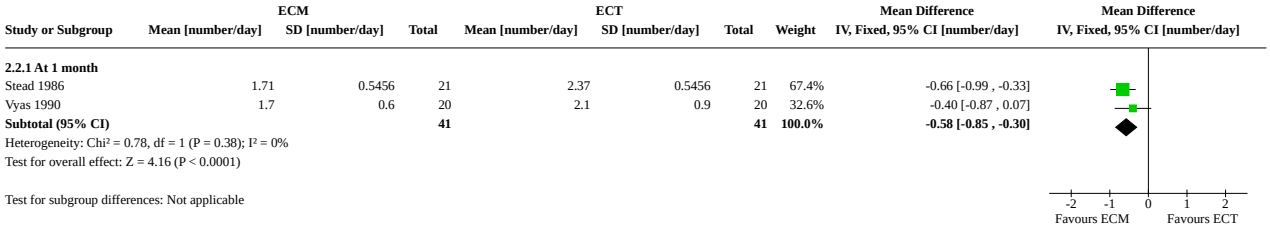
ECM versus NECT with adjuvant cimetidine

The trial (n = 12) comparing ECM to NECT with cimetidine reported a significant decrease in stool frequency (number per day) at one month, MD -0.70 (95% CI -0.90 to -0.50) (Stead 1987) (Analysis 1.2) (very low-quality evidence).

ECM versus ECT

The two trials (n = 41) comparing ECM to ECT also reported a significant decrease in stool frequency (number per day) in favour of ECM, MD -0.58 (95% CI -0.85 to -0.30) (Stead 1986; Vyas 1990) (Analysis 2.2) (Figure 1) (very low-quality evidence).

Figure 1. Forest plot of comparison: 2 ECM versus ECT, outcome: 2.2 Stool frequency [number/day].



ECM versus ECMM

One trial (59 participants) compared ECM to ECMM and reported no difference between treatment groups with a median stool frequency of two stools per day in both treatment groups (Patchell 1999) (very low-quality evidence).

ECM (Creon®) versus another ECM

The three trials comparing different formulations of ECM also reported that there was no significant difference in either treatment period (Elliott 1992; Taylor 2015; Williams 1990) (Analysis 4.2) (low-quality evidence).

ECM versus other enteric-coated preparations

Two trials did not provide sufficient data for inclusion in analysis, the trial comparing ECM to conventional pancreatic preparations (Henker 1987) and the trial comparing ECM to enteric-coated granules (Petersen 1984) reported finding significantly decreased stool frequency with ECM (very-low quality evidence).

Different doses of PERT

The trial comparing a high dose of enzymes to a low dose, while maintaining lipase intake as equal but halving the number of capsules of high-dose preparation, found no significant difference in stool frequency (Assoufi 1994) (very low-quality evidence).

b. abdominal pain

This outcome was reported in eight trials (382 participants) using clinical scores or questionnaires (Elliott 1992; Patchell 1999; Stead 1986; Stead 1987; Taylor 2015; Vyas 1990; Williams 1990; Konstan 2018a). Of the eight trials, only four reported sufficient data (n = 136), such that they could be included in analysis. (Stead 1986; Stead 1987; Taylor 2015; Vyas 1990).

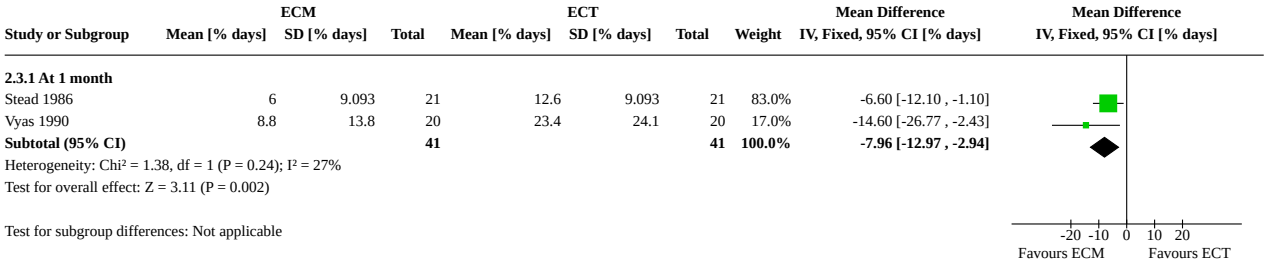
ECM versus NECT with adjuvant cimetidine

The trial (n = 12) comparing ECM to NECT with cimetidine reported a non-significant decrease in abdominal pain when receiving ECM compared to NECT with adjuvant cimetidine, MD -10.50 (95% CI -21.40 to 0.40) (Stead 1987) (Analysis 1.3) (very low-quality evidence).

ECM versus ECT

Combined data from the two trials (n = 41) comparing ECM to ECT reported a significant decrease in the percentage of days when abdominal pain is present in participants in the ECM group compared to those in the ECT group, MD -7.96 (95% CI -12.97 to -2.94) (Stead 1986; Vyas 1990) (Analysis 2.3) (Figure 2) (very low-quality evidence).

Figure 2. Forest plot of comparison: 2 ECM versus ECT, outcome: 2.3 Abdominal pain [% days].



ECM versus ECMM

The authors of the trial comparing ECM and ECMM observed no significant difference between the groups and reported that abdominal pain was mainly absent or mild throughout the trial (no data for analysis) (Patchell 1999) (very low-quality evidence).

ECM (Creon®) versus another ECM

Likewise, the trials comparing different formulations of ECM found no significant difference between the groups for this outcome (Elliott 1992; Williams 1990; Taylor 2015); only one trial provided any data for analysis (Analysis 4.3) (low-quality evidence).

Liprotamase versus porcine PERT

The trial comparing liprotamase to porcine PERT observed that symptom scores were worse for abdominal pain in the liprotamase group, but did not provide data for inclusion in the analysis (Konstan 2018a) (low-quality evidence).

c. flatulence

Two trials reported on this outcome (Patchell 1999; Taylor 2015).

ECM versus ECMM

The authors observed no treatment difference between the groups and flatulence was stated to be absent or mild throughout the trial; however no actual data were reported (Patchell 1999) (very low-quality evidence).

ECM (Creon®) versus another ECM

In the Taylor trial, there was no treatment difference between the two interventions, MD 0.00 (95% CI -0.12 to 0.12) (Analysis 4.4) (Taylor 2015) (low-quality evidence).

d. constipation

ECM (Creon®) versus another ECM

One trial comparing two forms of ECM measured this outcome and reported narratively that no significant difference was found between the two treatment periods (Elliott 1992).

e. DIOS

Different doses of PERT

Only the trial of ALTU-135 reported this outcome (Borowitz 2005). There was a single episode of DIOS requiring hospitalisation in a participant in the low-dose group; it resolved without any sequelae (very low-quality evidence).

2. Days in hospital

This outcome was not measured in any of the included trials.

3. QoL

Only two trials reported this outcome (Borowitz 2005; Taylor 2015).

ECM (Creon®) versus another ECM

The trial comparing two different forms of ECM used CFQ-R-Parent and CFQ-R-Teen/Adult to measure this outcome (Taylor 2015). The two forms were found to have similar effects on well-being with a nominally significant difference in favour of Zenpep®, but only for the respiratory domain.

Different doses of PERT

The trial of ALTU-135 reported this outcome (Borowitz 2005). The investigators used the Cystic Fibrosis Questionnaire-Revised (CFQ-R) (Quittner 2009) and reported finding little change from baseline after treatment, regardless of dose group. They attributed this to the short duration of the trial.

4. Number of times vitamin deficiency diagnosed

This outcome was not measured in any of the included trials.

5. Adverse events attributed to PERT

a. fibrosing colonopathy

This outcome was not measured in any of the included trials.

b. any other adverse events

This outcome was reported in only four trials (Assoufi 1994; Borowitz 2005; Konstan 2018a; Taylor 2015).

ECM (Creon®) versus another ECM

Taylor reported mostly mild adverse events, with abdominal pain, diarrhoea and flatulence being most common, and found the number of participants reporting adverse events was lower for Zenpep® (19.6%) than Creon® (25.6%) (Taylor 2015) (low-quality evidence).

Different doses of PERT

There were no noted side effects in the trial by Assoufi (Assoufi 1994), while Borowitz did not find any serious adverse events or deaths (Borowitz 2005) (very low-quality evidence).

Liprotamase versus porcine PERT

Konstan did not identify any serious adverse events thought to be due to the trial drug; treatment-emergent adverse events and serious adverse events were found to be similar between the two groups (Konstan 2018a) (low-quality evidence).

6. FFE or CFA

This outcome was measured in all 14 included trials (Assoufi 1994; Borowitz 2005; Elliott 1992; Henker 1987; Konstan 2018a; Lacy 1992; Patchell 1999; Petersen 1984; Stead 1986; Stead 1987; Taylor 2015; Vidailhet 1987; Vyas 1990; Williams 1990). Eight trials (n = 240) provided data which could be included in the analysis (Konstan 2018a; Patchell 1999; Stead 1986; Stead 1987; Taylor 2015; Vidailhet 1987; Vyas 1990; Williams 1990). The unit of measurement varied across the trials; some authors drew conclusions based on FFE and others drew conclusions based on CFA. Not all the trials provided detailed information as to how the variable was measured. For the purpose of this review, we have assumed either FFE and CFA were equivalent and the two trials whose data were combined, provided both the variables, as CFA is a calculated outcome, for which FFE is necessary.

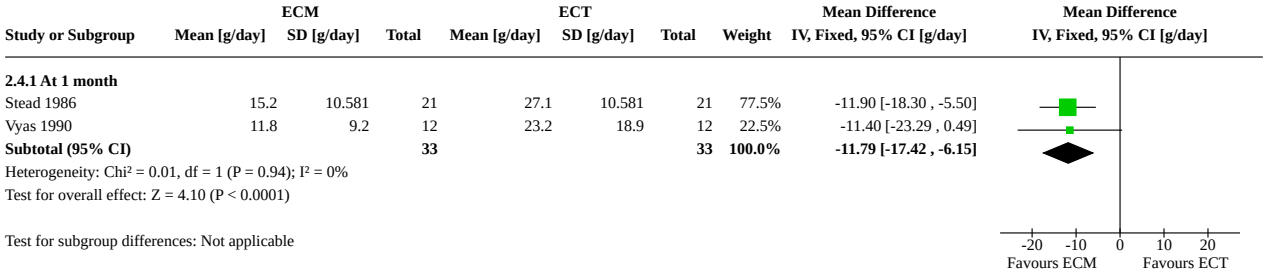
ECM versus NECT with adjuvant cimetidine

The trial (n = 12) comparing ECM to NECT with adjuvant cimetidine showed no significant difference in FFE between treatment groups, MD -6.70 (95% CI -14.70 to 1.30) (Stead 1987) (Analysis 1.4) (low-quality evidence).

ECM versus ECT

In contrast, the two trials (n = 33) comparing ECM and ECT reported a significant decrease in FFE in favour of ECM, MD -11.79 (95% CI -17.42 to -6.15) (Stead 1986; Vyas 1990) (Analysis 2.4; Figure 3) (low-quality evidence).

Figure 3. Forest plot of comparison: 2 ECM versus ECT, outcome: 2.4 FFE [g/day].



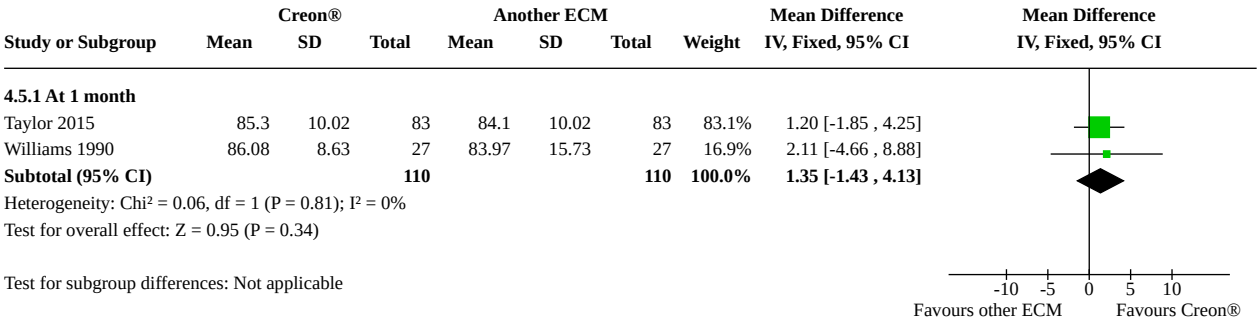
ECM versus ECMM

The comparison of ECM and ECMM by Patchell (n = 22) showed no significant difference in FFE between treatments, MD -1.70 (95% CI -6.57 to 3.17) (Patchell 1999) (Analysis 3.1) (very low-quality evidence).

ECM (Creon®) versus another ECM

The results from two trials (n = 110) showed no significant difference in CFA when two different formulations of ECM were compared, MD 1.35 (95% CI -1.35 to 4.13) (Taylor 2015; Williams 1990) (Analysis 4.5; Figure 4) (moderate-quality evidence). The trial comparing two preparations of ECM (Elliott 1992) and another comparing three preparations of ECM (Lacy 1992) found no significant difference for this outcome (no data available for analysis).

Figure 4. Forest plot of comparison: 4 ECM (Creon®) versus another ECM, outcome: 4.5 Coefficient of fat absorption [%].



ECM versus TPE

In the trial of ECM compared to TPE (n = 17), while FFE was lower in the ECM group, the result was not statistically significant, MD -1.60 (95% CI -3.31 to 0.11) (Vidailhet 1987) (Analysis 5.1) (very low-quality evidence).

ECM versus other enteric-coated preparations

One trial comparing ECM to conventional pancreatin reported finding no difference between the two treatment arms (Henker 1987); while another comparing ECM to enteric-coated granules found improved fat absorption on ECM, but the results were not statistically significant (Petersen 1984) (very low-quality evidence).

Different doses of PERT

The trial that compared a high dose of enzymes to a low dose (maintaining lipase intake as equal, but halving the number of capsules of the high-dose preparation) reported an FFE of 15.4 g/day on the high-dose enzyme and a FFE of 18.7 g/day on the low-dose enzyme. However, the difference was not statistically significant (Assoufi 1994) (very low-quality evidence).

One trial measured this outcome at 14 days on the treatment arm, even though the trial period was one month (Borowitz 2005). Since the inclusion criteria of the review require that the treatment period should be at least four weeks before measuring outcome, we have not included the results for this outcome from that trial in our analysis.

Liprotamase versus porcine PERT

The Konstan trial reported a significant decrease in CFA from baseline at seven weeks in the lipromatase group compared to the pancrelipase group, MD (SE) -11.85 (2.12) (low-quality evidence). Since this trial was a non-inferiority trial and the study investigators stated that lipromatase missed the non-inferiority criterion, we have decided not to analyse these data in this review and report the result narratively and as taken from the paper (Konstan 2018a).

7. Lung disease

a. number of exacerbations requiring oral or intravenous antibiotics

Different doses of PERT

The trial comparing different doses of ALTU-135 reported a total of 10 pulmonary exacerbations of CF requiring hospitalisation, but the distribution of events across groups was not reported (Borowitz 2005).

Liprotamase versus porcine PERT

Konstan reported a pulmonary exacerbation of CF in 4.6% of participants in the liprotamase group and in 7.9% of participants in the pancrelipase group, when analysed these data show no difference between groups, OR 0.56 (95% CI 0.13 to 2.45) (Konstan 2018a) (Analysis 6.1) (low-quality evidence).

b. rate of decline in FEV_1 and FVC

This outcome was not measured in any of the included trials.

DISCUSSION

Even though PERT has been used for many years, not all enzymes are equally effective at correcting maldigestion and sustaining normal growth and nutrition on a normal diet. The available enzyme products also vary greatly in their potency and properties. A number of factors contribute to this, including those related to the preparations, such as the delivery of the enzymes in the correct strength and at the correct location; and disease-related factors such as abnormal bile acid secretion, more acidic intestinal pH.

This review aimed to compare different preparations of PERT for their efficacy and safety in people with CF.

Summary of main results

For the review's primary outcome, 12 trials reported information on at least one of the measures of weight or height or BMI, but we are uncertain whether any of the formulations improves nutritional status more than others. People with CF taking ECM experienced a small increase in body weight; however, this was not statistically significant when compared to ECT or non-enteric-coated tablets NECT with adjuvant antacids.

With regards to the secondary outcomes, when compared to ECT, ECM may slightly improve: stool frequency, MD -0.58 (95% CI -0.85 to -0.30; P < 0.0001); the proportion of days with abdominal pain, MD -7.96% (95% CI -12.97 to -2.94; P = 0.002); and fecal fat excretion, MD -11.79 g (95% CI -17.42 to -6.15; P < 0.0001) (two cross-over trials; n = 33). Similarly, ECM may slightly improve stool frequency compared to NECT with adjuvant cimetidine, MD -0.70 (95% CI -0.90 to -0.50; P < 0.00001) (one cross-over trial; n = 12). Non-porcine PERT may slightly decrease measures of fat excretion compared to porcine PERT, MD -11.85 (95% CI -16.01 to -7.69) (one parallel trial; n = 128). No differences were seen with other comparisons, e.g. ECM compared to TPE. We found no difference between any of

the formulations in terms of other bowel symptoms (e.g. abdominal pain, flatulence, constipation or DIOS), QoL, adverse events or any measure of lung disease. No trial reported on the number of days in hospital or the incidence of vitamin deficiency.

Overall completeness and applicability of evidence

An important limitation in the review was that we did not find any trials meeting our inclusion criteria which compared the different preparations of PERT to placebo; therefore, we cannot comment on the relative efficacy of PERT in comparison to placebo. Another notable factor identified in our review was the lack of evidence for many outcomes that are likely to be important for people with CF and clinicians in evaluating a response to treatment. There were no comprehensive data on nutritional status (only some data on weight which could not be combined), QoL, vitamin deficiencies, or number of days in hospital. The included trials were all of short duration, so the long-term effects of treatment could not be assessed. Also, there was no information with respect to the severity of disease in participants (either in terms of lung function or degree of pancreatic insufficiency), so we cannot comment on the relative effectiveness of PERT in the different patient groups. This also limits the generalisation of evidence for all patient groups. Finally, with the exception of three trials (Borowitz 2005; Konstan 2018a; Taylor 2015), the included trials were relatively old; probably due to the fact that they were looking at PERT formulations developed in 1970s. There have been more recent trials for recombinant enzymes (Merispase and Altu) which were developed in last 10 years. The company developing Merispase is no longer trading and Altu is the subject of the Borowitz trial (Borowitz 2005).

Quality of the evidence

The review included only 14 trials with an unclear risk of bias from randomisation methods; 12 out of the 14 trials were cross-over in design and mostly also had a high risk of attrition bias and reporting bias. Attrition bias may be due to the duration of the trial periods; all trials had a run-in or dose stabilisation period followed by e.g. eight weeks in each of the two treatment arms. The included trials were of a short duration and this precludes any comments on the long-term effects of the intervention. Also, there was no evidence on the severity of the pancreatic insufficiency among the participants.

The quality of evdence of the included trials as assessed by the GRADE system ranged from moderate to very low (Schünemann 2011). We judged the overall quality of evidence to be low mainly due to uncertainty around randomisation and allocation concealment and small number participants in included trials. Also the trials looked at different forms of PERT due to which we were unable to combine the result for most of the data.

Potential biases in the review process

A potential bias introduced in the review process may be the time frame of four weeks chosen by the authors, which resulted in a number of trials being excluded from the review due to shorter treatment periods. Although clinical changes may be seen within one week of PERT, we felt that a period of four weeks reflects real life clinical practice more accurately.

A further potential bias is that since the included cross-over trials did not present separate first-arm data, we had to analyse these trials as if they were parallel trials. We are aware that doing so may produce conservative results which ignore any possible within-patient correlation and acknowledge that the two treatment groups are not independent as each participant will appear in both treatment and control groups. In the only comparison where we could combine data, the fact that these were cross-over trials is likely to underestimate the level of inconsistency between the results of the trials due to over-inflation of CIs from the individual trials.

There was no other additional bias identified in the review. Neither contributing author has any conflict of interest.

Agreements and disagreements with other studies or reviews

In our review, we found that ECM decreased FFE and abdominal symptoms, when compared to TPE or to non-enteric-coated preparations. This is similar to the findings of other authors (Beverley 1987; Chazalette 1988; Holsclaw 1979; Mischler 1982). Our finding that the different preparations of ECM showed no significant difference in any of the measured outcomes is in agreement with the findings of other trials (Hilman 1982; Khaw 1977; Santini 2000). That ECMM preparations did not showing any significant difference in FFE, weight gain or clinical symptoms when compared to ECM is corroborated by another trial (Duhamel 1998).

AUTHORS' CONCLUSIONS

Implications for practice

We found no evidence from any comparison of pancreatic enzyme replacement therapy (PERT) to placebo. The available evidence suggests that enteric-coated microspheres (ECM) are better at improving clinical symptoms in people with cystic fibrosis (CF) compared to non-enteric-coated enzyme preparations. This evidence is, however, limited and is from a few small trials which are prone to bias. There is a lack of evidence on the long-term benefits and risks of treatment and the relative dosages of PERT required for people with different severities of pancreatic insufficiency.

Implications for research

There is a need for large, multicentre robustly-designed parallel randomized controlled trials (RCTs) to assess the different forms of PERT, their efficacy, safety, role in improving nutritional status, quality of life and their long-term effects. There is also a necessity to investigate if the same amount of PERT is applicable to all ranges of pancreatic insufficiency in CF. Since the degree of pancreatic insufficiency can decline with age and consequently an adaptation of PERT based on residual function could be necessary for older people, this should be taken into account when planning a trial.

Future trials should be based on "real life clinical scenarios", where participants vary the amount of enzyme everyday with different meals and meal sizes. Different levels of PERT should be compared to placebo whenever possible.

Finally, when planning future trials researchers should take into account the high attrition rates seen in the trials included in this review, possibly due to run-in or dose stabilisation periods before the actual trial begins.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Assoufi 1994

Study characteristics

Assoufi 1994 *(Continued)*

Methods	Randomised, double-blind cross-over trial. Duration: there was a run-in period (duration not specified) followed by randomization to 1 of 2 arms. 28 days in each arm. UK based. Home setting.
Participants	17 individuals diagnosed with CF. Age: 18 to 42 years.
Interventions	Group 1: Nutrizyme GR (10000 BP units of lipase). Group 2: Nutrizyme 22 (22000 BP units of lipase). Lipase intake was equivalent to previous intake of participants and was kept constant during the trial.
Outcomes	Weight gain, appetite, stool consistency, stool frequency and FFE.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not given.
Allocation concealment (selection bias)	Unclear risk	Information not given.
Blinding of participants and personnel (performance bias) Participants	Low risk	When on Nutrizyme 22, participants took an equal number of placebo capsules and high-dose enzyme capsules to make the total number of capsules the same as when taking Nutrizyme GR.
Blinding of participants and personnel (performance bias) Clinicians	Unclear risk	Information not given.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information not given.
Incomplete outcome data (attrition bias) All outcomes	High risk	1 participant withdrew after the run-in period; reason was not given.
Selective reporting (reporting bias)	High risk	SDs were not presented for the outcome fecal fat excretion; other outcomes were reported in a way, that could not be included in analysis.
Other bias	Unclear risk	Information not given.

Borowitz 2005

Study characteristics	
Methods	Randomised, double-blind, 3-arm parallel, dose-ranging, multicentre trial. Duration: 29 days. Participants recruited from 26 CF Foundation-accredited centres in the USA. Home setting.
Participants	139 participants with previously diagnosed CF and undergoing treatment were screened and 129 enrolled as intention-to-treat population. Age: mean (SD) 21.5 (8.5) years. Gender split: 71% were males.
Interventions	Group 1: Altu-135 5000 units of lipase. Group 2: Altu-135 25,000 units of lipase. Group 3: Altu-135 100,000 units of lipase. Doses were not adjusted on basis of weight or food ingested, but were fixed per meal or snack. Lipase, protease & amylase were in a ratio of 1:1:0.15
Outcomes	CFA, CNA, adverse events, QoL using the CFQ-R.
Notes	The CFA and CNA were measured at baseline and at 14 days after randomization.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomized, but further information not given.
Allocation concealment (selection bias)	Unclear risk	Information not given.
Blinding of participants and personnel (performance bias) Participants	Low risk	All participants received equal number of unlabelled capsules.
Blinding of participants and personnel (performance bias) Clinicians	Unclear risk	Information not given.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information not given.
Incomplete outcome data (attrition bias) All outcomes	Low risk	129 participants were enrolled as intention-to-treat population, of whom 12 withdrew (4 due to gastrointestinal adverse events); 117 participants who received at least 1 dose were included in a modified intention-to-treat analysis.

Borowitz 2005 *(Continued)*

Selective reporting (reporting bias)	Low risk	All expected outcomes were reported.
Other bias	High risk	Trial sponsored and actively supported by Altus Pharmaceuticals.

Elliott 1992

Study characteristics	
Methods	Randomised, double-blind, cross-over trial. Duration: 4 weeks for each treatment arm with a 2-week run-in period. Single-centre trial in New Zealand. Home setting.
Participants	30 children previously diagnosed with CF using clinical and laboratory data. Age: median 10.1 years. Gender split: 17 girls, 13 boys.
Interventions	Group 1: Creon® (lipase 8000 BP, amylase 9000 BP, protease 210 BP). Group 2: Pancrease® (lipase 5000 BP, amylase 3000 BP, protease 350 BP). Participants were started on doses of lipase slightly lower or equivalent to pretrial period. Later they were allowed to adjust according to their requirement.
Outcomes	Mean weight gain, adequate daily intake of energy, fat and nitrogen, stool weight, FFE and nitrogen excretion.
Notes	For the outcomes of interest to the review, the results were given in a descriptive method; means and SDs not given.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Information not given.
Allocation concealment (selection bias)	Unclear risk	Information not given.
Blinding of participants and personnel (performance bias) Participants	Low risk	Both formulations were prepared in identical opaque capsules from commercial stock.
Blinding of participants and personnel (performance bias) Clinicians	Unclear risk	Information not given.

Elliott 1992 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information not given.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 participants withdrew consent and 1 participant was hospitalised due to respiratory exacerbations during the run-in period.
Selective reporting (reporting bias)	High risk	Results were reported in a narrative method and could not be included in analysis
Other bias	High risk	Boehringer Ingelheim (NZ) Limited Kali Chemie provided funding and trial materials.

Henker 1987

Study characteristics	
Methods	Randomized, open-label, cross-over trial. Duration: each arm was for 4 weeks. No run-in period specified. Single centre in the former East Germany.
Participants	45 participants with CF. Age: mean 11.8 years. Gender split: 24 boys and 21 girls.
Interventions	Group 1: Pancreon forte (conventional). Group 2: Creon® (acid protected microspheres).
Outcomes	Weight gain, height, stool frequency, FFE.
Notes	Outcomes were given in a descriptive method.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Information not given.
Allocation concealment (selection bias)	Unclear risk	Information not given.
Blinding of participants and personnel (performance bias) Participants	High risk	No blinding.
Blinding of participants and personnel (performance bias)	High risk	No blinding.

Henker 1987 *(Continued)*

Clinicians		
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information not given.
Selective reporting (reporting bias)	High risk	Narrative results only - could not be included in analysis.
Other bias	Unclear risk	Information not given.

Konstan 2018a

Study characteristics	
Methods	Randomized, parallel, open-label controlled trial. Duration: 7 weeks intervention and up to 20 weeks follow-up. Multicentre (46 clinical centres in Canada, Czech Republic, Hungary, Israel, Poland, Spain, and the USA).
Participants	129 participants (males and females) aged at least 7 years were randomised; 65 to liprotamase and 64 to pancrelipase. 1 participant dropped out of pancrelipase group before receiving any study drug, so 128 participants in mITT analysis. Age, mean (SD): liprotamase group 22.5 (8.54) years; pancrelipase group 21.0 (8.95) years. Gender split: liprotamase group 46.2% females; pancrelipase group 49.2% females. Weight, mean (SD): liprotamase group 57.8 (14.3) kg; pancrelipase group 54.4 (14.6) kg. Height, mean (SD): liprotamase group 163.3 (12.0) cm; pancrelipase group 160.1 (16.4) cm. BMI, mean (SD): liprotamase group 21.4 (3.3) kg/m^2; pancrelipase group 20.7 (3.0) kg/m^2. Gastric acid suppression use, n (%): liprotamase group 27 (41.5); pancrelipase group 24 (38.1). Use of lumacaftor, n (%): liprotamase group 1 (1.5); pancrelipase group 2 (3.2). Use of lumacaftor/ivacaftor combination, n (%): liprotamase group 11 (16.9); pancrelipase group 7 (11.1).
Interventions	Group 1: liprotamase (oral, soluble, non-enterically coated, non-porcine PERT) Group 2: porcine PERT (oral, enterically-coated PERT prepared from a porcine source). The dose of study drug was not allowed to exceed 10,000 units lipase/kg/day or 2500 units lipase/kg/meal. Concomitant medications for treatment of CF, including CFTR modulators, GAS, and vitamin supplements, were allowed if maintained throughout the study.
Outcomes	Weight CFA (change from baseline CFA to 7 weeks of stabilized therapy), CNA (change from baseline to week 7)

Konstan 2018a *(Continued)*

	Stool weight Levels of cholesterol, vitamin A, vitamin E, vitamin D, vitamin K, albumin, or pre-albumin Safety (malabsorption symptom scores for abdominal pain, bloating and steatorrhea) - number of participants with adverse events or laboratory abnormalities at 20 weeks.
Notes	SOLUTION study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised 1:1 in blocks of 4 to liprotamase or pancrelipase; stratified by age at enrollment and gastric acid suppressant use. No information on the method employed for randomisation.
Allocation concealment (selection bias)	Unclear risk	No information available.
Blinding of participants and personnel (performance bias) Participants	High risk	Open-label trial.
Blinding of participants and personnel (performance bias) Clinicians	High risk	Open-label trial.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant randomized to pancrelipase received no study drug and was excluded from all mITT analyses; all randomised participants who received at least 1 dose of study drug (mITT population) were included in analyses. 23 participants dropped out in total, but with reasons given. 18 dropped out of liprotamase group (adverse event n = 3; perceived lack of efficacy n = 4; withdrew consent n = 9; other n = 2) and 5 dropped out of pancrelipase group (loss to follow-up n = 1; withdrew consent n = 3; other n = 1).
Selective reporting (reporting bias)	High risk	Body weight was measured at 7 weeks but only the mean is given, no SD. Body weight, height and BMI were measured at 20 weeks, but details not given,.
Other bias	High risk	Trial was partially supported by Anthera pharmaceuticals.

Lacy 1992

Study characteristics

Methods	Randomized, double-blind, 3-arm cross-over trial of 3 different ECMs. Duration: each treatment arm lasted 4 weeks after an initial 2-week run-in period. Single-centre trial based in the UK.

Lacy 1992 *(Continued)*

Participants	22 children with CF. Age: 5 - 16 years. Gender split not given.
Interventions	Group 1: Nutrizyme GR. Group 2: Nutrizyme MP. Group 3: Creon®. The preparations were compared in a capsule for capsule basis, even though there was a difference in enzyme content.
Outcomes	Symptom scores, weight gain and CFA.
Notes	Results were given descriptively.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not given.
Allocation concealment (selection bias)	Unclear risk	Information not given.
Blinding of participants and personnel (performance bias) Participants	Unclear risk	Information not given.
Blinding of participants and personnel (performance bias) Clinicians	Unclear risk	Information not given.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information not given.
Incomplete outcome data (attrition bias) All outcomes	High risk	4 participants withdrew from trial, reasons were not given.
Selective reporting (reporting bias)	High risk	Outcomes were reported in a way that could not be included in analysis.
Other bias	Unclear risk	Information not given.

Patchell 1999

Study characteristics

Methods	Prospective, randomized, open-label, cross-over trial.

Patchell 1999 *(Continued)*

	Duration: treatment was for a period of 10 weeks; 2-week run-in, followed by randomization to 1 of the 2 arms for 4 weeks, and then cross over to alternative treatment for the next 4 weeks. Multicentre trial at 3 hospitals in the UK.
Participants	59 children with CF, diagnosed by 2 sweat tests or genotype, had proven pancreatic insufficiency. Age: mean (SD) age of 10 (3.5) years. Gender split: not given.
Interventions	Group 1: ECM (Creon 8000 MS®). Group 2: ECMM (Creon 10000 MMS ®). Dose was lipase for lipase. The median intake of lipase/kg body weight/day was 6689 for Creon 8000® and 8527 for Creon 10000 ®.
Outcomes	FFE, CFA, stool frequency, abdominal pain, participant preference.
Notes	The stool collection for CFA was done only in 1 centre, with 22 participants.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomized, further information not given.
Allocation concealment (selection bias)	Unclear risk	Information not given.
Blinding of participants and personnel (performance bias) Participants	High risk	No blinding.
Blinding of participants and personnel (performance bias) Clinicians	High risk	No blinding.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Stool collection data were from 1 hospital only with 22 participants in an intent-to-treat analysis. 54 participants completed the trial, 2 dropped out in run-in period due to abdominal pain and loose stools; a further 2 dropped out during the ECMM phase (1 due to abdominal pain and loose stools and 1 due to meconium ileus equivalent). The 5th participant dropped out during the ECMM phase due to an appendix abscess considered to be unrelated to treatment.
Selective reporting (reporting bias)	High risk	Data on stool frequency and abdominal pain reported in a way that could not be included in the analysis.
Other bias	Low risk	Study appears to be free of other sources of bias.

Petersen 1984

Study characteristics	
Methods	Randomized, double-blind, cross-over trial. Duration: each treatment arm lasted 4 weeks; no run-in period. Not clear if a single or multicentre trial based in Denmark.
Participants	11 children with documented CF. Age: 2 - 11 years of age. Gender split: 2 males and 9 females.
Interventions	Group 1: pH sensitive ECM Pancrease (1 - 2 capsules containing 330 FIP-u protease, 6200 FIP-u lipase, 3600 FIP-u amylase/capsule). Group 2: conventional ECM Pancreatin (10 - 35 ml containing 525 FIP-u trypsin, 12000 FIP-u lipase, 12750 FIP-u amylase). Participants were allowed to change doses depending on individual requirements
Outcomes	Symptom scores for stool frequency, consistency, colour, odour and abdominal cramps; weight gain; fat absorption.
Notes	Results reported as medians.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Information not given.
Allocation concealment (selection bias)	Unclear risk	Information not given.
Blinding of participants and personnel (performance bias) Participants	Low risk	During both periods placebo preparations were given in the form of capsules or granules.
Blinding of participants and personnel (performance bias) Clinicians	Unclear risk	Information not given.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information not given.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no withdrawals, with all 11 participants completing the trial.
Selective reporting (reporting bias)	High risk	The results were reported in medians due to which the data could not be included in the analysis.

Petersen 1984 *(Continued)*

Other bias	Low risk	No other sources of bias were found.

Stead 1986

Study characteristics	
Methods	Open-label randomized cross-over trial. Duration: 2 consecutive 28-day treatment periods. Single centre in the UK (Brompton Hospital Adolescent and Adult Cystic Fibrosis Clinic, London).
Participants	23 participants with CF diagnosed by sweat chloride concentration > 70 mmol/L, evidence of pancreatic insufficiency and symptomatic steatorrhea. Age: mean (SD) 24.8 (4.2) years. Gender split: 11 males and 12 females.
Interventions	Group 1: ECM (Creon® capsules). Group 2: ECT (Pancrex V Forte). Participants received either their usual regimen of ECT or ECM in a ratio of 0.7 capsules for each ECT. Declared lipase of Pancrex V forte to Creon® capsules is 0.7:1, protease is 1.6:1.
Outcomes	Change in weight, frequency of stools, abdominal pain, FFE and CFA.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomized but no further information given.
Allocation concealment (selection bias)	Unclear risk	Information not given.
Blinding of participants and personnel (performance bias) Participants	High risk	No blinding.
Blinding of participants and personnel (performance bias) Clinicians	High risk	No blinding.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 participants withdrew from trial and reasons were given.

Stead 1986 *(Continued)*

		1 participant was unable to swallow microsphere capsules and another took more lipase during 1 month than the other.
Selective reporting (reporting bias)	Low risk	Expected outcomes are reported.
Other bias	Unclear risk	Trial supported by Duphar Laboratories.

Stead 1987

Study characteristics		
Methods	Open-label, randomized, cross-over trial. Duration: 2 consecutive 28-day treatment periods. Single centre in the UK.	
Participants	14 participants with CF, diagnosed by sweat chloride > 70 mmol/L and typical pulmonary disease. Age: mean 21.4 years. Gender split: 8 males and 6 females.	
Interventions	Group 1: ECM (Creon®) with food. Group 2: NECT (Pancrex V) with food and adjuvant cimetidine 40 min before meals. Both contain 8000 BP units of lipase, number of capsules for each individual was same during both treatment periods.	
Outcomes	Change in weight, stool frequency, abdominal pain, FFE and CFA.	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomized, but further information not given.
Allocation concealment (selection bias)	Unclear risk	Information not given.
Blinding of participants and personnel (performance bias) Participants	High risk	No blinding.
Blinding of participants and personnel (performance bias) Clinicians	High risk	No blinding.
Blinding of outcome assessment (detection bias)	High risk	No blinding.

Stead 1987 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant withdrew due to inability to control frequency of stools. The treatment arm was not specified.
Selective reporting (reporting bias)	Low risk	Expected outcomes are reported.
Other bias	Unclear risk	Creon® was supplied by Duphar Laboratories.

Taylor 2015

Study characteristics	
Methods	Randomized, double-blind, cross-over trial. Duration: each treatment arm lasted 28 (± 2days); no washout period as investigators considered any residual lipase from the prior treatment period to have a negligible influence on the subsequent CFA-72 h determination. Multicentre international trial - 34 sites in seven European countries including Belgium, Bulgaria, Germany, Hungary, Italy, Poland, and the UK.
Participants	Participants diagnosed with CF by any of the following criteria: 1 clinical feature of CF and 2 disease causing mutations in genotype or sweat chloride conc >60 mmol/L. Demographics and baseline characteristics were well balanced between groups. Of the 96 participants randomized (48 to each group), 86 completed the trial, and CFA-72 hour data were available from both treatment periods for 83 participants. Age at screening in the 96 participants randomized was mean (SD) 19.2 (7.9) years.Group A mean (range) 20.4 (12 to 42) years, Group B mean (range) 18.0 (12 to 43) years. Gender split: 60.4% in each group were male.
Interventions	Group A: Zenpep® followed by Kreon® (know as Creon® in English-speaking regions). Group B: Creon® followed by Zenpep®. Zenpep (APT1008) and Creon® given at a dose as close as possible to participants' established pancreatic enzyme treatment. Daily dose could be rounded up from initial dose to a maximum of 10,000 lipase units/kg of body weight per day or 4000 lipase units/g of fat ingested per day, but not exceeding 10,000 lipase units/kg of body weight per day. Participants began each treatment period at the same starting dose. Dosage adjustment to relieve clinical symptoms allowed during the first 2 weeks of each treatment period. In consultation with a dietician, a mean (SD) daily 100 g (15 g) fat diet was maintained throughout the trial and participants were required to abstain from nutritional supplements containing high concentrations of (≥ 30%) medium-chain triglycerides.
Outcomes	Primary: CFA over 72 hours calculated from dietary fat intake and stools collected during the last 3 days (72 consecutive hours) of each treatment period. Secondary: CNA, change in body weight, control of signs and symptoms of pancreatic insufficiency (participant diaries), overall well-being, adverse events, CF symptoms as evaluated by the CFQ-R (at the beginning of each treatment period and at the end of the trial).

Taylor 2015 *(Continued)*

Notes	Stool samples were collected in a hospital or clinic or other controlled environment to ensure adherence to the prescribed diet and quantitative stool collection. Stools were collected for 72 consecutive hours starting on the morning of day 26 (±2 days) of each of the 28-day (±2 days) treatment periods. Treatment adherence, defined as percentage ≥75% and ≤125% of capsules taken versus capsules prescribed, was determined on the basis of diary entries and trial drug reconciliation and was evaluated at each visit.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization process not described.
Allocation concealment (selection bias)	Unclear risk	Information not given.
Blinding of participants and personnel (performance bias) Participants	Low risk	Stated that participants were masked.
Blinding of participants and personnel (performance bias) Clinicians	Low risk	Stated that caregivers and investigators were masked.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes assessor masked.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals from the trial were fully described; 13.5% of participants excluded from trial. The primary efficacy analysis of CFA-72 h was based on the completers population, defined as all randomized participants who received at least 1 dose of Zenpep or Creon® and finished both treatment periods with complete CFA-72 h data.
Selective reporting (reporting bias)	Low risk	All outcomes in protocol were reported and could be included in trial.
Other bias	High risk	Corresponding author is a consultant to Aptalis and Profile Pharma. Study was funded by Aptalis Pharma.

Vidailhet 1987

Study characteristics

Methods	Randomized, 2-arm cross-over trial. Duration: after an 8-day initial washout each treatment given for a period of 30 days. Single-centre trial in France. Home setting.

Vidailhet 1987 *(Continued)*

Participants	17 children with documented CF. Age: 1 - 12.5 years. Gender split was not given.
Interventions	Group 1: ECM (Creon®) (1.2 - 2.4 g/day). Group 2: lyophilised TPE (4 - 8 g/day).
Outcomes	Body weight, FFE, nutritional indicators (body weight to length index, subscapular skin fold, plasma cholesterol, pre-albumin, retinol, retinol binding protein, zinc and total essential fatty acids), therapeutic tolerance (drug acceptance, alanine amino transferase, prothrombin time, serum bilirubin and uric acid, urinary uric acid excretion).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomized, but further information not given.
Allocation concealment (selection bias)	Unclear risk	Information not given.
Blinding of participants and personnel (performance bias) Participants	Unclear risk	Information not given.
Blinding of participants and personnel (performance bias) Clinicians	Unclear risk	Information not given.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information not given.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information not given.
Selective reporting (reporting bias)	High risk	Change in body weight was incompletely reported and cannot be included in the review.
Other bias	Unclear risk	Information not given.

Vyas 1990

Study characteristics	
Methods	Randomized, double-blind, double-placebo cross-over trial. Duration: 4 weeks for each treatment arm.

Vyas 1990 *(Continued)*

	Single-centre trial in the UK (London).
Participants	20 children with CF diagnosed by sweat test sodium greater than 70 mmol/L Age: mean 9.9 years; range 4.1 - 15.3 years. All had steatorrhea and weight and height above 3rd percentile. The mean weight was 26.0 kg (range 14.2 kg - 50.7 kg) and the mean height was 1.32 metres (range 1.1 metres - 1.63 metres). Gender split not given.
Interventions	Group 1: active ECM plus placebo ECT. Group 2: placebo ECM plus active ECT. Dosage of ECM was calculated to provide equivalent dosage of lipase to ECT. The day-to-day dosage of active drug and placebo varied slightly depending on the participants' diet.
Outcomes	Change in weight, stool frequency, abdominal pain, FFE.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomized, but further information not given.
Allocation concealment (selection bias)	Unclear risk	Information not given.
Blinding of participants and personnel (performance bias) Participants	Low risk	While taking ECM, participants received a placebo of ECT and while taking ECT, they took a placebo preparation of ECM.
Blinding of participants and personnel (performance bias) Clinicians	Unclear risk	Information not given.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information not given.
Incomplete outcome data (attrition bias) All outcomes	High risk	Only 12 paired samples were analysed for FFE.
Selective reporting (reporting bias)	Low risk	Expected outcomes are reported.
Other bias	High risk	Duphar Ltd, UK supplied pancreatic enzyme supplements and supported the trial.

Williams 1990

Study characteristics	
Methods	Randomized, single blind cross-over trial. Duration: 10 weeks in total, 2-week run-in period followed by 4 weeks for each treatment arm. Not clear if multi- or single-centre trial based in the UK. Home setting.
Participants	39 children with symptoms of CF, at least 2 abnormal sweat chloride results and pancreatic insufficiency. Age: median (range) 9.7 (5 - 17) years. Clinical state, as measured by the Shwachman score (100 = normal) ranged from 37 to 91 with a median value of 79. 12 participants were unsuitable for analysis, the remaining 27 children (15 boys and 12 girls) completed the trial.
Interventions	Group 1: ECM Creon® (lipase 8000 BP units, amylase 9000 BP units, protease 210 BP units). Group 2: ECM Pancrease® (lipase 5000 BP units, amylase 2900 BP units, protease 330 BP units). Participants took same number of capsules per day during both treatment periods.
Outcomes	CFA, participant preference, nitrogen excretion, weight change, symptom score for appetite, number, colour and consistency of stools, abdominal pain and general condition.
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomized, but further information not given.
Allocation concealment (selection bias)	Unclear risk	Information not given.
Blinding of participants and personnel (performance bias) Participants	High risk	Blinding not done.
Blinding of participants and personnel (performance bias) Clinicians	Low risk	Study medication was issued by pharmacist and order of treatment was not known to the doctor.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding not done.
Incomplete outcome data (attrition bias) All outcomes	High risk	12 participants (31%) were withdrawn from trial for various reasons and not included in analysis:

Williams 1990 *(Continued)*

		• 7 withdrew because of respiratory exacerbations or infective illnesses that interfered with dietary intake such that their standard individualised menu could not be followed; • 1 failed to attend for follow up; • 1 withdrew because of intolerable symptoms of steatorrhea on Pancrease®, further assessment on Creon® (her usual treatment) showed poor control of fat malabsorption with a CFA of 77%; • 3 participants inadvertently took unequal numbers of capsules during the 2 treatment periods and were therefore excluded from the analysis.
Selective reporting (reporting bias)	High risk	Change in weight and symptom scores for abdominal pain, stool frequency were measured but were reported incompletely, so cannot be entered in a meta-analysis.
Other bias	High risk	Corresponding author was financially supported by Cilag Limited (Pancrease).

BMI: body mass index
CF: cystic fibrosis
CFTR: cystic fibrosis transmembrane conductance regulator
CFA: co-efficient of fat absorption
CFQ-R: Cystic Fibrosis Questionnaire-Revised
CNA: co-efficient of nitrogen absorption
ECM: enteric-coated microspheres
ECMM: enteric-coated mini-microspheres
ECT: enteric-coated tablets
FFE: fecal fat excretion
GAS: gastric acid suppression
mITT: modified intention to treat
PERT: pancreatic enzyme replacement therapy
NECT: non enteric-coated tablets
QoL: quality of life
SD: standard deviation
TPE: total pancreatic extracts

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ansaldi 1988	Cross-over study with PERT for 5 days in each arm.
Araujo 2011	Doesn't appear to have a control group, PERT dosage increased according to fecal fat levels.
Beker 1994	Cross-over study with PERT for 3 days in each arm.
Beverley 1987	Cross-over study with 3 arms of 15 days each.
Borowitz 2011	The study drugs were given for a period of 6 days only after randomisation.
Bouquet 1988	Cross-over study with each treatment period only 2 weeks.
Bowler 1993	Crossover study with 2 arms of 2 weeks each.
Brady 1991	Crossover study with 2 arms of 7 days each.
Brady 1992	Cross-over study of enzymes given before and during meals; 2 periods of 1 week each.

Study	Reason for exclusion
Brady 2006	Cross-over study with 2 treatment periods of 1 week each.
Breuel 1996	Study assesses pancreatic enzyme activity.
Butt 2001	Study assesses breath tests.
Chazalette 1988	Open label cross-over study with periods of 1 week each.
Chazalette 1993	Parallel group study for a period of 8 days.
Colombo 2001	Study compares different methods for assessing exocrine pancreatic function.
Dalzell 1992	Meets inclusion criteria, but data not in usable format and will not be made available in the future
De Boeck 1998	Single dose intervention.
Desager 2006	Parallel study period of 10 days.
Duhamel 1988	Cross-over study with 2 periods of 8 days each.
Duhamel 1998	Cross-over study with 2 periods of 14 days each. Study assessed patient preference, but also assessed clinical symptoms.
Durie 1980	Cross-over study with 4 preparations given for 1 week each.
Dutta 1988	Crossover study with each intervention given only on a single day.
Easley 1998	Cross-over study with each intervention given only on a single day.
Eiel 2018	Intervention not relevant
Ellis 1994	Cross-over study (assessing coating of PERT) with 2 weeks in each arm.
EUCTR 2007-004004-12	Participants not relevant (chronic pancreatitis & pancreatectomy)
EUCTR 2015-001219-11	Treatment period of 7 days
Foucaud 1989	Placebo-controlled, parallel study but treatment period for 1 week.
Gan 1994	Cross-over study with 2 arms of 14 days each.
Geyer 2019	Intervention not relevant
Goodchild 1974	Cross-over study with 2 weeks in each arm.
Gow 1981	Cross-over study of 4 periods of 14 days each.
Graff 2010	Intervention given for 5 days.
Heubi 2007	Cross-over placebo-controlled trial with 2 periods of 1 week each.
Heubi 2016	Cross-over study with 1 week in each arm.
Hill 1993	Letter reports cross-over trial to compare patient preference of different formulations; no other outcomes stated.

Study	Reason for exclusion
Hilman 1982	Cross-over study with a total 2-week study period.
Holsclaw 1979	Cross-over study of 6 treatment (Viokase vs Cotazyme vs Pancrelipase with and without bicarbonate) periods of 3 weeks each.
Hubbard 1984	Study assesses use of bentiromide screening test.
Kalnins 2005	Cross-over study with 2 treatment periods of 2 weeks each.
Kalnins 2006	Cross-over study with 2 treatment periods of 14 days each.
Katona 2000	Not an RCT or a quasi-RCT.
Khaw 1977	Cross-over study with two treatment periods of 12 days each.
Konstan 2004	Intervention given only for 6 days.
Konstan 2008	Cross-over trial with 2 treatment periods of 5 days each.
Konstan 2010	Treatment only 6 to 7 days in each arm of the 2-phase cross-over trial.
Kraisinger 1993	Cross-over trial with 2 treatment periods of 4 days each.
Lancellotti 1996	Open-label, cross-over study with 2 treatment periods of 5 days each.
Lazaro 1990	Cross-over trial with 2 periods of 6 days each.
Leitz 2009	Placebo-controlled trial with a treatment period of 1 day.
Lubin 1979	Study assesses use of antacids in conjunction with PERT intervention not relevant.
Mack 1991	Cross-over study assessing antibiotic absorption with PERT compared to without in a single intervention.
Mischler 1980	Cross-over study with 2 arms of 5 days each.
Mischler 1982	Cross-over trial 2 periods of 5 days each.
Morrison 1992	Not an RCT or quasi-RCT.
Munck 2009	Cross-over study with 2 treatment periods of 2 weeks each.
Munoz 1987	Cross-over study with 2 treatment periods of 1 week each.
NCT00217204	Treatment period of 5 days.
NCT00449904	Not an RCT
NCT01327703	Cross-over trial with treatment period of 14 days in each arm
NCT01652157	Not an RCT
NCT01851694	Intervention and outcomes not relevant.
NCT01858519	Not an RCT

Study	Reason for exclusion
NCT02137382	Cross-over study with Creon/Creon N for 5 days in each arm.
NCT03746483	Cross-over study with 3 weeks in each arm
Neijens 1982	Cross-over study with treatment periods of 2 weeks each.
Perano 2014	Cross-over trial with 2 single interventions on separate days.
Ritz 2004	Study evaluated a breath test used to assess fat malabsorption and not PERT.
Robinson 1989	Cross-over study with 2 treatment periods of 2 weeks each.
Robinson 1998	Cross-over study with 2 periods of 2 weeks each.
Santini 2000	Cross-over study with 2 treatment periods of 1 week each.
Shah 1993	PERT taken for 2-week period only.
Sinaasappel 1998	Cross-over trial with 2 periods of 14 days each.
Stapleton 2001	Study assessing knowledge and education of PERT.
Stern 2000	Parallel RCT but duration only 5 - 7 days.
Thomson 1993	Cross-over trial with 3 periods of 7 days each.
Trapnell 2009	Cross-over RCT with 5-day course of PERT and same for placebo.
van der Haak 2016	Intervention not relevant.
Van de Vijver 2011	Treatment period only 5 days.
Vitti 1975	Study assesses antibiotic absorption when given with PERT.
Warwick 1982	Cross-over study with 2 treatment periods of 1 week each.
Weber 1979	Cross-over study with 2 periods of 8 days each.
Wooldridge 2009	Cross-over study with 2 periods of 7 days each, followed by a non-randomised extension study.
Zentler 1992	RCT with 3 interventions for 2 weeks each.

PERT: pancreatic enzyme replacement therapy
RCT: randomized controlled trial
vs: versus

Characteristics of studies awaiting classification *[ordered by study ID]*

Brekke 2019

Methods	Randomised, cross-over study of 8 weeks duration (4 weeks in each arm).
Participants	Participants with cystic fibrosis, under 18 years of age.

Brekke 2019 *(Continued)*

Interventions	Pancreatic enzyme replacement prior to and after meals.
Outcomes	Anthropometrics, assessment of gastrointestinal symptoms and quality of life.
Notes	

Holsclaw 1980

Methods	Possibly randomized, not clear. Duration: 14 months for intervention, control not clear. USA-based trial.
Participants	20 participants with CF.
Interventions	Pancrease (enteric-coated) - dose 9 to 11 per day - compared with usual supplement (Viokase or Cotazyme) for a period of 14 months in pancrease arm, duration of other usual supplement not given.
Outcomes	Body weight, urine uric acid, serum albumin, abdominal symptoms.
Notes	Not stated whether patients were randomized or not. Possible extension of excluded trial Holsclaw 1979.

Knill 1973

Methods	Randomized double-blind cross-over trial with 3 arms. Duration: 3 months in total, each arm lasted 1 month, not clear if washout period was used.
Participants	11 adults with CF and 1 adult with chronic pancreatitis.
Interventions	Pancrex V Forte: 3 tablets equivalent to 3 g pancreatine BP. Nutrizym: 2 tablets equivalent to 3.2 g pancreatine BP. Nutrizym plus bromelin: 2 tablets equivalent to 3.2 g pancreatine BP also containing 50g bromelin. Nutrizym tablets looked the same whether containing bromelin or not, but not identical to Pancrex V Forte. Participants not allowed to tell outcome assessors how many tablets they were taking.
Outcomes	Self-reported bowel habits, general health and respiratory symptoms (daily diary), FFE.
Notes	Combined data given for all participants (CF data not split out). Full trial in French - needs translation. 2 participants who had been on high doses of Pancrex V Forte (9 - 12 per meal) took double the normal preparations in the trial.

Konstan 2018b

Methods	Randomized, parallel, open-label trial.
Participants	140 participants with CF.
Interventions	Liprotamase versus porcine PERT.
Outcomes	CFA (8 weeks), CNA (8 weeks), safety(6 months).
Notes	NCT03051490 (RESULT); Study completed in June 2018; Results not posted.

Lenoir 2008

Methods	Single-blind cross-over and parallel design. Single-centre trial.
Participants	24 adults with CF.
Interventions	Recombinant acid lipase marketed as MERISPASE®. Session 1: all participants received low-dose pancreatic extract. Session 2: 3 different doses of lipase (MERISPASE®) compared with 84,000 units of pancreatic extract. Session 3: all participants received low doses of CREON®, 3 groups receiving MERISPASE® continued.
Outcomes	Safety, tolerance, CFA.
Notes	Meristem Therapeutics went out of business in September 2008; clinical trials blocked in phase II. No one appears to be producing or using this agent.

Regele 1996

Methods	Randomized, double-blind cross-over trial without placebo. Duration: 28 days in each arm. Not clear if single center or multicenter, based in Germany.
Participants	16 participants (9 females, 7 males) diagnosed with CF by at least 2 sweat chloride values of ≥ 70 mM and pancreatic insufficient. Age: mean 9.9 years, range 3 - 27.
Interventions	Treatment A: Creon® 25000 (per capsule: 25000 U of lipase, 18000 U of amylase and 1000 U of protease). Treatment B: Panzyrtat (per capsule: 20000 U of lipase, 18000 U of amylase and 1000 U of protease). Both groups received the same number of capsules in each arm.
Outcomes	FFE, fecal chymotrypsin, fecal immunoreactive human lipase and serum immunoreactive trypsin.

Regele 1996 *(Continued)*

Notes	Mean FFE for both the arms together was given. FFE for individual treatment periods not given.

Stern 1988

Methods	Not clear.
Participants	17 participants with pancreatic insufficiency due to CF.
Interventions	2 enzyme preparations that are equal in acid protection, but with different release of enzyme acivities.
Outcomes	Stool weight, stool fat excretion, complaints, body weight, stool frequency.
Notes	Only translated abstract available; original article in German.

Taylor 1993

Methods	Open prospective trial; not clear if randomized. Cross-over trial, each arm 3 months. Consecutive so implies no washout.
Participants	23 participants with CF. Age: range 1.3 - 16.8 years.
Interventions	Creon 25000 ® compared with conventional microsphere preparations.
Outcomes	FFE, BMI, height SD score, lean body mass, clinical symptoms (diary), dietary intake, spirometry, Schwachman and Crispin Norman scores, stool frequency.
Notes	

BMI: body mass index
CF: cystic fibrosis
CFA: co-efficient of fat absorption
ECM: enteric-coated microspheres
FFE: fecal fat excretion
PERT: pancreatic enzyme replacement therapy
SD: standard deviation

Characteristics of ongoing studies *[ordered by study ID]*

NCT03924947

Study name	A phase 4 study to compare US marketed Creon drug product with drug product manufactured with a modernized process at an alternate manufacturing site, in subjects with exocrine pancreatic insufficiency (EPI) due to cystic fibrosis
Methods	Randomised, cross-over, quadruple blinded (participants, care provider, investigator, outcomes).
Participants	28 participants with CF.

NCT03924947 *(Continued)*

Interventions	Pancrelipase delayed-release capsules, manufactured by modern technology and currently marketed capsules.
Outcomes	CFA, stool fat, CNA, stool weight.
Starting date	October 23, 2019.
Contact information	AbbVie.
Notes	EUCTR 2017-000578-12; Estimated completion date February 2021.

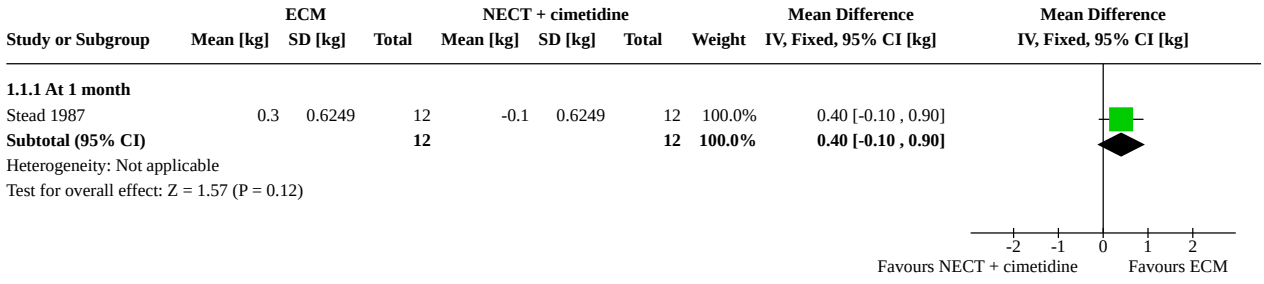
CF: cystic fibrosis
CFA: coefficient of fat absorption
CNA: coefficient of nitrogen absorption
PERT: pancreatic enzyme replacement therapy

DATA AND ANALYSES

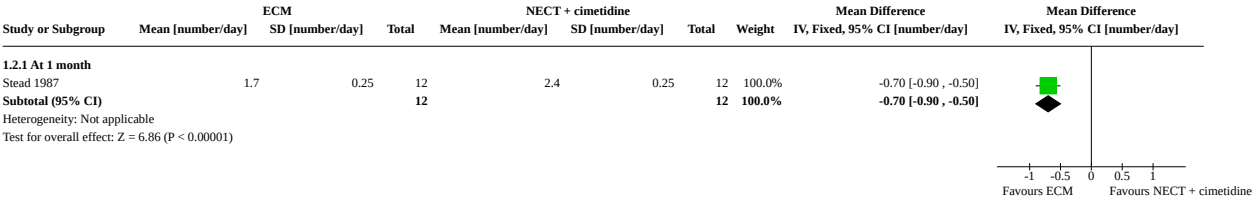
Comparison 1. ECM versus NECT + adjuvant cimetidine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Change in weight	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1.1 At 1 month	1	24	Mean Difference (IV, Fixed, 95% CI)	0.40 [-0.10, 0.90]
1.2 Stool frequency	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.2.1 At 1 month	1	24	Mean Difference (IV, Fixed, 95% CI)	-0.70 [-0.90, -0.50]
1.3 Abdominal pain	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.3.1 At 1 month	1	24	Mean Difference (IV, Fixed, 95% CI)	-10.50 [-21.40, 0.40]
1.4 FFE	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.4.1 At 1 month	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

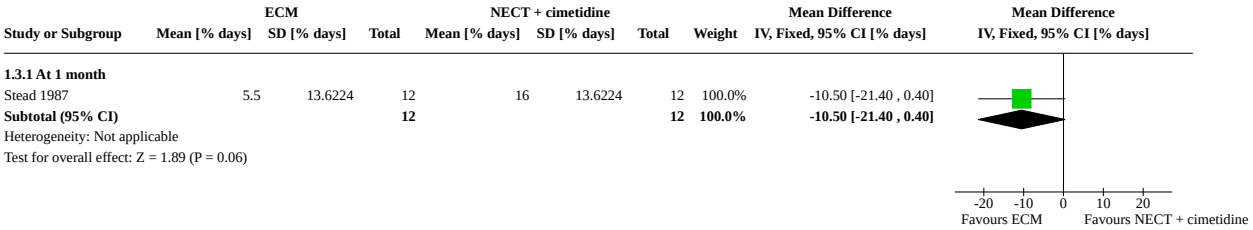
Analysis 1.1. Comparison 1: ECM versus NECT + adjuvant cimetidine, Outcome 1: Change in weight



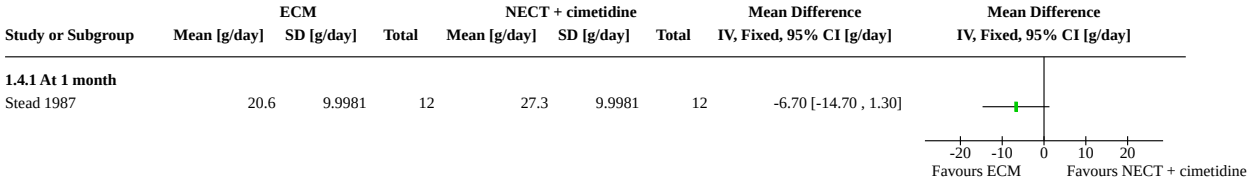
Analysis 1.2. Comparison 1: ECM versus NECT + adjuvant cimetidine, Outcome 2: Stool frequency



Analysis 1.3. Comparison 1: ECM versus NECT + adjuvant cimetidine, Outcome 3: Abdominal pain



Analysis 1.4. Comparison 1: ECM versus NECT + adjuvant cimetidine, Outcome 4: FFE



Comparison 2. ECM versus ECT

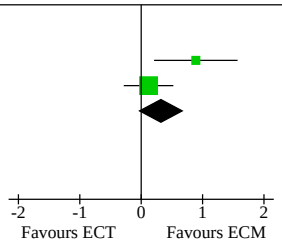
Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
2.1 Change in weight	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1.1 At 1 month	2	82	Mean Difference (IV, Fixed, 95% CI)	0.32 [-0.03, 0.67]
2.2 Stool frequency	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.2.1 At 1 month	2	82	Mean Difference (IV, Fixed, 95% CI)	-0.58 [-0.85, -0.30]
2.3 Abdominal pain	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.3.1 At 1 month	2	82	Mean Difference (IV, Fixed, 95% CI)	-7.96 [-12.97, -2.94]
2.4 FFE	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.4.1 At 1 month	2	66	Mean Difference (IV, Fixed, 95% CI)	-11.79 [-17.42, -6.15]

Analysis 2.1. Comparison 2: ECM versus ECT, Outcome 1: Change in weight

Study or Subgroup	ECM Mean [kg]	ECM SD [kg]	ECM Total	ECT Mean [kg]	ECT SD [kg]	ECT Total	Weight	Mean Difference IV, Fixed, 95% CI [kg]
2.1.1 At 1 month								
Stead 1986	0.9	1.1242	21	0.01	1.1242	21	26.1%	0.89 [0.21 , 1.57]
Vyas 1990	0.54	0.6	20	0.42	0.7	20	73.9%	0.12 [-0.28 , 0.52]
Subtotal (95% CI)			**41**			**41**	**100.0%**	**0.32 [-0.03 , 0.67]**

Heterogeneity: Chi² = 3.64, df = 1 (P = 0.06); I² = 73%
Test for overall effect: Z = 1.81 (P = 0.07)

Test for subgroup differences: Not applicable

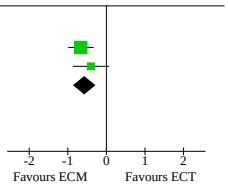


Analysis 2.2. Comparison 2: ECM versus ECT, Outcome 2: Stool frequency

Study or Subgroup	ECM Mean [number/day]	ECM SD [number/day]	ECM Total	ECT Mean [number/day]	ECT SD [number/day]	ECT Total	Weight	Mean Difference IV, Fixed, 95% CI [number/day]
2.2.1 At 1 month								
Stead 1986	1.71	0.5456	21	2.37	0.5456	21	67.4%	-0.66 [-0.99 , -0.33]
Vyas 1990	1.7	0.6	20	2.1	0.9	20	32.6%	-0.40 [-0.87 , 0.07]
Subtotal (95% CI)			**41**			**41**	**100.0%**	**-0.58 [-0.85 , -0.30]**

Heterogeneity: Chi² = 0.78, df = 1 (P = 0.38); I² = 0%
Test for overall effect: Z = 4.16 (P < 0.0001)

Test for subgroup differences: Not applicable

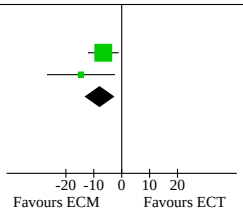


Analysis 2.3. Comparison 2: ECM versus ECT, Outcome 3: Abdominal pain

Study or Subgroup	ECM Mean [% days]	ECM SD [% days]	ECM Total	ECT Mean [% days]	ECT SD [% days]	ECT Total	Weight	Mean Difference IV, Fixed, 95% CI [% days]
2.3.1 At 1 month								
Stead 1986	6	9.093	21	12.6	9.093	21	83.0%	-6.60 [-12.10 , -1.10]
Vyas 1990	8.8	13.8	20	23.4	24.1	20	17.0%	-14.60 [-26.77 , -2.43]
Subtotal (95% CI)			**41**			**41**	**100.0%**	**-7.96 [-12.97 , -2.94]**

Heterogeneity: Chi² = 1.38, df = 1 (P = 0.24); I² = 27%
Test for overall effect: Z = 3.11 (P = 0.002)

Test for subgroup differences: Not applicable

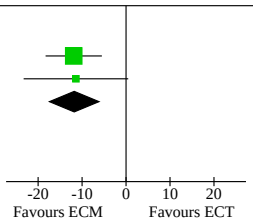


Analysis 2.4. Comparison 2: ECM versus ECT, Outcome 4: FFE

Study or Subgroup	ECM Mean [g/day]	ECM SD [g/day]	ECM Total	ECT Mean [g/day]	ECT SD [g/day]	ECT Total	Weight	Mean Difference IV, Fixed, 95% CI [g/day]
2.4.1 At 1 month								
Stead 1986	15.2	10.581	21	27.1	10.581	21	77.5%	-11.90 [-18.30 , -5.50]
Vyas 1990	11.8	9.2	12	23.2	18.9	12	22.5%	-11.40 [-23.29 , 0.49]
Subtotal (95% CI)			**33**			**33**	**100.0%**	**-11.79 [-17.42 , -6.15]**

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.94); I² = 0%
Test for overall effect: Z = 4.10 (P < 0.0001)

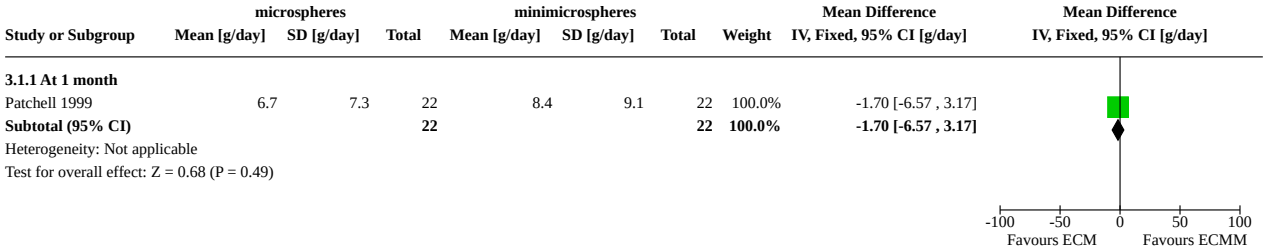
Test for subgroup differences: Not applicable



Comparison 3. ECM versus ECMM

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 FFE	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1.1 At 1 month	1	44	Mean Difference (IV, Fixed, 95% CI)	-1.70 [-6.57, 3.17]

Analysis 3.1. Comparison 3: ECM versus ECMM, Outcome 1: FFE

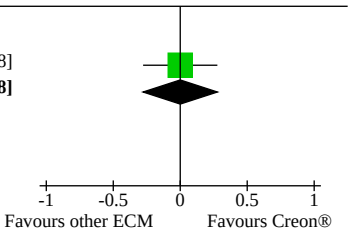


Comparison 4. ECM (Creon®) versus another ECM

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Change in body weight [kg]	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1.1 At 1 month	1	166	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.28, 0.28]
4.2 Stool frequency (number/day)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.2.1 At 1 month	1	166	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.28, 0.28]
4.3 Proportion of days with abdominal pain	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.3.1 At 1 month	1	166	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.06, 0.06]
4.4 Proportion of days with flatulence	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.4.1 At 1 month	1	166	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.12, 0.12]
4.5 Coefficient of fat absorption [%]	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.5.1 At 1 month	2	220	Mean Difference (IV, Fixed, 95% CI)	1.35 [-1.43, 4.13]

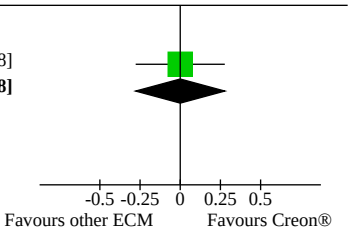
Analysis 4.1. Comparison 4: ECM (Creon®) versus another ECM, Outcome 1: Change in body weight [kg]

Study or Subgroup	Creon® Mean	Creon® SD	Creon® Total	Other ECM Mean	Other ECM SD	Other ECM Total	Weight	Mean Difference IV, Fixed, 95% CI
4.1.1 At 1 month								
Taylor 2015	0.5	0.911	83	0.5	0.911	83	100.0%	0.00 [-0.28 , 0.28]
Subtotal (95% CI)			**83**			**83**	**100.0%**	**0.00 [-0.28 , 0.28]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
Test for subgroup differences: Not applicable								



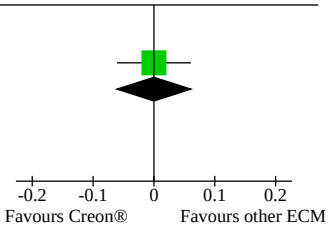
Analysis 4.2. Comparison 4: ECM (Creon®) versus another ECM, Outcome 2: Stool frequency (number/day)

Study or Subgroup	Creon® Mean	Creon® SD	Creon® Total	Other ECM Mean	Other ECM SD	Other ECM Total	Weight	Mean Difference IV, Fixed, 95% CI
4.2.1 At 1 month								
Taylor 2015	1.5	0.911	83	1.5	0.911	83	100.0%	0.00 [-0.28 , 0.28]
Subtotal (95% CI)			**83**			**83**	**100.0%**	**0.00 [-0.28 , 0.28]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
Test for subgroup differences: Not applicable								



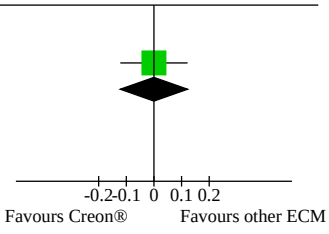
Analysis 4.3. Comparison 4: ECM (Creon®) versus another ECM, Outcome 3: Proportion of days with abdominal pain

Study or Subgroup	Creon® Mean	Creon® SD	Creon® Total	Other ECM Mean	Other ECM SD	Other ECM Total	Weight	Mean Difference IV, Fixed, 95% CI
4.3.1 At 1 month								
Taylor 2015	0.1	0.2	83	0.1	0.2	83	100.0%	0.00 [-0.06 , 0.06]
Subtotal (95% CI)			**83**			**83**	**100.0%**	**0.00 [-0.06 , 0.06]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
Test for subgroup differences: Not applicable								



Analysis 4.4. Comparison 4: ECM (Creon®) versus another ECM, Outcome 4: Proportion of days with flatulence

Study or Subgroup	Creon® Mean	Creon® SD	Creon® Total	Other ECM Mean	Other ECM SD	Other ECM Total	Weight	Mean Difference IV, Fixed, 95% CI
4.4.1 At 1 month								
Taylor 2015	0.4	0.4	83	0.4	0.4	83	100.0%	0.00 [-0.12 , 0.12]
Subtotal (95% CI)			**83**			**83**	**100.0%**	**0.00 [-0.12 , 0.12]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
Test for subgroup differences: Not applicable								

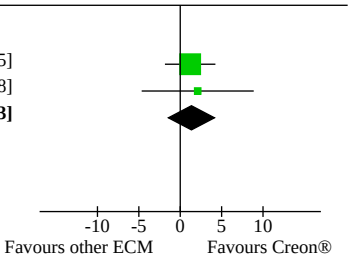


Analysis 4.5. Comparison 4: ECM (Creon®) versus another ECM, Outcome 5: Coefficient of fat absorption [%]

Study or Subgroup	Creon® Mean	Creon® SD	Creon® Total	Another ECM Mean	Another ECM SD	Another ECM Total	Weight	Mean Difference IV, Fixed, 95% CI
4.5.1 At 1 month								
Taylor 2015	85.3	10.02	83	84.1	10.02	83	83.1%	1.20 [-1.85 , 4.25]
Williams 1990	86.08	8.63	27	83.97	15.73	27	16.9%	2.11 [-4.66 , 8.88]
Subtotal (95% CI)			**110**			**110**	**100.0%**	**1.35 [-1.43 , 4.13]**

Heterogeneity: Chi² = 0.06, df = 1 (P = 0.81); I² = 0%
Test for overall effect: Z = 0.95 (P = 0.34)

Test for subgroup differences: Not applicable



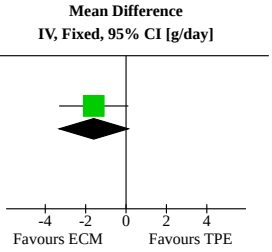
Comparison 5. ECM versus TPE

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
5.1 FFE	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1.1 At 1 month	1	34	Mean Difference (IV, Fixed, 95% CI)	-1.60 [-3.31, 0.11]

Analysis 5.1. Comparison 5: ECM versus TPE, Outcome 1: FFE

Study or Subgroup	ECM Mean [g/day]	ECM SD [g/day]	ECM Total	TPE Mean [g/day]	TPE SD [g/day]	TPE Total	Weight	Mean Difference IV, Fixed, 95% CI [g/day]
5.1.1 At 1 month								
Vidailhet 1987	5	2	17	6.6	3	17	100.0%	-1.60 [-3.31 , 0.11]
Subtotal (95% CI)			**17**			**17**	**100.0%**	**-1.60 [-3.31 , 0.11]**

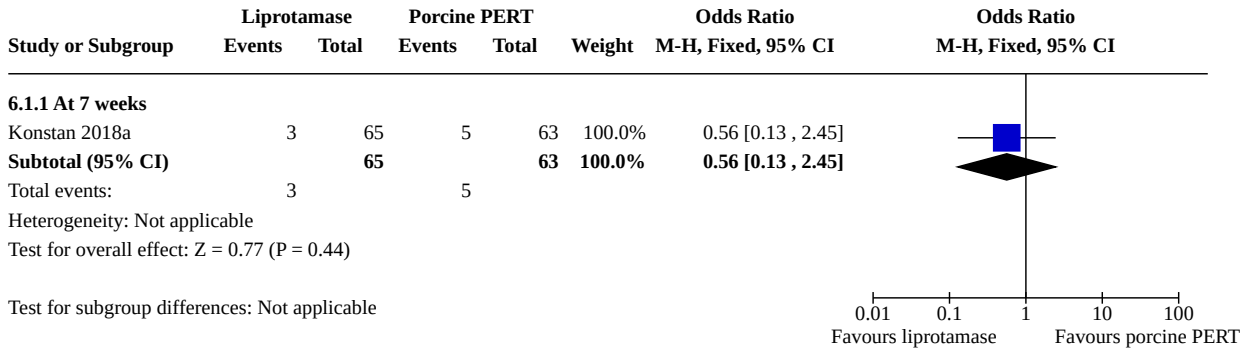
Heterogeneity: Not applicable
Test for overall effect: Z = 1.83 (P = 0.07)



Comparison 6. Liprotamase versus porcine PERT

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
6.1 Pulmonary exacerbation	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1.1 At 7 weeks	1	128	Odds Ratio (M-H, Fixed, 95% CI)	0.56 [0.13, 2.45]

Analysis 6.1. Comparison 6: Liprotamase versus porcine PERT, Outcome 1: Pulmonary exacerbation



ADDITIONAL TABLES

Table 1. Glossary of terms

Term/abbreviation	Definition
BMI	body mass index
CF	cystic fibrosis
CFA	coefficient of fat absorption
chyme	the semi-fluid mass of partly digested food expelled by the stomach into the duodenum
DIOS	distal intestinal obstruction syndrome
ECM	enteric coated microspheres
FFE	fecal fat excretion
hyperuricemia	an excess of uric acid in the blood
hyperuricosuria	the presence of excessive amounts of uric acid in the urine
Ileocecum	the combined ileum (end of the small intestine) and cecum (start of the large intestine)
NECM	non-enteric coated microspheres
PERT	pancreatic enzyme replacement therapy
PI	pancreatic insufficiency
porcine	relating to or suggesting swine (pigs)
RCT	randomized controlled trial
steatorrhea	loss of fat in the stools

APPENDICES

Appendix 1. Glossary

Medical term	Lay term
acid steatocrit	an estimate of the amount of fat in stool (feces)
distal intestinal obstruction syndrome	blockage of the large bowel due to partly digested food
duodenum	first part of the small intestine
enteric-coated	protected against damage by acid in the stomach
exocrine pancreatic insufficiency	insufficient production of digestive enzymes
fibrosing colonopathy	scarring and narrowing of the large intestine, thought to be related to high doses of some enzymes
gastrointestinal motility	normal movement of food through the digestive system
gastrointestinal tract	digestive system
hyperuricemia	high levels of uric acid in the blood
hyperuricosuria	high levels of uric acid in the urine
perianal redness	sore bottom (in this context)

WHAT'S NEW

Date	Event	Description
29 September 2020	Amended	In the comparison of liprotamase versus porcine pancreatic enzyme replacement therapy the analysis of the co-efficient of fat absorption has been removed and we report the results narratively (taken directly from the paper).

HISTORY

Protocol first published: Issue 1, 2010
Review first published: Issue 10, 2014

Date	Event	Description
27 July 2020	New search has been performed	A search of the Cystic Fibrosis and Genetic Disorders Review Group's Cystic Fibrosis Trials Register identified 16 new references potentially eligible for inclusion in the review. Six references were added to five already excluded trials (Heubi 2007; Heubi 2016; Konstan 2008; Perano 2014; Trapnell 2009).

Date	Event	Description
		Three references were added to a study listed as ongoing, which has now been included (Konstan 2018a). Four references were to four new studies that has been excluded (Eiel 2018; Geyer 2019; NCT01851694; Warwick 1982). Three references are to three new studies listed as 'Awaiting classification' (Brekke 2019; Konstan 2018b; Stern 1988). A search of ongoing trials databases identified nine references to nine studies that have been excluded (EUCTR 2007-004004-12; EUCTR 2015-001219-11; NCT00217204; NCT00449904; NCT01327703; NCT01652157; NCT01851694; NCT01858519; NCT03746483) and one study that is listed as ongoing (NCT03924947). A summary of findings table has been added for each comparison presented in the review.
27 July 2020	New citation required but conclusions have not changed	Despite the addition of new studies to the review (ongoing and awaiting assessment) our conclusions remain the same.
22 November 2016	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorders Review Group's Cystic FIbrosis Trials Register identified eight references which were potentially eligible for inclusion in the review. One new study (two references) has been included (Taylor 2015). Two references were additional references to two already excluded studies (Borowitz 2011; Wooldridge 2009). The remaining four references to two studies have been excluded (Heubi 2016; van der Haak 2016).
22 November 2016	New citation required but conclusions have not changed	Despite the inclusion of a new study, our conclusions remain the same.

CONTRIBUTIONS OF AUTHORS

Protocol stage: Paramita Cifelli and Robyn Huggins partly drafted the protocol with significant contributions from Alan Smyth.

Initial review and update stage: Usha Rani Somaraju and Arturo Solis Moya both selected trials for inclusion in the review, extracted data and assessed the risk of bias. Usha Rani Somaraju drafted the review with comments from Arturo Solis Moya. Usha Rani Somaraju is guarantor of the review.

DECLARATIONS OF INTEREST

Neither author has any interests to declare.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In line with current Cochrane guidance, summary of findings tables were added at the 2020 update.

INDEX TERMS

Medical Subject Headings (MeSH)

Abdominal Pain [epidemiology]; Age Factors; Capsules [administration & dosage]; Cystic Fibrosis [*therapy]; Delayed-Action Preparations; Enzyme Replacement Therapy [adverse effects] [*standards]; Gastrointestinal Agents [therapeutic use]; Microspheres; Nutritional Status; Pancreas [enzymology]; Randomized Controlled Trials as Topic; Weight Gain

MeSH check words

Adult; Child; Humans