G.8 Mucoactive agents

Review question: What is the effectiveness of mucoactive or mucolytic agents, including rhDNase, nebulised saline (isotonic and hypertonic) and mannitol?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Wilmott, R. W., Amin, R. S., Colin, A. A., DeVault, A., Dozor, A. J., Eigen, H., Johnson, C., Lester, L. A., McCoy, K., McKean, L. P., Moss, R., Nash, M. L., Jue, C. P., Regelmann, W., Stokes, D. C., Fuchs, H. J., Aerosolized recombinant human DNase in hospitalized cystic fibrosis patients with acute pulmonary exacerbations, American Journal of Respiratory & Critical Care Medicine, 153, 1914-7, 1996 Ref Id 333930	Sample size See Yang 2016 Characteristics See Yang 2016 Inclusion criteria See Yang 2016 Exclusion criteria See Yang 2016	Interventions See Yang 2016	Details See Yang 2016	Results See Yang 2016	Limitations See Yang 2016 Other information See Yang 2016

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out See Yang 2016 Study type See Yang 2016 Aim of the study See Yang 2016 Study dates See Yang 2016 Source of funding See Yang 2016					
Full citation Suri,R., Wallis,C., Bush,A., Thompson,S., Normand,C., Flather,M., Grieve,R., Metcalfe,C., Lees,B., A comparative study of hypertonic saline, daily and alternate-day rhDNase in children with cystic fibrosis, Health Technology Assessment, 6, -, 2002	Sample size See Yang 2016 Characteristics See Yang 2016 Inclusion criteria See Yang 2016 Exclusion criteria See Yang 2016	Interventions See Yang 2016	Details See Yang 2016	Results See Yang 2016	Limitations See Yang 2016 Other information See Yang 2016

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 238945 Country/ies where the study was carried out See Yang 2016 Study type See Yang 2016 Aim of the study See Yang 2016 Study dates See Yang 2016 Source of funding See Yang 2016					
Full citation Gupta, S., Ahmed, F., Lodha, R., Gupta, Y. K., Kabra, S. K., Comparison of effects of 3 and 7% hypertonic saline nebulization on lung function in children with cystic fibrosis: a double-blind randomized, controlled trial,	Sample size N=31 were randomized. 30 completed the 28 days follow-up (15 in each group). Characteristics Children and young people with CF Mean (SD) age: 3% sodium chloride (n=15): 10.6 (2.87) vs 7% sodium chloride (n=15): 10.87 (3.64) Females: 3% sodium chloride (n=15): 6	Interventions Intervention: 3% sodium chloride BD 28 days Comparison: 7% sodium chloride BD 28 days (high dose)	Details Setting. Pediatric Chest Clinic of All India Institute of Medical Sciences, New Delhi, India. Randomization. The subjects were randomized to receive either 3 or 7% hypertonic saline nebulization. Random sequence was generated using a computer program by a person not involved	Results FEV1 Mean difference (95% CI) between % change in the 3% sodium chloride group (n=15) and the 7% sodium chloride group (n=15) at 2 weeks: -14.35 lower (-27.8 to -0.9)* Mean difference (95% CI) between % change in the 3% sodium chloride group (n=15) and the 7% sodium chloride group (n=15) at 2 weeks: -13 lower (-25.27 to -0.73)* *Calculated by the NGA technical team	Limitations Risk of bias assessed with the Cochrane risk of bias tool: Random sequence generation (selection bias): Low risk (Random sequence was generated using a computer program) Allocation concealment (selection bias): Low risk (Random sequence was generated using a computer program by a person not involved in the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Journal of Tropical Pediatrics, 58, 375-81, 2012 Ref Id 360188 Country/ies where the study was carried out India Study type Double-blind RCT, parallel design Aim of the study To compare the effects of 3 and 7% hypertonic saline administered by nebulization on lung function in children with cystic fibrosis. Study dates Not reported Source of funding Not reported. Baxter Pharmaceuticals Limited provided technical assistance for preparing the study drugs.	(40%) vs 7% sodium chloride (n=15): 2 (13.33%) Inclusion criteria Confirmed diagnosis of CF. Age between 6 and 16. On a regular follow-up for at least the previous 12 months. Able to perform reproducible pulmonary function test. Exclusion criteria Exclusion criteria: Fall in FEV1 by >15% following administration of bronchodilator and test dose of study drug by nebulization; required change in antibiotic treatment during the 4 weeks prior to enrollment; not performing regular chest physiotherapy at home. Children who were already receiving hypertonic saline nebulisation were eligible for the study after discontinuation of hypertonic saline nebulisation for 2 weeks.		in the study. The interventions solutions were sequentially numbered as per the random number list by another person not involved in the study. The collapsible bags were similar in appearance. The study was double-blinded. Data collection. Spirometry was performed according to the American Thoracic Society guidelines using Super Spiro Micromedics UK. Data analysis. T-tests were used to analyse if the mean FEV1 % predicted was significantly different between baseline, day 14 and day 28; t-tests were also used to compare percentage change in FEV1 in the 3% sodium chloride group vs the 7% sodium chloride group.		study. The interventions solutions were sequentially numbered as per the random number list by another person not involved in the study. The collapsible bags were similar in appearance.) Blinding (performance bias and detection bias): Low risk (The study was double-blinded, although it is unclear if both participants, clinicians and outcome assessors were blinded. The collapsible bags were similar in appearance.) Incomplete outcome data (attrition bias): Low risk (30 completed the study out of 31) Selective reporting (reporting bias): Low risk (FEV1 was reported both in the methods section as primary outcome and in the results section) Other bias: Low risk (None identified) Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Suri, R., Metcalfe, C., Lees, B., Grieve, R., Flather, M., Normand, C., Thompson, S., Bush, A., Wallis, C., Comparison of hypertonic saline and alternate-day or daily recombinant human deoxyribonuclease in children with cystic fibrosis: a randomised trial, Lancet, 358, 1316-21, 2001 Ref Id 360190 Country/ies where the study was carried out See Yang 2016 Study type See Yang 2016 Aim of the study See Yang 2016 Study dates See Yang 2016	Sample size See Yang 2016 Characteristics See Yang 2016 Inclusion criteria See Yang 2016 Exclusion criteria See Yang 2016	Interventions See Yang 2016	Details See Yang 2016	Results See Yang 2016	Limitations See Yang 2016 Other information See Yang 2016

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding See Yang 2016					
Full citation Minasian, C., Wallis, C., Metcalfe, C., Bush, A., Comparison of inhaled mannitol, daily rhDNase and a combination of both in children with cystic fibrosis: a randomised trial, Thorax, 65, 51-6, 2010 Ref Id 360191 Country/ies where the study was carried out See Nolan 2015 Study type See Nolan 2015 Aim of the study See Nolan 2015 Study dates See Nolan 2015 Source of funding See Nolan 2015	Sample size See Nolan 2015 Characteristics See Nolan 2015 Inclusion criteria See Nolan 2015 Exclusion criteria See Nolan 2015	Interventions See Nolan 2015	Details See Nolan 2015	Results See Nolan 2015	Limitations See Nolan 2015 Other information See Nolan 2015

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Elkins, M. R., Robinson, M., Rose, B. R., Harbour, C., Moriarty, C. P., Marks, G. B., Belousova, E. G., Xuan, W., Bye, P. T., National Hypertonic Saline in Cystic Fibrosis Study, Group, A controlled trial of long-term inhaled hypertonic saline in patients with cystic fibrosis, New England Journal of Medicine, 354, 229-40, 2006 Ref Id 360204 Country/ies where the study was carried out See Wark 2010 Study type See Wark 2010 Aim of the study See Wark 2010 Study dates See Wark 2010 Source of funding See Wark 2010	Sample size See Wark 2010 Characteristics See Wark 2010 Inclusion criteria See Wark 2010 Exclusion criteria See Wark 2010	Interventions See Wark 2010	Details See Wark 2010	Results See Wark 2010	Limitations See Wark 2010 Other information See Wark 2010

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Ratjen, F., Wonne, R., Posselt, H. G., Stover, B., Hofmann, D., Bender, S. W., A double-blind placebo controlled trial with oral ambroxol and N-acetylcysteine for mucolytic treatment in cystic fibrosis, European Journal of Pediatrics, 144, 374-8, 1985 Ref Id 360254 Country/ies where the study was carried out Germany Study type RCT Aim of the study To compare the effect of oral N-acetylcysteine and placebo in people with CF. Study dates Not reported Source of funding	Sample size N=21 N-acetylcysteine: n=10 Placebo: n=11 Characteristics People with CF. Age range: 6 to 21. Inclusion criteria Confirmed diagnosis of CF. People with mild to moderate lung disease were asked to participate when old enough to cooperate with pulmonary function tests. They had X-ray scores greater than 15 according to Schwachman and Kulczycki and less than 15 following the Chrispin-Norman score. Exclusion criteria Atopic patients and those receiving bronchodilators.	Interventions Intervention: Acetycysteine 200 mg, 3 times daily for 12 weeks Comparison: Placebo	Details Setting. Not reported. Randomization and blinding. 36 people were randomly assigned to 3 therapy groups with the help of a computer program, matched on the basis of Chrispin-Norman scores and age. Patients of the second group received acetylcysteine and patients in the third group received placebo. The drugs were given in granular presentation and could not be distinguished with regard to taste, colour and odour. Data collection. People were examined after a washout period of 14 days and after 6 and 12 weeks of trial. Lung function tests were performed exactly 2 hours after physiotherapy. The tests were always done between 11am and 2pm. Data analysis. Mean (SD)	Results Difference (95% CI) in FEV1 between mean change in acetylcysteine group (n=10) and mean change in placebo group (n=11): 5 (-10.84 to 20.84)	Limitations Assessed with the Cochrane risk of bias tool: Random sequence generation (selection bias): Low risk (People were randomly assigned to groups with the help of a computer program, matched on the basis of Chrispin-Norman scores and age) Allocation concealment (selection bias): Unclear risk (Not reported) Blinding (performance bias and detection bias): Low risk (Double-blinded, although unclear if both participants, personnel and outcome assessors were blinded. The drugs were given in granular presentation and could not be distinguished with regard to taste, colour and odour) Incomplete outcome data (attrition bias): Unclear risk (4/36 dropped out of the study: 2 due to irregular drug intake (unclear in which group), 1 due to missed appointments (unclear in which group), 1 in the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Not reported			values of FEV1 were provided at baseline and after 12 weeks.		placebo group showed clinical impairment and deterioration of lung function tests after 4 weeks. No intention-to-treat analysis.) Selective reporting (reporting bias): Low risk (relevant outcome mentioned in methods and outcomes section) Other bias: Low risk (None detected) Other information
Full citation Fuchs, H. J., Borowitz, D. S., Christiansen, D. H., Morris, E. M., Nash, M. L., Ramsey, B. W., Rosenstein, B. J., Smith, A. L., Wohl, M. E., Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis,	Sample size See Yang 2016 Characteristics See Yang 2016 Inclusion criteria See Yang 2016 Exclusion criteria See Yang 2016	Interventions See Yang 2016	Details See Yang 2016	Results See Yang 2016	Limitations See Yang 2016 Other information See Yang 2016

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
New England Journal of Medicine, 331, 637-642, 1994 Ref Id 360261 Country/ies where the study was carried out See Yang 2016 Study type See Yang 2016 Aim of the study See Yang 2016 Study dates See Yang 2016 Source of funding See Yang 2016					
Full citation Amin,R., Subbarao,P., Lou,W., Jabar,A., Balkovec,S., Jensen,R., Kerrigan,S., Gustafsson,P., Ratjen,F., The effect of dornase alfa on ventilation inhomogeneity in patients with cystic fibrosis, European Respiratory	Sample size See Yang 2016 Characteristics See Yang 2016 Inclusion criteria See Yang 2016 Exclusion criteria See Yang 2016	Interventions See Yang 2016	Details See Yang 2016	Results See Yang 2016	Limitations See Yang 2016 Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Journal, 37, 806-812, 2011 Ref Id 310599 Country/ies where the study was carried out See Yang 2016 Study type See Yang 2016 Aim of the study See Yang 2016 Study dates See Yang 2016 Source of funding See Yang 2016					
Full citation Laube, B. L., Auci, R. M., Shields, D. E., Christiansen, D. H., Lucas, M. K., Fuchs, H. J., Rosenstein, B. J., Effect of rhDNase on airflow obstruction and mucociliary clearance in cystic fibrosis, American Journal of Respiratory & Critical Care Medicine, 153, 752-60, 1996	Sample size See Yang 2016 Characteristics See Yang 2016 Inclusion criteria See Yang 2016 Exclusion criteria See Yang 2016	Interventions See Yang 2016	Details See Yang 2016	Results See Yang 2016	Limitations See Yang 2016 Other information See Yang 2016

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 333688 Country/ies where the study was carried out See Yang 2016 Study type See Yang 2016 Aim of the study See Yang 2016 Study dates See Yang 2016 Source of funding See Yang 2016					
Full citation McCoy, K., Hamilton, S., Johnson, C., Effects of 12-week administration of dornase alfa in patients with advanced cystic fibrosis lung disease. Pulmozyme Study Group, Chest, 110, 889-95, 1996 Ref Id 360298 Country/ies where the study was carried out	Sample size See Yang 2016 Characteristics See Yang 2016 Inclusion criteria See Yang 2016 Exclusion criteria See Yang 2016	Interventions See Yang 2016	Details See Yang 2016	Results See Yang 2016	Limitations See Yang 2016 Other information See Yang 2016

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
See Yang 2016 Study type See Yang 2016 Aim of the study See Yang 2016 Study dates See Yang 2016 Source of funding See Yang 2016					
Full citation Suri,R., Marshall,L.J., Wallis,C., Metcalfe,C., Bush,A., Shute,J.K., Effects of recombinant human DNase and hypertonic saline on airway inflammation in children with cystic fibrosis, American Journal of Respiratory and Critical Care Medicine, 166, 352-355, 2002 Ref Id 210686 Country/ies where the study was carried out See Yang 2016	Sample size See Yang 2016 Characteristics See Yang 2016 Inclusion criteria See Yang 2016 Exclusion criteria See Yang 2016	Interventions See Yang 2016	Details See Yang 2016	Results See Yang 2016	Limitations See Yang 2016 Other information See Yang 2016

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type See Yang 2016 Aim of the study See Yang 2016 Study dates See Yang 2016 Source of funding See Yang 2016					
Full citation Ranasinha, C., Assoufi, B., Shak, S., Christiansen, D., Fuchs, H., Empey, D., Geddes, D., Hodson, M., Efficacy and safety of short-term administration of aerosolised recombinant human DNase I in adults with stable stage cystic fibrosis, Lancet, 342, 199-202, 1993 Ref Id 360317 Country/ies where the study was carried out See Yang 2016 Study type	Sample size See Yang 2016 Characteristics See Yang 2016 Inclusion criteria See Yang 2016 Exclusion criteria See Yang 2016	Interventions See Yang 2016	Details See Yang 2016	Results See Yang 2016	Limitations See Yang 2016 Other information See Yang 2016

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
See Yang 2016 Aim of the study See Yang 2016 Study dates See Yang 2016 Source of funding See Yang 2016					
Full citation Ramsey, B. W., Astley, S. J., Aitken, M. L., Burke, W., Colin, A. A., Dorkin, H. L., Eisenberg, J. D., Gibson, R. L., Harwood, I. R., Schidlow, D. V., et al.,, Efficacy and safety of short-term administration of aerosolized recombinant human deoxyribonuclease in patients with cystic fibrosis, American Review of Respiratory Disease, 148, 145-51, 1993 Ref Id 360318	Sample size See Yang 2016 Characteristics See Yang 2016 Inclusion criteria See Yang 2016 Exclusion criteria See Yang 2016	Interventions See Yang 2016	Details See Yang 2016	Results See Yang 2016	Limitations See Yang 2016 Other information See Yang 2016

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out See Yang 2016 Study type See Yang 2016 Aim of the study See Yang 2016 Study dates See Yang 2016 Source of funding See Yang 2016					
Full citation Ballmann, M., von der Hardt, H., Hypertonic saline and recombinant human DNase: a randomised cross-over pilot study in patients with cystic fibrosis, Journal of Cystic Fibrosis, 1, 35-7, 2002 Ref Id 360356 Country/ies where the study was carried out See Yang 2016 Study type See Yang 2016 Aim of the study	Sample size See Yang 2016 Characteristics See Yang 2016 Inclusion criteria See Yang 2016 Exclusion criteria See Yang 2016	Interventions See Yang 2016	Details See Yang 2016	Results See Yang 2016	Limitations See Yang 2016 Other information See Yang 2016

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
See Yang 2016 Study dates See Yang 2016 Source of funding See Yang 2016					
Full citation Ballmann, M., von der Hardt, H., Hypertonic saline and recombinant human DNase: a randomised cross-over pilot study in patients with cystic fibrosis [abstract], 22nd European Cystic Fibrosis Conference, 1998 Ref Id 360357 Country/ies where the study was carried out See Yang 2016 Study type See Yang 2016 Aim of the study See Yang 2016 Study dates See Yang 2016 Source of funding See Yang 2016	Sample size See Yang 2016 Characteristics See Yang 2016 Inclusion criteria See Yang 2016 Exclusion criteria See Yang 2016	Interventions See Yang 2016	Details See Yang 2016	Results See Yang 2016	Limitations See Yang 2016 Other information See Yang 2016

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Amin, R., Subbarao, P., Jabar, A., Balkovec, S., Jensen, R., Kerrigan, S., Gustafsson, P., Ratjen, F., Hypertonic saline improves the LCI in paediatric patients with CF with normal lung function, Thorax, 65, 379-83, 2010 Ref Id 360358 Country/ies where the study was carried out Canada Study type Crossover RCT Aim of the study To study the ability of lung clearance index (LCI) to detect a treatment response to hypertonic saline inhalation in paediatric patients with CF with normal spirometry.	Sample size N=20 randomized 19 participants were included in the analysis. 17 participants had complete crossover data available. Characteristics People with CF Mean (SD) age: 10.5 (3.1). Females: 12/19 Inclusion criteria Confirmed diagnosis of CF. Age range: 6 to 18. Ability to perform reproducible spirometry. Baseline FEV1% predicted ≥80% at screening visit. Oxyhaemoglobin saturation ≥90% on room air. Exclusion criteria Airway cultures yielding Burkholderia cepacia complex in the previous 2 years or non-tuberculous mycobacteria in the past year; oral corticosteroid use; oxygen supplementation; lung transplantation; intravenous antibiotics	Interventions Intervention: 7% sodium chloride 4ml BD 4 week Comparison: 0.9% sodium chloride 4ml BD 4 week	Details Setting. Hospital for Sick Children, Toronto, Canada. Randomization. Concealed, computer-generated randomisation performed by a research pharmacist not otherwise involved in the study. Clinicians and research personnel remained unaware of the treatment assignments throughout the study, including the primary efficacy analysis. Washout period. 4-week-long washout period between 4 week-long treatment periods. Data collection. At a screening visit, demographic characteristics, clinical data, physical examination and spirometry were recorded. Data analysis. Data were analysed using intention-to-treat analysis.	Results FEV1 % predicted Absolute difference for isotonic saline vs hypertonic saline, Mean (SD) [95% CI]: -1.8 (12.0) [-7.9 to 4.4] Quality of life (QOL) CFQ-R respiratory domain, Absolute difference for isotonic saline vs hypertonic saline, Mean (SD) [95% CI]: -5.2 (14.2) [-17.4 to 7.1] CFQ-R parent respiratory domain, Absolute difference for isotonic saline vs hypertonic saline, Mean (SD) [95% CI]: -5.9 (16.2) [-14.9 to 3.0]	Limitations Risk of bias assessed with the Cochrane risk of bias tool: Random sequence generation (selection bias): Low risk (Computer-generated randomisation) Allocation concealment (selection bias): Low risk (Concealed randomisation performed by a research pharmacist not otherwise involved in the study) Blinding (performance bias and detection bias): Low risk (Clinicians and research personnel remained unaware of the treatment assignments throughout the study, including the primary efficacy analysis) Incomplete outcome data (attrition bias): Low risk (Intention-to-treat analysis, 1/20 participants excluded from analysis) Selective reporting (reporting bias): Low risk (Relevant outcomes were reported both in the methods and results sections) Other bias: Low risk (None detected) Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates All tests were performed between March and December 2008. Source of funding Canadian Institute of Health Research, the Canadian Cystic Fibrosis Foundation-Breathe Program and the Irwin (Arnold and Lynn) family donation.	or oral quinolones within 14 days of enrolment; or investigational drugs within 30 days of enrolment.				
Full citation Shah, P. L., Scott, S. F., Knight, R. A., Marriott, C., Ranasinha, C., Hodson, M. E., In vivo effects of recombinant human DNase I on sputum in patients with cystic fibrosis, Thorax, 51, 119-25, 1996 Ref Id 360384	Sample size 71 patients sampled and randomised. n=41 suitable for analysis. 30 patients excluded due to inadequate sputum samples for rheology analyses. Characteristics People with CF Age: not reported Sex: not reported No significant difference in baseline pulmonary function between treatment groups.	Interventions treatment: 2.5mg rhDNase BD for 10 days placebo: 150mmol NaCl + 1.5 mmol CaCl2 BD for 10 days Follow-up 42 days	Details Study drug delivered using Pulmo-Aide compressor and Acorn II jet nebuliser. PFTs performed at each study visit. Intrapatients variability accounted for by performing PFTs at same time of day and reproducibility assessed before administering study drug. Microlab 3000 series spirometer used for	Results Mean FEV1 (SE) (L) on day 10 of study: Dornase alfa (n=20): before treatment: 1.58 (0.2) ; after treatment: 1.78 (0.2) vs placebo (n=21): before treatment: 1.44 (0.13); after treatment: 1.46 (0.17) % change in FEV (SE): Dornase alfa (n=20): 13.32 (5.57) vs placebo (n=21): 0.15 (3.08) % change in FEV (SD): Dornase alfa (n=20): 13.32 (24.91)# vs placebo (n=21): 0.15 (14.11)# #SD calculated by the NGA technical team	Limitations Risk of bias assessed with Cochrane risk of bias tool: Adequate sequence generation (selection bias): Unclear risk (Method of randomisation not reported) Allocation concealment (selection bias): Unclear risk (Not mentioned) Blinding (performance bias and detection bias); Low risk (described as double blind, however unclear if both participants, personnel

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out United Kingdom Study type Phase II short-term double-blind placebo controlled trial Aim of the study To evaluate the effects of rhDNase on sputum rheology in vivo and to determine whether any changes produced are associated statistically with improvements in pulmonary function. Study dates Not reported Source of funding Genetech Inc supplied rhDNase	Inclusion criteria older than 15 years, with a FVC>40% predicted documented CF either by sweat Na+ concentration >70mmol/L by quantitative pilocarpine iontophoresis or homozygous for ΔF508 marker on genetic testing with clinica history indicative of CF Stable condition for 14 days prior to enrolment No changes to concomitant medications including oral steroids, antibiotics or bronchodilators. Exclusion criteria Not reported		PFTs using American Thoracic society guidelines. Standardised for age, sex and height using Knudson tables. Randomisation: method not described Allocation concealment: not described Statistics: PFTs presented as means and converted to percentage predicted values using Knudson tables.	FEV1 returned to baseline by day 42	and outcome assessors were blinded) Incomplete outcome data (attrition bias): Low risk (30 people excluded due to poor sputum samples; hwoever the authors state that the baseline characteristics of the 41 people included in the analysis were similar to those for the overall population of N=71. Moreover the authors state that the improvement in FEV1 in the group that received dornase alfa was similar to the improvement in FEV1 seen in patients who also received dornase alfa but were excluded from analysis due to inadequate sputum samples for rheology.) Selective reporting (reporting bias): Low risk (FEV1 mentioned in both the methods and results section) Other bias: Low risk (None detected) Other information
Full citation Bilton, D., Robinson, P.,	Sample size	Interventions See National Institute for Health	Details	Results See National Institute for Health and Clinical Excellence (2012)	Limitations

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Cooper, P., Gallagher, C. G., Kolbe, J., Fox, H., Jaques, A., Charlton, B., C. F. Study Investigators, Inhaled dry powder mannitol in cystic fibrosis: an efficacy and safety study, European Respiratory Journal, 38, 1071-80, 2011 Ref Id 360399 Country/ies where the study was carried out See National Institute for Health and Clinical Excellence (2012) Study type See National Institute for Health and Clinical Excellence (2012) Aim of the study See National Institute for Health and Clinical Excellence (2012) Study dates	See National Institute for Health and Clinical Excellence (2012) Characteristics See National Institute for Health and Clinical Excellence (2012) Inclusion criteria See National Institute for Health and Clinical Excellence (2012) Exclusion criteria See National Institute for Health and Clinical Excellence 2012)	and Clinical Excellence (2012)	See National Institute for Health and Clinical Excellence (2012)		See National Institute for Health and Clinical Excellence (2012) Other information See National Institute for Health and Clinical Excellence (2012)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
See National Institute for Health and Clinical Excellence (2012) Source of funding See National Institute for Health and Clinical Excellence (2012)					
Full citation Rosenfeld, M., Ratjen, F., Brumback, L., Daniel, S., Rowbotham, R., McNamara, S., Johnson, R., Kronmal, R., Davis, S. D., Isis Study Group, Inhaled hypertonic saline in infants and children younger than 6 years with cystic fibrosis: the ISIS randomized controlled trial, JAMA, 307, 2269-77, 2012 Ref Id 360408 Country/ies where the study was carried out USA and Canada	Sample size N= 321 were randomized: 7% sodium chloride: n=158 0.9% sodium chloride: n=163 15 participants withdrew from the 7% sodium chloride group and 14 from the 0.9% sodium chloride group. Characteristics Age < 6 years. Approx. 60% were <30 months at enrollment. Mean (SD) age: 7% sodium chloride (n=158): 2.2 (1.4) vs 0.9% sodium chloride (n=163): 2.3 (1.5) N (%) males: 7% sodium chloride (n=158): 84 (53%) vs	Interventions Intervention: 7% sodium chloride Twice daily for 48 weeks Comparison: 0.9% sodium chloride Twice daily for 48 weeks	Details Setting. 30 CF centres in the USA and Canada. Randomization. Participants were randomized 1:1 to 7% sodium chloride and 0.9% sodium chloride, base on random permuted blocks stratified by age (4 to 29 months, 30 to 60 months) and site, via a secure website. Participants, their families, health care providers and research personnel were blinded to treatment assignment. Data collection. The rate of pulmonary exacerbations (events per person-year) was defined as treatment with oral, inhaled or	Results Need for intravenous antibiotics for pulmonary exacerbations Total number of treatment days for a pulmonary exacerbation, adjusted mean difference (95% CI) 7% sodium chloride / 0.9% sodium chloride: 1.11 (0.89 to 1.37) (adjusted for age category and site) Time to next pulmonary exacerbation First pulmonary exacerbation, adjusted hazard ratio (95% CI) 7% sodium chloride / 0.9% sodium chloride: 0.94 (0.73 to 1.22) (adjusted for age category and site) Quality of life Adjusted mean difference (95% CI) for change in CFQ-R respiratory score between 7% sodium chloride group and 0.9% sodium chloride group: 3.3 (0.0 to 6.7) (adjusted by age category, site, and measure at randomization)	Limitations Risk of bias assessed with the Cochrane Risk of Bias tool: Random sequence generation (selection bias): Low risk (Participants were randomized 1:1, based on random permuted blocks stratified by age and site) Allocation concealment (selection bias): Unclear risk (Not reported) Blinding (Performance bias and detection bias): Low risk (Participants, their families, health care providers and research personnel were blinded to treatment assignment). Incomplete outcome data (attrition bias): Low risk (Withdrawals; 15/158 in 7% sodium chloride group and 14/163 in the 0.9%

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type Multicentre double-blind RCT Aim of the study To determine if hypertonic saline reduces the rate of pulmonary exacerbations in people with CF <6 years of age. Study dates The study was conducted from April 2009 to October 2011. Source of funding Receipt of funding is reported for each author. Sources are: CF Foundation Therapeutics, Inc; the National Institutes of Health; CF Canada; Canadian Institute for Child Health; Inspire, Inc; NHLBI; CFFT.	0.9% sodium chloride (n=163): 92 (56%) Inclusion criteria Age < 6 years. Upper age limit of 60 months. Other inclusion criteria "detailed in the eMethods" Exclusion criteria Exclusion criteria "detailed in the eMethods".		intravenous antibiotics for 1 or more pre-specified signs and symptoms within the 3 days prior to antibiotic start date through antibiotic stop date. Quality of life was measured with CFQ-R. Data analysis. Pulmonary exacerbation rate was compared between groups according to intent-to-treat analysis using a Poisson log-linear regression model. The rate ratio was also analysed with adjustment for age category and site. The probability of remaining free of a pulmonary exacerbation was estimated by the Kaplan-Meier method and the hazard ratio for first pulmonary exacerbation with a proportional hazards regression model. The difference in mean change in CFQ-R was estimated by a linear regression model with and without		sodium chloride group. Intention to treat analysis). Selective reporting (reporting bias): Low risk (Relevant outcomes mentioned both in the methods and results section). Other bias: Low risk (None detected) Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			adjustment for age category, site, and baseline measure.		
Full citation Jaques, A., Daviskas, E., Turton, J. A., McKay, K., Cooper, P., Stirling, R. G., Robertson, C. F., Bye, P. T., Lesouef, P. N., Shadbolt, B., Anderson, S. D., Charlton, B., Inhaled mannitol improves lung function in cystic fibrosis, Chest, 133, 1388-96, 2008 Ref Id 360418 Country/ies where the study was carried out See Nolan 2015 Study type See Nolan 2015 Aim of the study See Nolan 2015 Study dates See Nolan 2015 Source of funding	Sample size See Nolan 2015 Characteristics See Nolan 2015 Inclusion criteria See Nolan 2015 Exclusion criteria See Nolan 2015	Interventions See Nolan 2015	Details See Nolan 2015	Results See Nolan 2015	Limitations See Nolan 2015 Other information See Nolan 2015

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
See Nolan 2015					
Full citation Aitken, M. L., Bellon, G., De Boeck, K., Flume, P. A., Fox, H. G., Geller, D. E., Haarman, E. G., Hebestreit, H. U., Lapey, A., Schou, I. M., Zuckerman, J. B., Charlton, B., C. F. Investigators, Long-term inhaled dry powder mannitol in cystic fibrosis: an international randomized study, American Journal of Respiratory & Critical Care Medicine, 185, 645-52, 2012 Ref Id 360445 Country/ies where the study was carried out See National Institute for Health and Clinical Excellence (2012) Study type	Sample size See National Institute for Health and Clinical Excellence (2012) Characteristics See National Institute for Health and Clinical Excellence (2012) Inclusion criteria See National Institute for Health and Clinical Excellence (2012) Exclusion criteria See National Institute for Health and Clinical Excellence (2012)	Interventions See National Institute for Health and Clinical Excellence (2012)	Details See National Institute for Health and Clinical Excellence (2012)	Results See National Institute for Health and Clinical Excellence (2012)	Limitations See National Institute for Health and Clinical Excellence (2012) Other information See National Institute for Health and Clinical Excellence (2012)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
See National Institute for Health and Clinical Excellence (2012) Aim of the study See National Institute for Health and Clinical Excellence (2012) Study dates See National Institute for Health and Clinical Excellence (2012) Source of funding See National Institute for Health and Clinical Excellence (2012)					
Full citation Conrad, C., Lymp, J., Thompson, V., Dunn, C., Davies, Z., Chatfield, B., Nichols, D., Clancy, J., Vender, R., Egan, M. E., Quittell, L., Michelson, P., Antony, V., Spahr, J., Rubenstein, R. C., Moss, R. B., Herzenberg, L. A., Goss, C. H., Tirouvanziam, R., Long-term	Sample size N=70 were enrolled and randomized. acetylcysteine group: n=36 placebo group: n=34 6 in the acetylcysteine group and 2 in the placebo group were withdrawn or lost to follow-up. Of these, only 1 in the placebo group was excluded from the analysis. Characteristics People with CF.	Interventions Intervention: Acetylcysteine 3 times a day for 24 weeks. Comparison: Placebo 3 times a day for 24 weeks.	Details Setting. 11 accredited CF Foundation care centres in the United States. Randomization and blinding. An adaptive randomization strategy was used to stratify according to baseline FEV1 % predicted (moderate: 40% ≤ FEV1 ≤ 60%; mild: 60%< FEV1 ≤ 85%); age (7 to 17 years vs ≥ 18 years), gender, and	Results FEV1 Difference (95% CI) between mean change in FEV1 % predicted Acetylcysteine group and mean change in placebo group at 24 weeks: 4.4 (0.83 to 7.9) Inflammatory markers Difference (95% CI) between mean change in sputum IL-8 (log10) in Acetylcysteine group and mean change in placebo group at 24 weeks:0.19 (-0.03 to 0.42) Pulmonary exacerbations	Limitations Risk of bias assessed with the Cochrane risk of bias tool: Random sequence generation (selection bias): Low risk (An adaptive randomization strategy was used to stratify according to baseline FEV1 % predicted; age; gender; and indicators for chronic oral and inhaled antibiotic and chronic ibuprofen use.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
treatment with oral N-acetylcysteine: affects lung function but not sputum inflammation in cystic fibrosis subjects. A phase II randomized placebo-controlled trial, Journal of Cystic Fibrosis, 14, 219-27, 2015 Ref Id 360447 Country/ies where the study was carried out USA Study type RCT Aim of the study To evaluate the effects of oral N-acetylcysteine (NAC), which replenishes systemic glutathione, on decreasing inflammation and improving lung function in CF airways. Study dates	Age range: 9 to 59. Females: 35/70 (50%) Inclusion criteria Confirmed diagnosis of CF. Clinically stable. Stable mild-moderate lung disease FEV1 ≥40% and ≤85% predicted. Ability to tolerate sputum induction with 3% hypertonic saline. Followed restrictions on consumption of anti-oxidants, antibiotics and anti-inflammatory medications. Exclusion criteria Not reported.		indicators for chronic oral and inhaled antibiotic and chronic ibuprofen use. Randomization assignments and a series of blinded drug kit numbers were generated by PPD, Inc. Kits were distributed to each centre and were assigned with the use of a centralized secure randomization system at the coordinating centre. All study personnel and participants were blinded to treatment assignment. The randomization codes for each participant were revealed to the researchers once recruitment, data collection and data analyses were completed. Data collection. Spirometry and sputum induction were obtained at the screening visit (day 0). The CFQ-R was administered to measure quality of life. If a patient discontinued the use of the study drug or	Incidence of pulmonary exacerbations at 24 weeks: Acetylcysteine group (n=36): 15 vs placebo group (n=34): 17. Quality of life Difference (95% CI) between mean change in CFQ-R respiratory domain in Acetylcysteine group and mean change in placebo group at 24 weeks: -0.34 (-6.3 to 5.67)	Allocation concealment (selection bias): Low risk (Randomization assignments and a series of blinded drug kit numbers were generated by PPD, Inc. Kits were distributed to each centre and were assigned with the use of a centralized secure randomization system at the coordinating centre) Blinding (performance bias and detection bias): Low risk (All study personnel and participants were blinded to treatment assignment. The randomization codes for each participant were revealed to the researchers once recruitment, data collection and data analyses were completed.) Incomplete outcome data (attrition bias): Low risk (6/36 in the acetylcysteine group and 2/34 in the placebo group were withdrawn or lost to follow-up. All but 1 in the placebo group, who was lost to follow-up, were included in the analysis -

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
The trial was conducted between 4th of November 2008 and 30th of June 2011. Source of funding Not reported.			withdrew for any reason, they were asked to undergo evaluation at an early termination visit and to complete all remaining scheduled visits and procedures. Data analysis. Intention to treat analysis. Differences were calculated between mean change in the intervention group and mea change in the placebo group.		intention-to-treat analysis.) Selective reporting (reporting bias): Low risk (Relevant outcomes mentioned both in the methods and outcomes section) Other bias: Low risk (None detected) Other information
Full citation Wark,Peter, McDonald,Vanessa M., Nebulised hypertonic saline for cystic fibrosis, Cochrane Database of Systematic Reviews, -, 2010 Ref Id 257227 Country/ies where the study was carried out Australia Study type Wark 2010	Sample size Elkins 2006 N=164. 2 people were excluded from the analysis: 1 person in each group voluntarily withdrew before first dose.* 17 people were lost to follow-up*: 7 in the hypertonic saline group (2 owing to time constraints, 2 owing to insufficient perceived benefit from trial solution, 2 owing to adverse reaction to	Interventions Elkins 2006 Intervention: 7% sodium chloride BD for 48 weeks Comparison: 0.9% sodium chloride BD for 48 weeks* *Information extracted from primary study	Details Randomised, double-blind, parallel group trial	Results Elkins 2006 Mean (SD) % change in FEV1 at 12 weeks: Hypertonic saline (n=76): 3.96 (15.13) vs isotonic saline (n=73): -0.14 (10.61). Mean difference [95% CI]: 4.10 [-0.08, 8.28] Mean (SD) % change in FEV1 at 24 weeks: Hypertonic saline (n=75): 4.46 (13.31) vs isotonic saline (n=65): -0.91 (12.85). Mean difference [95% CI]: 5.37 [1.03, 9.71] Mean (SD) % change in FEV1 at 36 weeks: Hypertonic saline (n=69): 5 (15.61) vs isotonic saline (n=65): 1.37 (15.05).	Limitations Wark 2010 AMSTAR score: 9/11 (Publication bias not mentioned; declarations of interest by authors of the systematic review are included but declarations of interest or sources of support related to included studies are not provided) Elkins 2006 Assessed with the Cochrane risk of bias tool based on primary study: Random sequence generation (selection bias): Low risk (Computer-

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Cochrane systematic review Elkins 2006 RCT, parallel design Aim of the study Wark 2010 The aim of the Cochrane systematic review was to investigate the effects of nebulised hypertonic saline in cystic fibrosis compared to placebo or other treatments for mucociliary clearance. Elkins 2006 To test the safety and efficacy of inhaled hypertonic saline in a long-term trial* *Information extracted from primary study Study dates Wark 2010 The most recent search for the Cochrane systematic review was 31 July 2008.	trial solution (cough), 1 provided no reason)* 10 in the control group (5 owing to time constraints, 3 owing to insufficient perceived benefit from trial solution, 1 failed to attend, 1 provided no reason)* 15 people stopped inhalation but continued visits*: 8 in the hypertonic saline group (4 had adverse reactions to trial solution (1 cough and vomiting, 1 pharyngitis and wheezing, 1 had voice changes, 1 had chest tightness), 2 could not tolerate taste of trial solution, 1 had insufficient benefit from trial solution, 1 lost interest)* 7 in the control group (3 owing to time constraints, 2 had adverse reaction to trial solution (1 tonsillitis and 1 lethargy), 1 had insufficient benefit from trial solution, 1 provided no reason)*			Mean difference [95% CI]: 3.63 [-1.56, 8.82] Mean (SD) % change in FEV1 at 48 weeks: Hypertonic saline (n=68): 4.75 (14.71) vs isotonic saline (n=66): 2.44 (14.97). Mean difference [95% CI]: 2.31 [-2.72, 7.34] Please note that % change in FEV1 at 2 to 4 weeks is provided in the Cochrane SR however it was not extracted because more specific follow-ups were prioritised. Mean (SD) change from baseline in quality of life measured with CFQ 14+ at 48 weeks: Hypertonic saline (n=46): 1.09 (10.92) vs isotonic saline (n=45): -6.68 (17.09). Mean difference [95% CI]: 7.77 [1.86, 13.68] Mean (SD) change from baseline in quality of life measured with CFQ parent at 48 weeks: Hypertonic saline (n=34): 0.9 (11.93) vs isotonic saline (n=33): 2.03 (14.48). Mean difference [95% CI]: -1.13 [-7.49, 5.23]	generated randomization. A minimization algorithm was used to balance the two groups with respect to age, FEV1, and presence or absence of long-term treatment with dornase alfa, use or non-use of physiotherapy, and study centre*). Allocation concealment (selection bias): Low risk (Concealed randomization performed by a person not otherwise involved in the study*). Blinding (performance and detection bias): Low risk (Described as double-blind*) Incomplete outcome data (attrition bias): Unclear risk (2 people excluded from the analysis, 17 lost to follow-up, 15 stopped inhalation but continued visits. Reasons for lost to follow-up or stopped inhalation included adverse reactions, insufficient perceived benefits, and "could not tolerate taste of trial solution" in addition to other reasons such as time constraints, failed to attend, lost interest, provided no reason*)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Elkins 2006 The study was conducted between September 2000 and November 2003.* *Information extracted from primary study Source of funding Wark 2010 Not reported Elkins 2006 Supported by the US CF Foundation, the National Health and Medical Research Council of Australia, and the Australian CF Research Trust. * *Information extracted from primary study	*Information extracted from primary study Characteristics Wark 2010 People of all ages and of both sexes with CF, including all degrees of disease severity. Elkins 2006 People with CF from 16 hospitals.* Males: 93. Females: 71. * Information extracted from primary study Inclusion criteria Elkins 2006 Age ≥6 years.* Clinically stable condition.* FEV1 at screening had to be within 10% of the best value obtain within the previous 6 months.* FEV1% predicted ≥40%.* *Information extracted from primary study Exclusion criteria Elkins 2006 Pregnant or breast-feeding women. Persons colonized with Burkholderia cepacia. Cigarette				Selective reporting (reporting bias): Low risk (Relevant outcomes mentioned both in the methods and results sections*) Other bias: Low risk (None detected) *Information extracted from primary study Other information Elkins 2006 Pfizer Pharmaceuticals provided hypertonic saline and normal saline but otherwise did not participate in the design and conduct of the study.* *Information extracted from primary study

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	smokers. Use of hypertonic saline or non-routine antibiotics in the previous 14 days.* *Information extracted from primary study				
Full citation Shah, P. I., Bush, A., Canny, G. J., Colin, A. A., Fuchs, H. J., Geddes, D. M., Johnson, C. A., Light, M. C., Scott, S. F., Tullis, D. E., et al.,, Recombinant human DNase I in cystic fibrosis patients with severe pulmonary disease: a short-term, double-blind study followed by six months open-label treatment, European Respiratory Journal, 8, 954-8, 1995 Ref Id 333859 Country/ies where the study was carried out	Sample size See Yang 2016 Characteristics See Yang 2016 Inclusion criteria See Yang 2016 Exclusion criteria See Yang 2016	Interventions See Yang 2016	Details See Yang 2016	Results See Yang 2016	Limitations See Yang 2016 Other information See Yang 2016

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
See Yang 2016 Study type See Yang 2016 Aim of the study See Yang 2016 Study dates See Yang 2016 Source of funding See Yang 2016					
Full citation Quan, J. M., Tiddens, H. A., Sy, J. P., McKenzie, S. G., Montgomery, M. D., Robinson, P. J., Wohl, M. E., Konstan, M. W., Pulmozyme Early Intervention Trial Study, Group, A two-year randomized, placebo-controlled trial of dornase alfa in young patients with cystic fibrosis with mild lung function abnormalities, Journal of Pediatrics, 139, 813-20, 2001 Ref Id	Sample size See Yang 2016 Characteristics See Yang 2016 Inclusion criteria See Yang 2016 Exclusion criteria See Yang 2016	Interventions See Yang 2016	Details See Yang 2016	Results See Yang 2016	Limitations See Yang 2016 Other information See Yang 2016

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
360681 Country/ies where the study was carried out See Yang 2016 Study type See Yang 2016 Aim of the study See Yang 2016 Study dates See Yang 2016 Source of funding See Yang 2016					
Full citation Nolan Sarah, J., Thornton, Judith, Murray Clare, S., Dwyer, Tiffany, Inhaled mannitol for cystic fibrosis, Cochrane Database of Systematic Reviews, 2015 Ref Id 431814 Country/ies where the study was carried out Nolan 2015: N/A Aitken 2012: See National Institute for Health and Clinical Excellence (2012)	Sample size Aitken 2012 See National Institute for Health and Clinical Excellence (2012) Bilton 2011 See National Institute for Health and Clinical Excellence (2012) Jaques 2008 N=39 4 withdrawals. All 39 participants were included in the analysis. Minasian 2010 N=28 45 were recruited but only 28 were randomised. 8 participants withdrew	Interventions Aitken 2012 See National Institute for Health and Clinical Excellence (2012) Bilton 2011 See National Institute for Health and Clinical Excellence (2012) Jaques 2008 Intervention Inhaled dry powder mannitol 420 mg 2x daily,14 x 30 mg capsules. Fine particle fraction > 40%. Children < 12 years: administered via low resistance	Details Aitken 2012 See National Institute for Health and Clinical Excellence (2012) Bilton 2011 See National Institute for Health and Clinical Excellence (2012) Jaques 2008 Double-blind, randomised, cross-over study. Multicentre. Minasian 2010 Open-label, randomised, cross-over study. Multicentre: 2 centres.	Results Aitken 2012 See National Institute for Health and Clinical Excellence (2012) Bilton 2011 See National Institute for Health and Clinical Excellence (2012)Jaques 2008 Mean (SD) change from baseline in FEV1% predicted at 2 weeks: Mannitol (n=36): 3.86 (6.48) vs Control (n=36): -0.09 (6.48) Adverse events: haemoptysis (mild) (n/N) at 2 weeks: Mannitol (n=38): 2/38 vs Control (n=36): 2/36 Adverse events: haemoptysis (severe) (n/N) at 2 weeks: Mannitol (n=38): 0/38 vs Control (n=36): 0/36 Minasian 2010	Limitations Nolan 2015 AMSTAR score: 11/11 Aitken 2012 See National Institute for Health and Clinical Excellence (2012) Bilton 2011 See National Institute for Health and Clinical Excellence (2012) Jaques 2008 Random sequence generation (selection bias): Low risk (Randomisation code externally generated in small block design stratified to site and dornase alfa)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Bilton 2011: See National Institute for Health and Clinical Excellence (2012) Jaques 2008: Australia, New Zealand Minasian 2010: UK Study type Nolan 2015 Cochrane SR Aitken 2012 See National Institute for Health and Clinical Excellence (2012) Bilton 2011 See National Institute for Health and Clinical Excellence (2012) Jaques 2008 Double-blind, randomised, cross-over study. Multicentre. Minasian 2010 Open-label, randomised, cross-over study. Multicentre: 2 centres. Aim of the study Nolan 2015	Characteristics Aitken 2012 See National Institute for Health and Clinical Excellence (2012) Bilton 2011 See National Institute for Health and Clinical Excellence (2012) Jaques 2008 People with CF. Mean age: 19.1 years. Age range: 8 to 48. Females: 59% All participants clinically stable at start of study, mean (SD) baseline FEV1 % predicted 64.9 (13.6) for the mannitol group and 64.4 (11.8) for the control group. 46.2% received concomitant dornase alfa. Minasian 2010 People with CF. Considering randomised participants (results different from those who completed treatment in all arms and were analysed): 28 participants with CF: Mean (SD) age: 13.3 (2.24) years. Gender split: 36%	dry powder inhaler RS01 Plastiape, Osnago, Italy. Children >= 12 years and adults: administered via higher resistance dry powder inhaler, Inhalator, Boeringer-Ingelheim, Ingelheim, Germany. Control Non-respirable mannitol with afine particle fraction <2%. Identical in appearance and taste to mannitol capsules. 14 capsules 2x daily using same inhaler devices as for mannitol Minasian 2010 Pre-treated with participant's usual bronchodilator 15 minutes beforehand. Each intervention period lasted 12 weeks, with a 2-week washout period in between. Intervention 1		Mean difference (SE) [95% CI] in % change from baseline in FEV1 at 3 months, mannitol + dornase alfa (n=20) vs dornase alfa (n=20): -4.30 (5) [-14.10 to 5.50) Mean difference (SE) [95% CI] in % change from baseline in FEV1 at 3 months, mannitol (n=20) vs dornase alfa (n=20): 2.80 (3.88) [-4.80 to 10.40]	Allocation concealment (selection bias): Unclear risk (Not discussed) Blinding (performance bias and detection bias): Participants and clinicians: Low risk (Described as double-blind; mannitol and control capsules identical in taste and appearance. Same inhaler devices for mannitol and control). Outcome assessors: Low risk (Described as double blinded, it was stated that study staff and investigators were blinded. Same inhaler devices for mannitol and control. Pharmaxis confirmed the statistician is part of the study staff and therefore was blinded) Incomplete outcome data (attrition bias): High risk (56 days follow-up data not reported. 4 participants withdrew and one of these was due to "Unexplained withdrawal" by physician. Unclear how many participants were evaluated for each outcome) Selective reporting (reporting bias): Unclear

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To assess whether inhaled dry powder mannitol is well tolerated, whether it improves the quality of life and respiratory function in people with cystic fibrosis and which adverse events are associated with the treatment. Aitken 2012 See National Institute for Health and Clinical Excellence (2012) Bilton 2011 See National Institute for Health and Clinical Excellence (2012) Jaques 2008 To examine the efficacy and safety of therapy with inhaled mannitol over a 2-week period.* Minasian 2010 To compare inhaled mannitol with dornase alfa	male, 64% female. All participants clinically stable at start of study Characteristics of the 20 participants who completed treatment: Mean (SD) age: 13.2 (2.4) years. 70% female. Mean (SD) baseline FEV1: 1.67 (0.50) litres, 64 (10)% of predicted FEV1. Inclusion criteria Nolan 2015 Adults (18 years old and over) and children (under 18 years old) with CF (diagnosed clinically and by sweat or genetic testing and including all degrees of disease severity). Aitken 2012 See National Institute for Health and Clinical Excellence (2012) Bilton 2011 See National Institute for Health and Clinical Excellence (2012) Jaques 2008 No hypertonic saline within 2 weeks of start of study. Clinical stability, defined as the absence of being	Mannitol 400 mg 2x daily, 10 x 40 mg capsules. Manufacturer of mannitol not reported but assumed to be Pharmaxis as study was sponsored by this company. Administered via breath-actuated device Osmohaler, Plastiape, Osnago, Italy Intervention 2 Dornase alfa alone - 2.5 mg Pulmozyme® 2x daily via participant's usual device Intervention 3 Mannitol (as above) plus dornase alfa (dose unclear).			risk (All outcomes specified were reported, but little detail). Other bias: High risk (Participants underwent a mannitol tolerance test at screening; those who failed the test or in whom the test was incomplete were not entered into the study and thus, the study population included only those with CF who passed the tolerance test and not all potential participants with CF. Sponsored by Pharmaxis; authors or study staff worked for Pharmaxis or had financial interest) Minasian 2010 Random sequence generation (selection bias): Low risk (Described as randomised, but details of randomisation process not discussed in paper. Dr Minasian provided additional information - participants were allocated a unique randomisation number and treatment schedule with equal probability for assignment to treatment sequences. Randomisation was carried out in balanced

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
in children and young people.* *Information extracted from primary study Study dates Nolan 2015 Date of the last search: 16 April 2015 Aitken 2012 See National Institute for Health and Clinical Excellence (2012) Bilton 2011 See National Institute for Health and Clinical Excellence (2012) Jaques 2008 Not reported* Minasian 2010 Not reported* *Information extracted from primary study Source of funding Nolan 2015 No internal sources of support. External sources: National Institute for Health Research, UK	systematically unwell from any cause in the week leading up to study entry and the absence of additional antibiotic therapy in the 2 weeks before study enrollment.* Aged >8 years, with FEV1 between 41% and 91% predicted, and were capable of performing reproducible spirometry.* Minasian 2010 Age between 8 and 18 years.* Ability to perform repeatable reliable spirometry*. Either currently receiving dornase alfa or having an FEV1 >40% and <70% predicted (and therefore judged eligible to receive dornase alfa).* * Information extracted from primary study Exclusion criteria Aitken 2012 See National Institute for Health and Clinical Excellence (2012) Bilton 2011				blocks with separate schedules created for each of the 2 recruiting centres) Allocation concealment (selection bias): Unclear risk (Not discussed) Blinding (performance bias and detection bias): High risk (open study) Incomplete outcome data (attrition bias): High risk (Results in the paper only reported for participants who completed all 3 arms of the study. The desired sample size was 48 participants: 45 were recruited but only 28 were randomised and 8 children withdrew) Selective reporting (reporting bias): Low risk (Limited information was reported in the study publication regarding outcomes of HRQoL, pulmonary exacerbations, sputum microbiology and no information reported on: time off work or school, nonroutine antibiotics, hospitalisations, tolerability or burden of treatment. Additional data were provided by Pharmaxis and primary

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aitken 2012 See National Institute for Health and Clinical Excellence (2012) Bilton 2011 See National Institute for Health and Clinical Excellence (2012) Jaques 2008 The study was sponsored by Pharmaxis. Minasian 2010 The study was sponsored by Pharmaxis.	See National Institute for Health and Clinical Excellence (2012) Jaques 2008 Pregnancy, breast feeding, current asthma, recent hemoptysis of >60mL, Burkholderia cepacia colonization, terminal illness, or the need for home oxygen.* No hypertonic saline within 2 weeks of start of study. Minasian 2010 Using hypertonic saline. Known hypersensitivity to mannitol, rhDNase or bronchodilators, sputum infection with methicillin-resistant Staphylococcus aureus (MRSA), or Burkholderia cepacia, portal hypertension or varices, significant haemoptysis (>60 ml) in the previous 12 months, breast feeding or pregnancy. Patients had to have no changes in treatment or new respiratory symptoms				investigator Dr Minasian on request for all primary outcomes of this review and many secondary outcome) Other bias: High risk (Participants underwent a mannitol tolerance test at screening; participants who failed the test or in whom the test was incomplete were not entered into the study and thus, the participant population included only those participants with CF who passed the tolerance test and not all potential participants with CF. Underpowered study, many dropouts (48%of required sample size were analysed in the published analysis). Actual dropout rate was 8/28 = 29%. Cross-over design - state that no carryover effect observed, but more details needed. Sponsored by Pharmaxis; authors or study staff worked for Pharmaxis or had financial interest) Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	in the 2 weeks prior to the study.* *Information extracted from primary paper				
Full citation Dentice, R. L., Elkins, M. R., Middleton, P. G., Bishop, J. R., Wark, P. A., Dorahy, D. J., Harmer, C. J., Hu, H., Bye, P. T., A randomised trial of hypertonic saline during hospitalisation for exacerbation of cystic fibrosis, Thorax, 71, 141-7, 2016 Ref Id 425806 Country/ies where the study was carried out Australia Study type RCT, parallel design Aim of the study To determine the effects of hypertonic saline inhalation during	Sample size N=132 Intervention: 67 Control: 65 Characteristics Adults with CF Mean age (SD), range: Intervention: 28 (9), 17 to 62 years Control: 27 (9), 18 to 63 years Females, n/N (%) Intervention: 35/67 (52%) Control: 30/65 (46%) Inclusion criteria A confirmed diagnosis of CF. Admission for management of a pulmonary exacerbation for a minimum of 7 days. Exclusion criteria Major haemoptysis within the past year; thrombocytopenia; allergy to quinine sulfate; glucose 6-phosphate	Interventions Intervention: sodium chloride 4ml 7% 3 times daily throughout hospital admission (on average 12 days) Control: 0.12% sodium chloride 3 times daily throughout hospital admission (on average 13 days) Both groups received usual care.	Details Setting. Participants were recruited from Royal Prince Alfred Hospital, Westmead Hospital and John Hunter Hospital in New South Wales, Australia. Enrolment of participants occurred within 24 hours of hospital admission. Randomization. Participants were randomly allocated to the intervention or control group. The randomisation process used minimisation to adaptively balance the active and control treatment allocations at each enrolment site. This process also ensured that randomisation was stratified for deoxyribonuclease use, FEV1 (≥/<50% predicted on admission), gender	Results Lung function: FEV1, FVC Failed to regain pre-exacerbation FEV1 by discharge, n (%): Intervention (n=67): 17 vs Control (n=65): 28. RR: 0.59 (0.36 to 0.96) Time to next pulmonary exacerbation HR: 0.86 (CI 0.57 to 1.30) Quality of life (CFQ) Mean (SD) change in CFQ physical from admission to day 7:intervention (n=67): 11 (16) vs control (n=65): 9 (14). Between-group mean difference:2 (-4 to 7) Mean (SD) change in CFQ burden from admission to day 7:intervention (n=67): 0 (14) vs control (n=65): 0 (14). Between-group mean difference:-1 (-6 to 4) Mean (SD) change in CFQ health from admission to day 7:intervention (n=67): 12 (19) vs control (n=65):14 (17). Between-group mean difference: -2 (-8 to 4) Mean (SD) change in CFQ respiratory from admission to day 7:intervention (n=67): 13	Limitations Limitations assessed with Cochrane risk of bias tool: Random sequence generation (selection bias): Low risk (The randomisation process used minimisation to adaptively balance the active and control treatment allocations at each enrolment site. This process also ensured that randomisation was stratified for deoxyribonuclease use, FEV1, gender and fall in FEV1) Allocation concealment (selection bias): Unclear risk (Concealed randomisation, method unclear) Blinding (performance bias and detection bias): Low risk (All participants, clinicians and investigators remained blinded to treatment group allocation throughout the study)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
hospitalisation for exacerbation of CF on lung function, symptoms, time to next hospitalisation and other outcomes. Study dates Enrolment began in December 2005 and was completed in 6 years. Follow-up of hospital readmissions finished in February 2013. Source of funding The study was supported by the National Health and Medical Research Council Cooperative Centre for Research Excellence in Respiratory and Sleep Medicine postgraduate research scholarship and the US Cystic Fibrosis Foundation grant BYE04A0.	dehydrogenase deficiency; immune thrombocytopenic purpura; pregnancy; breastfeeding; Burkholderia cepacia or mycobacteria ever isolated from the sputum; or lung transplant.		and fall in FEV1 (≥/<25% fall from best outpatient FEV1 in the past 6 months. Data collection. FEV1 and FVC were measured by spirometry daily; quality of life was measured with SF36 and CFQ; time to next exacerbation was recorded with a minimum follow-up of 1 year. Data analysis. All analyses were by intention to treat.	(19) vs control (n=65): 12 (16). Between-group mean difference: 1 (-5 to 7) Mean (SD) change in CFQ physical from admission to discharge:intervention (n=67): 16 (19) vs control (n=65): 14 (17). Between-group mean difference: 3 (-4 to 9) Mean (SD) change in CFQ burden from admission to discharge:intervention (n=67): 1 (15) vs control (n=65): -1(20). Between-group mean difference: 1 (-4 to 7) Mean (SD) change in CFQ health from admission to discharge:intervention (n=67): 20 (21) vs control (n=65): 18 (20). Between-group mean difference: 2 (-5 to 10) Mean (SD) change in CFQ respiratory from admission to discharge:intervention (n=67): 19 (21) vs control (n=65): 21 (18). Between-group mean difference:-2 (-8 to 5)	Incomplete outcome data (attrition bias): Low risk (Intention to treat analysis, no withdrawals) Selective reporting (reporting bias): Low risk (Results for primary and secondary outcomes are reported) Other bias: Low risk (none identified) Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Yang, C., Chilvers, M., Montgomery, M., Nolan, S. J., Dornase alfa for cystic fibrosis, Cochrane Database of Systematic ReviewsCochrane Database Syst Rev, 4, CD001127, 2016 Ref Id 537299 Country/ies where the study was carried out Please see methods section for countries where studies were conducted Study type Cochrane SR Aim of the study - Study dates - Source of funding -	Sample size Amin 2011 N:19 randomised 17 completed Ballmann 2002 (trial also reported in Ballmann 1998) N: 14 Withdrawals were not discussed within the paper. Fuchs 1994 N: 968 25 people withdrew from the study, 8 in the placebo group and once-daily group and 9 in the twice-daily group Laube 1996 N: 20 The published paper stated that there were no withdrawals. McCoy 1996 N: 320 40 participants withdrew from the trial, five due to adverse events, 10 withdrew consent, 1 did not comply with the study protocol, 15 died, 2 were unavailable for follow up and 7	Interventions Amin 2011. Treatment and control administered via PARI LC1 Star® nebuliser (Pari, Midlothian, VA, USA) Intervention: 2.5mg dornase alfa once daily Control: placebo once daily Ballmann 2002 (trial also reported in Ballmann 1998) Intervention: 2 puffs salbutamol via a spacer prior to nebulization of 2.5 mg dornase alfa od Comparison: 2 puffs salbutamol via a spacer prior to nebulization of 10 ml HS Fuchs 1994 Intervention: Nebulized dornase alfa 2.5 mg od (n=322) or bd (n=321) over 24 weeks	Details Amin 2011 Randomised, placebo controlled trial. Cross-over design. A 4-week washout period. Single centre. Ballman 2002 (trial also reported in Ballmann 1998) Open cross-over pilot trial 2 treatment periods of 3 weeks. A 3-week washout period. Participants were assessed before and after each period. Fuchs 1994 Randomised, double-blind parallel trial with 3 arms over 24 weeks. More participants aged 17 - 23 years were in the once daily dornase alfa arm. Measurements taken on days 7, 14 and every 14 days thereafter. Laube 1996	Results Where possible data was extracted from the Cochrane SR. The full copy of the study was checked for accuracy and completeness. Additional data extracted is marked with a *. All data for Amin 2011 was extracted from primary study as the Yang Cochrane SR was only idenfied during re-runs. Amin 2011 Mean (SD) FEV1 % predicted: Dornase alfa before treatment: 92.09 (6.57) and after treatment: 97.72 (9.96) vs placebo before treatment: 89.68 (10.68) and placebo after treatment: 90.44 (7.80)* Change in FEV1% predicted: Dornase alfa: -39 (140) vs placebo: -1 (135ml) * Mean (SD) CFQ-R: Dornase alfa before treatment: 80.56 (12.50) and after treatment: 70.07 (21.24) vs placebo before treatment: 79.17 (17.68) and placebo after treatment: 73.89 (16.98) * Mean (SD) CFQ-R parent: Dornase alfa before treatment: 80.95 (16.27) and after treatment: 76.39 (22.57) vs placebo before treatment: 75.42 (12.58) and placebo after treatment: 79.53 (21.30)*	Limitations Yang 2016 AMSTAR score: 10/11 (Sources of support or funding related to included studies not reported) Amin 2011 Random sequence generation (selection bias): Low risk (Concealed computer-generated randomisation) Allocation concealment (selection bias): Low risk (Randomisation performed by a research pharmacist not otherwise involved in the trial) Blinding (performance bias and detection bias): Low risk (All participants (solutions indistinguishable from each other), clinicians and outcome assessors blinded to treatment assignment) Incomplete outcome data (attrition bias): Unclear risk (Reported that data analysed according to the intention-to-treat principle, however, data only reported on 17 who completed trial compared to the 19 that were

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	stopped for a medical procedure Quan 2001 239 participants randomized to dornase alfa and 235 to placebo. 410 completed the study, 60 participants withdrew from the study, 472 (out of 474) had follow-up data. The ITT population was 470. Ramsey 1993 N: 181 Data collected on all participants at the end of trial. The paper stated that there were no withdrawals. Ranasinha 1993 N: 71 Shah 1995a N: 70 participants allocate 70 participants allocated; 35 placebo, 35 dornase alfa. Specified 5 dropouts (2 died, 2 withdrew consent, 1 had a heart lung transplant) Suri 2001 (trial also reported in Suri 2002a and Suri 2002b)	Comparison: placebo (n=325) over 24 weeks Laube 1996 Intervention: 2.5 mg nebulized dornase alfa (n = 10) bd Comparison: placebo (n = 10) bd McCoy 1996 Intervention: Nebulized dornase alfa 2.5 mg od (n=158) over 12 weeks Comparison: Placebo (n=162) over 12 weeks Quan 2001 Intervention: 2.5 mg dornase alfa od Comparison: placebo Ramsey 1993 Intervention: nebulized dornase alfa * 0.6 mg (n = 45), 2.5 mg (n = 44) or 10 mg (n =44) bd for 10 days Comparison: placebo (n=48) Ranasinha 1993 Intervention: Nebulized dornase	Randomised, double-blind parallel design trial over 6 days. Measurements taken on day 6 only and reported in the paper. McCoy 1996 Randomised, double-blind, parallel trial over 12 weeks. Measurements taken on days 8, 15, 29, 57 and 85. Quan 2001 Randomised, double-blind parallel placebo controlled trial over 96 weeks, involving 49 CF centres. Measurements taken at week 4, 12 and every 12 weeks thereafter. Ramsey 1993 Randomised, double-blind, parallel trial with 3 treatment arms over 10 days. Participants were followed up for a further 32 days. Measurements taken on days 1, 3, 6, 10 with follow-up data on days 14, 21, 28 and 42.	Ballman 2002 (trial also reported in Ballmann 1998) FEVI increase (mean(SD)): dornase alfa 9.3% (11.7%) vs HS 7.7% (14%). Reported narratively. Adverse events not reported, salbutamol was given to prevent acute bronchospasm Fuchs 1994 Relative mean % change in FEVI at six months: N: 322; Mean(SD): 5.8(12.56) vs N: 325; Mean (SD): 0 (10.82). Mean number of days IV AB used at six months: Once daily N:322; Mean: 8.5. Twice daily: N: 321; Mean: 9.0. Placebo N: 325; Mean: 11.2 Please note the article reports this without SD. RhDNase od: 2.7 fewer days receiving parenteral antibiotics as compared with placebo (P<0.05). RhDNase bd: 2.2 fewer days receiving parenteral antibiotics (P<0.05) as compared with placebo. * Number of people experiencing exacerbations at six months (n/N): 71/322 vs 89/325 Adverse events: Haemoptysis at six months (n/N): 17/322 vs 21/325 Adverse events: Dyspnoea at six months (n/N): 37/322 vs 43/325 Adverse events: Pnemothorax at six months (n/N): 1/322 vs 1/325	randomised. Missing data from 2 participants: the LCI results of 1 participant failed to meet the quality control criteria for 1 of the 4 trial visits; 1 other participant dropped out of the trial after 2 visits because of a pulmonary exacerbation requiring IV antibiotics (protocol identified reason for withdrawal from trial), but not clear what treatment the participant had completed before withdrawal) Selective reporting (reporting bias): Low risk (All outcomes reported) Other bias: Low risk (Cross-over design with washout period of 4 weeks which should be adequate for lung function to return to baseline) Ballmann 2002 (trial also reported in Ballmann 1998) Adequate sequence generation: Unclear (Described as randomised, but method not clear) Allocation concealment: Unclear (Method unclear) Blinding (all outcomes): Unclear (Not blinded, due

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	N: 48 randomised. 45 completed first treatment period, 44 completed the second treatment period and 40 completed the third treatment period. 28 of the 48 patients produced sputum samples at the beginning and end of at least one of the treatment periods and were included in the analyses. * Wilmott 1996 N: 80 No withdrawals mentioned in the paper Characteristics Amin 2011 Mean age (SD): 10.1 (3.1) years* Female sex: 11* Ballmann 2002 (trial also reported in Ballmann 1998) Mean age: 13.3 With mild to moderate pulmonary involvement. Fuchs 1994 Age: Over 5.	alfa 2.5 mg bd (n = 36) for 10 days Comparison: placebo (n = 35) for 10 days Shah 1995a Intervention: 2.5 mg nebulised dornase alfa bd (n=35) for 14 days Comparison: Placebo (n=35) for 14 days Suri 2001 (trial also reported in Suri 2002a and Suri 2002b) Intervention: 2.5 mg dornase alfa od; alternate day 2.5 mg dornase alfa; 5 mL 7%hypertonic saline bd Comparison1: 2.5 mg dornase alfa od vs 5 mL 7%hypertonic saline bd. Comparison 2: 2.5 mg dornase alfa od vs alternate day 2.5 mg dornase alfa Wilmott 1996 Dornase alfa 2.5 mg bd (n = 43) nebulised over 15 days	Ranasinha 1993 Randomised, double-blind, parallel design safety and efficacy trial over 10 days with follow up to 42 days. Measurements taken at days 3, 6 and 10. Shah 1995a Randomised double-blind, parallel design trial over 14 days, with 6 month open follow up. ITT was not discussed. Suri 2001 (trial also reported in Suri 2002a and Suri 2002b) Open cross-over trial 3 treatment periods of 12 weeks A 2-week wash out period between each period. Measurements were taken at the start and end of each 12-week period Wilmott 1996. Randomised double-blind parallel designed trial over 15 days during a	Adverse events: Voice alteration at six months (n/N): 12/322 vs 7/325 Adverse events: Voice alteration (bd vs od treatment) (n/N): bd 16/321 vs od 12/322 Laube 1996 Relative mean % change in FEVI at one month: N: 10; Mean (SD): 9.4 (11.07) vs N: 10; Mean (SD): -1.8 (5.38) (Moderate disease severity subgroup) McCoy 1996 Relative mean % change in FEVI at three months: N: 158; Mean (SD): 9.4 (16.3) vs N: 162; Mean (SD): 2.1 (13.3). Mean number of days IV antibiotics used at three months: N: 158; Mean (SD): 25.35 (19.58) vs N: 162; Mean (SD): 28.31 (19.94) Mean number of days inpatient treatment at three months: N: 158; Mean (SD): 19.33 (15.91) vs N: 162; Mean (SD): 18.4 (12.31) There were no statistically significant differences in the risks of developing pulmonary exacerbations between the placebo and dornase alfa groups. The age-adjusted relative risk of one or more such events occurring over the study period in dornase alfa-treated patients, compared with the	to the taste of the hypertonic saline) Incomplete outcome data addressed (all outcomes): Unclear (No discussion of whether ITT analysis performed. Withdrawals were not discussed within the paper). Free of selective reporting: Unclear (None identified) Fuchs 1994 Adequate sequence generation: Unclear (Stated as randomised but no method was described). Allocation concealment: Unclear (Method unclear). Blinding (all outcomes): Unclear (Described as double blind, no further details). Incomplete outcome data addressed (all outcomes): Unclear (ITT principle was used. 25 people withdrew from the study, 8 in the placebo group and once-daily group and 9 in the twice-daily group) Free of selective reporting: Unclear (Measurements were taken on days 7, 14 and every 14 days

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Confirmed diagnosis of CF FVC: > 40% predicted Clinically stable Laube 1996 Age: Over 18 With stable stage CF FVC: 35%-75% predicted Non-smokers McCoy 1996 Confirmed CF diagnosis Age: 7-57 FVC: < 40% predicted. Baseline lung function in the treatment group was lower than that of the control group, P<0.05 Quan 2001 Age: 6-10 (mean age 8.4) FVC>85% predicted Ramsey 1993 Stable stage CF Age: 8-65 FVC>= 40% predicted Ranasinha 1993 Age: Adults Confirmed CF diagnosis All participants had stable disease	Placebo (n=37) ove r 15 days	respiratory exacerbation. Measurements taken on days 1, 8 and 15. Potential confounder; type of AB used. 8 of 36 placebo participants received oral AB versus 8 out of the 44 treatment group Country where studies were conducted Amin 2011: Canada* Ballmann 2002 (trial also reported in Ballmann 1998): Germany* Fuchs 1994: USA* Laube 1996: USA* McCoy 1996: USA* Quan 2001: (Australia, Belgium, Canada, Denmark, Germany, Ireland, Israel, Netherlands, Norway, Spain, Switzerland and the United States)* Ramsey 1993: Country not reported* Ranasinha 1993; Country not reported (however quality of copy available of primary study is	placebo group, was 0.925 (CI: 0.69;1.21. p=0.52) However, the adjusted power was 40%. * Adverse events: Dyspnoea at three months (n/N): 93/158 vs 97/162 Adverse events: Voice alteration at three months (n/N): 28/158 vs 10/162 Adverse events: The article states: Cf-related adverse events such as hemoptysis and chest pain occurred with similar frequency in both groups, as did dyspnea * Adverse events: In neither group was there an accelerated occurrence of pulmonary exacerbations * Quan 2001 Absolute mean % change in FEVI at two years: N: 204; Mean (SD): 0.04 (11.43) vs N: 206; Mean (SD): -3.2 (11.43) Number of people experiencing exacerbations at two years (n/N): 40/236 vs 56/234 Adverse events: Voice alteration at two years (n/N): 26/236 vs 27/234 Adverse events: Incidence of serious hemoptysis: 0% vs 0.4% * Ramsey 1993 Relative mean % change in FEVI at one month: N: 44; Mean (SD): 13.8 (13.27) vs N: 48; Mean	thereafter. The published trial reported the end of study results only) Laube 1996 Adequate sequence generation: Unclear (Stated as randomised but no method was described) Allocation concealment: Unclear (Method unclear) Blinding (all outcomes): Unclear (Described as double blind, no further details) Incomplete outcome data addressed (all outcomes): Unclear (ITT analysis was used in this study. The published paper stated that there were no withdrawals) Free of selective reporting: Unclear (None identified) McCoy 1996: Adequate sequence generation: Unclear (Stated as randomised but no method was described) Allocation concealment: Unclear (Method unclear) Blinding (all outcomes): Unclear

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	FVC > 40% predicted Shah 1995a Age: 5 years or more Confirmed diagnosis of CF Severe (FVC < 40% predicted) lung disease Suri 2001 (trial also reported in Suri 2002a and Suri 2002b Age: 7.3-17 Baseline characteristics of these 28 children were comparable to that of the entire study population according to the authors: * F/M: 14/14 Age: Mean (SD): 12.1 (3.1) FEV1 % predicted: Mean (SD): 46.0 (16.0) Sputum inflammatory mediator levels: Total IL-8, ng/g: n: 25; Median: 102.4; 90% Range: 63.2 - 219.0 *, Free IL-8, ng/g: n: 28; Median: 1.6; 90% Range: 0.2 - 41.5 * Wilmott 1996 Age: Over 5		missing some rows)* Shah 1995a: USA, Canada, UK* Suri 2001 (trial also reported in Suri 2002a and Suri 2002b): UK* Wilmott 1996: USA* *Information extracted from primary study	(SD): -1.6 (9). Moderate disease severity subgroup Administration of rhDNase od reduced the use of parenteral antibiotics for protocol-defined respiratory tract infection relative to placebo by 22.5% (p=0.110) and twice daily reduced the use by 34.3% (p=0.012). If adjusted by age, rhDNase od reduced it by 28.4% (p=0.037) relative to placebo and rhDNase bd reduced it by 36.9% (p=0.006).* Adverse events Voice alteration at one month (n/N): 12/44 vs 0/48 Ranasinha 1993 Relative mean % change in FEVI at one month: N: 36; Mean (SD): 12.8 (18.6) vs N: 35; Mean (SD): -1.5 (11.24) (moderate disease severity subgroup) Adverse events: Haemoptysis at one month (n/N): 2/36 vs 0/35 Adverse events: Dyspnoea at one month (n/N): 15/36 vs 11/35 Adverse events: Pnemothorax at one month (n/N): 0/36 vs 0/35 Adverse events: Voice alteration at one month (n/N): 0/36 vs 0/35 Shah 1995a Relative mean % change in FEVI: N: 31; Mean(SD): 1.4 (11.7) vs N: 34; Mean(SD): 4.2 (12.8) (severe disease severity subgroup)	(Described as double blind, no further details) Incomplete outcome data addressed (all outcomes): Unclear (ITT principle used. 2 participants from the dornase alfa arm of the trial did not have lung function recorded. 3 participants inadvertently received dornase alfa instead of placebo (the results for these participants for lung function and respiratory exacerbations were analysed on an ITT basis, for safety data the results for these participants were published as if they had been randomised to dornase alfa). 40 participants withdrew from the trial, 5 due to adverse events, 10 withdrew consent, 1 did not comply with the study protocol, 15 died, 2 were unavailable for follow up and 7 stopped for a medical procedure) Free of selective reporting: Unclear (Measurements were taken on days 8, 15, 29, 57 and 85. The 85 day

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Admitted to hospital for at least 1 night for treatment of a chest exacerbation (protocol defined) with FVC > 35% predicted Confirmed CF diagnosis Both groups had analog dyspnea scores of 32 to 36, which represents a moderate clinical degree of dyspnea. * *Extracted from primary study Inclusion criteria - Exclusion criteria -			Adverse events: Haemoptysis at one month (n/N): 2/35 vs 3/35 Adverse events: Dyspnoea at one month (n/N): 11/35 vs 7/35 Adverse events: Pnemothorax at one month (n/N): 0/35 vs 1/35 Adverse events: Voice alteration at one month (n/N): 1/35 vs 3/35 Suri 2001 (trial also reported in Suri 2002a and Suri 2002b) Mean % change in FEVI (dornase alfa od vs hypertonic saline): Treatment difference (SE): 8 (3.06). Mean % change in FEVI (dornase alfa od vs dornase alfa on alternate days): Mean difference (SE): 2 (3.5714) Mean % change in quality of life score (dornase alfa od vs hypertonic saline): Treatment difference (SE): 0.03 (0.0205) Mean % change in quality of life score (dornase alfa od vs dornase alfa on alternate day): Treatment difference (SE): 0.01 (0.0153) Mean number of days of inpatient treatment (dornase alfa od vs hypertonic saline): Treatment difference (SE): -0.4 (0.9796) Mean number of days of inpatient treatment (dornase alfa od vs dornase alfa alternate day): Treatment difference (SE): -0.93 (1.1789)	mean was reported in the paper) Quan 2001 Adequate sequence generation: Yes (Adequate, done by computer stratifying by centre using a permuted block design) Allocation concealment: Yes (Adequate, carried out by a pharmacy) Blinding (all outcomes): Unclear (Described as double blind, no further details) Incomplete outcome data addressed (all outcomes): Unclear (ITT approach was used. 60 participants withdrew from the study, 472 (out of 474) had follow-up data. The ITT population was 470) Free of selective reporting: Unclear (Measurements taken at week 4, 12 and every 12 weeks thereafter. The end of study results were reported) Ramsey 1993: Adequate sequence generation: Unclear (State d as randomised but no method was described)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Number of children who experienced one or more pulmonary exacerbations . During the HS treatment period N: 15. During the daily rhDNase treatment period N: 18 During the alternate-day rhDNase treatment period N: 17 . (the numbers of treatment period where an individual had one or more pulmonary exacerbations were compared) (cross-over trial). There was no evidence of differences between treatments, as the exact McNemar significance probability was 1.00 when daily rhDNase was compared with alternate-day rhDNase and HS. * Adverse events: Number of patients with haemoptysis (n/N): dornase alfa od: 0/43; dornase alfa on alternate day: 2/43; HS: 0/40 * Adverse events: Number of patients with breathlessness (n/N): dornase alfa od: 1/43; dornase alfa on alternate day: 4/43; HS: 2/40 * Adverse events: There was not significant difference in the number of adverse effects between the groups in the trial. 3 participants receiving HS had significant bronchospasm with the initial dose (reported narratively)	Allocation concealment: Unclear (Method unclear) Blinding (all outcomes): Unclear (Described as double blind, no further details) Incomplete outcome data addressed (all outcomes): Unclear (Analysed on an ITT basis. The paper stated that there were no withdrawals) Free of selective reporting: Unclear (Measurements taken on days 1, 3, 6, 10 with follow-up data on days 14, 21, 28 and 42. Data were reported in the paper on days 3, 10, 21 and 42. Ranasinha 1993: Adequate sequence generation: Yes (Adequate. Participants were assigned a carton number based on a randomisation list generated by Genentech on a permuted block design) Allocation concealment: Yes (Adequate. Unidentifiable cartons of active drug and placebo were numbered and

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				Changes in inflammatory mediator levels (geometric mean ratios are of post over pretreatment values): Total IL-8, ng/g (geometric mean ratio (95% CI)): Daily rhDNase: 90% (73, 111%); Alternate Day dhDNase: 103% (77, 137%); Hypertonic Saline: 107% (83,186%) - No significant change. * Changes in inflammatory mediator levels (geometric mean ratios are of post over pretreatment values): Free IL-8, ng/g: (geometric mean ratio (95% CI)): Daily rhDNase: 116% (54, 247%); Alternate Day dhDNase: 192% (106, 346%) ; Hypertonic Saline: 98% (47, 204%) - There is a significant mean increase in free IL-8 with alternate-day rhDNase only (p=0.03). * Wilmott 1996 Relative mean % change in FEVI (in participants with acute exacerbations) up to one month: N: 43; Mean(SD): 20 (19.67) vs N: 37; Mean(SD): 19 (42.58). Adverse events: Pnemothorax (n/N): 1/43 vs 0/37 Adverse events: Voice alteration (in participants with acute exacerbations): 6/43 vs 2/37 Adverse events: Dyspnea *: the mean change in dyspnea measured on a visual analog scale improved in both groups of	provided to the pharmacist for dispensing) Blinding (all outcomes): Unclear (Described as double blind, no further details) Incomplete outcome data addressed (all outcomes): Unclear (ITT was not discussed) Free of selective reporting: Unclear (Measurements taken at days 3, 6 and 10, none were reported in the paper) Shah 1995a: Adequate sequence generation: Unclear (Stated as randomised but no method was described) Allocation concealment: Unclear (Method unclear) Blinding (all outcomes): Unclear (Described as double blind, no further details) Incomplete outcome data addressed (all outcomes): Unclear (ITT not possible for some outcomes. 5 out of 70 participants did not complete the 14-day trial period, 1 received a heart-lung transplant, 2 withdrew consent and

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				patients (rhDNase 2.5 mg bd N:43; placebo N: 37). The mean percent change was significantly greater in the rhDNase-treated patients at Day 8 ($p<0.01$) but not significant at Day 15 ($p=0.10$) using an ANCOVA adjusted for baseline differences.* The improvement in the actively treated group was by 10% more than in the control group. This difference is of the order of 0.5 standard deviation, which is a moderate statistical effect size that is likely to to be of clinical significance. The dyspnea assessment by quality of life questionnaire improved in both groups of patients, but the change was not statistically significant. * * Information extracted from primary study	2 from the dornase alfa treated group died. Changes in lung function could therefore not be analysed on an ITT basis but adverse events and deaths were analysed on this basis.) Free of selective reporting: Unclear (None identified) Suri 2001 (trial also reported in Suri 2002a and Suri 2002b) Adequate sequence generation: Yes (Adequate (block randomisation was used). Randomisation carried out by telephone to an independent trials co-ordinating unit, and stratified by hospital and balanced after each group of 12 children). Allocation concealment: Yes (Adequate (independent trials co-ordinator). Blinding (all outcomes): Unclear (Not blinded, due to the taste of the hypertonic saline). Incomplete outcome data addressed (all outcomes): Unclear (48 children randomised, 45 completed 1st treatment

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					period, 44 completed the 2nd treatment period and 40 completed the 3rd treatment period) Free of selective reporting: Unclear (none identified). Wilmott 1996: Adequate sequence generation: Unclear (Unclear). Allocation concealment: Unclear (Method unclear). Blinding (all outcomes): Unclear (Described as double blind, no further details) Incomplete outcome data addressed (all outcomes): Unclear (ITT. No withdrawals mentioned in the paper) Free of selective reporting: Unclear (Measurements taken on days 1, 8 and 15, no reported results, graph shown in the paper). Other information Fuchs 1994. The study compared od and bd to placebo *, Cochrane does not specify what it is reporting, but likely to be reporting od. Shah 1995a. 6-month open-ended

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					phase not included in the Cochrane review as no control group.
Full citation Mainz, J. G., Schumacher, U., Schadlich, K., Hentschel, J., Koitschev, C., Koitschev, A., Riethmuller, J., Prenzel, F., Sommerburg, O., Wiedemann, B., Staab, D., Gleiber, W., Fischer, R., Beck, J. F., Arnold, C., Cooperators,, Sino nasal inhalation of isotonic versus hypertonic saline (6.0%) in CF patients with chronic rhinosinusitis - Results of a multicenter, prospective, randomized, double-blind, controlled trial, Journal of Cystic FibrosisJ Cyst Fibros, 4, 4, 2016 Ref Id	Sample size N=69 Characteristics People with CF with chronic rhinosinusitis Mean age (SD): 22.8 (12) Females: 29/69 (42%) Inclusion criteria Age ≥6 years. Confirmed diagnosis of CF. Chronic symptoms of rhinosinusitis. Exclusion criteria Not reported.	Interventions Intervention: 6% sodium chloride once daily for 28 days Comparison: 0.9% sodium chloride once daily for 28 days	Details Setting. Participants were enrolled in 11 German CF outpatient clinics. Randomization. Participants were randomized to either hypertonic or isotonic saline. Wash-out period. After a wash-out period of at least 28 days, participants crossed over to the alternative treatment. Treatment with intravenous antibiotics within the wash-out period delayed the start of the second period for another 28 days. Data collection. Methods to measure FEV1 were not reported. Data analysis. Values of visit 1, day 1 (period 1) and visit 3, day 57 (period 2) were used as baseline values. The authors calculated change in	Results Mean (SD) change in FEV1 % predicted at day 29: 6% sodium chloride (n=62 at baseline and n=60 at day 29): 0.04 (6.73) vs 0.9% sodium chloride (n=63): -0.3 (6.9)	Limitations Assessed with risk of bias Cochrane tool: Random sequence generation (selection bias): Unclear risk (method not reported) Allocation concealment (selection bias): Unclear risk (not reported) Blinding (performance bias and detection bias): Low risk (Double-blinded study, although unclear whether double-blind refers to participants, clinicians or outcome assessors) Incomplete outcome data (attrition bias): Low risk (Intention-to-treat analysis was carried out, however 5/69 people were excluded from the analysis. The reasons were: diary not evaluable, study medication was taken too early, private reason, stopped medication and rejected inhalation because of vibration)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
542074 Country/ies where the study was carried out Germany Study type Multi-centre crossover RCT Aim of the study To compare 6% sodium chloride to 0.9% sodium chloride. Study dates The study was registered at ClinicalTrials.gov in March 2010. Participants were enrolled between April 2010 and June 2013. Source of funding The study was supported by a financial grant from "Association Luxemburgeoise de Lutte contre la Mucoviscidose a.s.b.l." in cooperation with Mukoviszidose Insitut gGmbH, Bonn, the research and development arm			FEV1 for each treatment sequence.		Selective reporting (reporting bias): Unclear risk (FEV1 not mentioned in the methods section but results were provided) Other bias: Low risk (None identified) Other information

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of German Cystic Fibrosis Association Mukoviszidose e.V (grant number: S03/09). The PARI GmbH provided the study centres with nebulizers and blinded medication.					
Full citation National Institute for Health and Clinical Excellence, Mannitol dry powder for inhalation for treating cystic fibrosis. Single technology appraisal, 2012 Ref Id 589512 Country/ies where the study was carried out NICE 2012: N/A CF-301 (Bilton 2011): Australia, New Zealand, UK, Ireland) CF-302 (Aitken 2012):	Sample size DPM-CF-301 (Bilton 2011) N=295 Mannitol: n=177 Control: n=118 DPM-CF-302 (Aitken 2012) N=305 Mannitol: n=184 Control: n=121 Characteristics DPM-CF-301 (Bilton 2011) Subjects with CF. Baseline characteristics: N (%) children aged 6 to 11: mannitol (n=177): 31 (1.75%) vs control (n=118): 17 (14.4%)	Interventions DPM-CF-301 (Bilton 2011) Intervention: dry powder mannitol for inhalation 400mg (in 40 mg capsules) BD for 26 weeks. Administered with a hand-held, breath activated device. Control: dry powder mannitol for inhalation 50mg (in 5 mg capsules) BD for 26 weeks. Administered with a hand-held, breath activated device. DPM-CF-302 (Aitken 2012) Intervention: dry powder mannitol for	Details DPM-CF-301 (Bilton 2011) Double-blinded multinational, multicentre RCT. People were from recruited from 40 sites. Subjects that were using rhDNase routinely prior to enrolment in this clinical trial continued to use rhDNase throughout the trial. FEV1 was measured at 6,14 and 26 weeks. Method of randomisation: All subjects from a site were given consecutive enrolment numbers in	Results DPM-CF-301 (Bilton 2011)* FEV1 % predicted Mean difference (SE) [95% CI] in change from baseline in FEV1 % predicted at 2 months, Mannitol (n=177) vs control (n=118): 2.588 (1.184) [0.27, 4.91] Mean difference (SE) [95% CI] in change from baseline in FEV1 % predicted at 4 months, Mannitol (n=177) vs control (n=118): 3.602 (1.2534) [1.15, 6.06] Mean difference (SE) [95% CI] in change from baseline in FEV1 % predicted at 6 months, Mannitol (n=177) vs control (n=118): 3.595 (1.3419) [0.96, 6.23] Time to next exacerbation at 26 weeks**	Limitations DPM-CF-301 (Bilton 2011)* Random sequence generation (selection bias): Low risk (Described as randomised using 3:2 ratio (mannitol versus control) and stratified according to current dornase alfa use. Pharmaxis confirmed participants were randomised to a treatment arm via an IVRS using the site-subject identification number, date of birth, initials and dornase alfa use as requisites. A master randomisation list, stratified by region (Australia and Europe) and dornase alfa use (yes/no), was prepared by an external company.

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USA, Canada, Argentina, Europe Study type NICE 2012 Technology appraisal DPM-CF-301 (Bilton 2011) Multi-centre RCT, parallel design DPM-CF-302 (Aitken 2012) Multi-centre RCT, parallel design Aim of the study DPM-CF-301 (Bilton 2011) To determine the effect of Bronchitol compared to control on FEV1 in patients with CF DPM-CF-302 (Aitken 2012) To determine whether inhaled Bronchitol compared to control improves FEV1 in patients with cystic fibrosis (CF). Study dates	N (%) young people aged 12 to 17: mannitol (n=177): 32 (18.1%) vs control (n=118): 25 (21.2%) N (%) people aged 18 and over: mannitol (n=177): 114 (64.4%) vs control (n=118): 76 (64.4%) Mean (SD) age: mannitol (n=177): 23.1 (11.7) vs control (n=118): 22.8 (10.8) N (%) females: mannitol (n=177): 71 (40.1%) vs control (n=118): 61 (51.7%) N (%) caucasians: mannitol (n=177): 169 (95.5%) vs control (n=118): 115 (97.5%) Mean (SD) BMI (kg/m2): mannitol (n=177): 21.1 (4.0) vs control (n=118): 20.4 (3.6) N (%) dornase alfa use: mannitol (n=177): 96 (54.2%) vs control (n=118): 67 (56.8%) FEV1 % predicted at baseline: mannitol (n=177): 62.4 (16.45)	inhalation 400mg (in 40 mg capsules) BD for 26 weeks. Administered with a hand-held, breath activated device. Control: dry powder mannitol for inhalation 50mg (in 5 mg capsules) BD for 26 weeks. Administered with a hand-held, breath activated device.	successive order of inclusion. Enrolment numbers were generatedelectronically and were correlated to one of two randomisation schedules. The randomisation schedules were independently generated in blocks of five, for a parallel study design and stratified according to region and rhDNase use. For every three subjects randomised to active treatment, two subjects were allocated to control. Method of blinding: The investigators, site staff, pharmacists, subjects, monitors, project managers and data managers remained blinded throughout the study. Sealed randomisation individual code break envelopes were kept with the study pharmacist. Both active and control treatments consisted of ten identical opaque capsules with	Hazard ratio [95% CI] for time to first protocol defined pulmonary exacerbation, Mannitol (n=177) vs control (n=118): 0.68 [0.42, 1.11]. log [hazard ratio] (SE): -0.3857 (0.25) Need for intravenous antibiotics for pulmonary exacerbations People needing additional IV antibiotics at 4 months follow-up (n/N): Mannitol: 63/177 vs control: 60/118. Risk ratio [95% CI]: 0.70 [0.54 to 0.91] People needing additional IV antibiotics at 6 months follow-up (n/N): Mannitol: 63/177 vs control: 60/118. Risk ratio [95% CI]: 0.70 [0.54 to 0.91] Quality of life Mean (SD) change in quality of life - respiratory at 4 months follow-up: Mannitol (n=128): 0.3 (16.3) vs control (n=101): 0.1 (15.62) . Mean difference [95% CI]: 0.20 [-3.95, 4.35] Mean (SD) change in quality of life - vitality at 4 months follow-up: Mannitol (n=92): -0.2 (17.56) vs control (n=74): -3.5 (18.71). Mean difference [95% CI]: 3.30 [-2.27, 8.87] Mean (SD) change in quality of life - physical at 4 months follow-up: Mannitol (n=127): -2.7 (16.55) vs control (n=100): -1.5	Randomisation numbers (for both mannitol and control) were generated for each stratum, in blocks of 5. The randomisation number was assigned sequentially within each stratum) Allocation concealment (selection bias): Low risk (Pharmaxis confirmed randomisation was managed via an IVRS, therefore the investigator was unaware prior to randomising the participant which specific blinded pack of treatment they would be allocated to) Blinding (performance bias and detection bias) - participants: Low risk (Participants blinded to treatment allocation through using a subtherapeutic does of mannitol and the same inhaler devices were used for both treatment arms (not specifically stated in the published paper but Pharmaxis confirmed use of same inhaler device with 10 capsules for both 400 mg mannitol and control (50 mg mannitol))

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DPM-CF-301 (Bilton 2011) 5 April 2007 to 31 March 2009 DPM-CF-302 (Aitken 2012) 3 September 2008 to 12 April 2010 Source of funding NICE 2012 Technology appraisal submitted by Pharmaxis to NICE DPM-CF-301 (Bilton 2011) Pharmaxis DPM-CF-302 (Aitken 2012) Pharmaxis	vs control (n=118): 61.4 (16.13) DPM-CF-302 (Aitken 2012) Subjects with CF. N (%) children aged 6 to 11: mannitol (n=184): 35 (19.0%) vs control (n=121): 24 (19.8%) N (%) young people aged 12 to 17: mannitol (n=184): 56 (30.4%) vs control (n=121): 39 (32.2%) N (%) people aged 18 and over: mannitol (n=184): 93 (50.5%) vs control (n=121): 58 (47.9%) Mean (SD) age: mannitol (n=184): 19.6 (9.3) vs control (n=121): 20.4 (10.2) N (%) females: mannitol (n=184): 90 (48.9%) vs control (n=121): 58 (47.9%) N (%) caucasians: mannitol (n=184): 182 (98.9%) vs control (n=121): 119 (98.3%) Mean (SD) BMI (kg/m2): mannitol (n=184): 20.2 (4.12) vs		indistinguishable taste. Several strategies were put in place to minimize the subject's association between MTT and study drug. Addition of a second open label phase (the OLEP) which was added to ensure that a minimum of 100 subjects would receive 12 months of active treatment – this added two more safety visits to the open label phase. DPM-CF-302 (Aitken 2012) Double-blinded multinational, multicentre RCT. People were recruited from 53 sites. Subjects that were using dornase alfa routinely prior to enrolment in this clinical trial continued to use dornase alfa throughout the trial. Method of randomisation: Subje ct identification numbers were generated electronically when	(15.1). Mean difference [95% CI]: -1.20 [-5.33, 2.93] Mean (SD) change in quality of life - emotion at 4 months follow-up: Mannitol (n=128): -1.5 (15.4) vs control (n=100): -0.1 (13.94). Mean difference [95% CI]: -1.40 [-5.22, 2.42] Mean (SD) change in quality of life - eating at 4 months follow-up: Mannitol (n=128): 0.6 (15.1) vs control (n=99): 0.6 (14.23). Mean difference [95% CI]: 0.0 [-3.83, 3.83] Mean (SD) change in quality of life - health at 4 months follow-up: Mannitol (n=93): -0.1 (18.45) vs control (n=72): 2.3 (19.73). Mean difference [95% CI]: -2.40 [-8.30, 3.50] Mean (SD) change in quality of life - social at 4 months follow-up: Mannitol (n=128): -1.4 (15.6) vs control (n=98): -0.8 (11.54). Mean difference [95% CI]: -0.60 [-4.14, 2.94] Mean (SD) change in quality of life - body at 4 months follow-up: Mannitol (n=126): -1.2 (16.94) vs control (n=97): 1.6 (16.97). Mean difference [95% CI]: -2.80 [-7.29, 1.69] Mean (SD) change in quality of life - role at 4 months follow-up: Mannitol (n=92): 0.5 (18.05) vs control (n=72): -2.4 (15.66). Mean difference [95% CI]: 2.90 [-2.27, 8.07]	Blinding (performance bias and detection bias) - clinicians: Low risk (Study personnel blinded to treatment allocation. Pharmaxis confirmed that investigators and study staff including statisticians were blinded. Low-dose mannitol used as control which was identical in taste and appearance to the 400 mg mannitol Blinding (performance bias and detection bias) - outcome assessors: Low risk (Pharmaxis confirmed investigators and study staff, including statisticians and all outcome assessors at investigator sites e.g. spirometry technicians were blinded) Incomplete outcome data (attrition bias): Low risk (High dropout rates in blinded phase of study in both arms: 37% in mannitol arm and 28% in control arm. However, sensitivity analyses conducted by Pharmaxis (methods of imputation of missing data for withdrawals) showed a consistent treatment effect

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	control (n=121): 19.8 (3.70) N (%) dornase alfa use: mannitol (n=184): 137 (74.5%) vs control (n=121): 92 (76.0%) FEV1 % predicted at baseline: mannitol (n=184): 64.8 (15.7) vs control (n=121): 62.5 (16.0) Inclusion criteria NICE 2012 The TA focused on adults with CF. However neither study was powered to specifically show efficacy in this patient group, therefore the data from the total population is reported first. DPM-CF-301 (Bilton 2011) Age ≥6. FEV1 >30 and <90% predicted. Able to perform techniques necessary to measure lung function. Negative mannitol tolerance test (MTT). MTT was administered at the screening visit of the study. This MTT was necessary to assess bronchial		the subject's screening visit data were entered into the eCRF. The identification number was allocated sequentially and comprised a site number-subject number combination. Randomisation to treatment arm was carried out via Interactive Voice Response System (IVRS) using the site-subject identification number, date of birth, initials and rhDNase use as requisites. Randomisation was stratified by country and generated in paired blocks of five, one block for rhDNase users and one block for non-users. Within each block for every three subjects randomised to active treatment, two subjects were allocated to control. FEV1 was measured at 6,14 and 26 weeks. Method of blinding: The subjects,	Mean (SD) change in quality of life - weight at 4 months follow-up: Mannitol (n=92): 1.4 (26.11) vs control (n=73): 7.3 (29.53). Mean difference [95% CI]: -5.90 [-14.52, 2.72] Mean (SD) change in quality of life - digestion at 4 months follow-up: Mannitol (n=128): 0.8 (17.2) vs control (n=99):0.2 (17.75). Mean difference [95% CI]: -1.00 [-5.59, 3.59] Mean (SD) change in quality of life - respiratory at 6 months follow-up: Mannitol (n=114): 1.3 (15.95 vs control (n=87): -2.5 (17.55. Mean difference [95% CI]: 3.80 [-0.91, 8.51] Mean (SD) change in quality of life - vitality at 6 months follow-up: Mannitol (n=80): 2.1 (15.88) vs control (n=62): -5.1 (18.13). Mean difference [95% CI]: 7.20 [1.50, 12.90] Mean (SD) change in quality of life - physical at 6 months follow-up: Mannitol (n=113): -0.5 (16.22) vs control (n=87): -4.7 (17.56). Mean difference [95% CI]: 4.20 [-0.55, 8.95] Mean (SD) change in quality of life - emotion at 6 months follow-up: Mannitol (n=114): 0.3 (11.7) vs control (n=87): 0.5 (13.66) . Mean difference [95% CI]: -0.80 [-4.38, 2.78] Mean (SD) change in quality of life - eating at 6 months follow-	in favour of mannitol and no change to conclusions) Selective reporting (reporting bias): Low risk (Limited information was reported in the study publication; particularly HRQoL and lung function. Additional data were provided by Pharmaxis on request for all primary outcomes of this review and many secondary outcomes) Other bias: High risk (Participants underwent a mannitol tolerance test at screening; those who failed the test or in whom the test was incompletewere not entered into the study and thus, study population included only those with CF who passed the tolerance test and not all potential participants with CF. Sponsored by Pharmaxis; authors or study staff worked for Pharmaxis or had financial interest) DPM-CF-302 (Aitken 2012)* Random sequence generation (selection bias): Low risk (Further

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	responsiveness to Bronchitol and was necessary to exclude patients with airway hyperresponsiveness. The MTT assessment entails 6 steps where incremental doses of dry powder Bronchitol are administered in cumulative doses and lung function measurements are performed. Only patients who passed the MTT were randomised to treatment. DPM-CF-302 (Aitken 2012) Age ≥6. FEV1 >40% and <90% predicted. Negative Bronchitol tolerance test (MTT). MTT was administered at the screening visit of the study. This MTT was necessary to assess bronchial responsiveness to Bronchitol and was necessary to exclude patients with airway hyperresponsiveness. The MTT assessment entails 6 steps where incremental doses of		investigators, pharmacists and Pharmaxis clinical and statistical staff were blinded to treatment allocations. The study pharmacist could access the allocation using the IVRS if necessary to unblind a subject. Both active and control treatments consisted of ten identical opaque capsules with indistinguishable taste. Several strategies were put in place to minimize the subject's association between MTT and study drug. Change in % predicted FEV1 was not in protocol however was included in the statistical analysis plan.	up: Mannitol (n=114): 2.3 (15.47) vs control (n=87): 1.9 (13.89). Mean difference [95% CI]: 0.40 [-3.67, 4.47] Mean (SD) change in quality of life - health at 6 months follow-up: Mannitol (n=79): 1.4 (17.47) vs control (n=62): 1.1 (18.3). Mean difference [95% CI]: 0.30 [-5.67, 6.27] Mean (SD) change in quality of life - social at 6 months follow-up: Mannitol (n=113): 0.3 (13.75) vs control (n=87): -0.7 (13.74). Mean difference [95% CI]: 1.00 [-2.84, 4.84] Mean (SD) change in quality of life - body at 6 months follow-up: Mannitol (n=111): 1.6 (16.26) vs control (n=86): 1.8 (15.14). Mean difference [95% CI]: -0.20 [-4.60, 4.20] Mean (SD) change in quality of life - role at 6 months follow-up: Mannitol (n=80): -0.4 (16.66) vs control (n=62): -1.6 (15.15). Mean difference [95% CI]: 1.20 [-4.05, 6.45] Mean (SD) change in quality of life - weight at 6 months follow-up: Mannitol (n=80): 3.7 (23.72) vs control (n=62): 6.5 (31.85). Mean difference [95% CI]: -2.80 [-12.28, 6.68] Mean (SD) change in quality of life - digestion at 6 months follow-up: Mannitol (n=114): -0.7 (19.46) vs control (n=87): 0	details were provided by Pharmaxis: the master randomisation list, stratified by country and dornase alfa user (yes/no) for a parallel design was prepared usingSAS Version 8.1 by an external company. 300 randomisation numbers (180 active and 120 control) were generated for each country and each dornase alfa user/non user group. Randomization blocking by country was done in paired blocks of 5, 1 block for dornase alfa users and 1 block for non users)) Allocation concealment (selection bias): Low risk (Pharmaxis confirmed randomisation managed via an IVRS, therefore the investigator was unaware prior to randomising the participant which specific blinded pack of treatment they would be allocated to. This provided an extra level of security (over and above the blinded nature of the study) against selection bias)) Blinding (performance bias and detection bias) - participants: Low risk

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	dry powder Bronchitol are administered in cumulative doses and lung function measurements are performed. Only patients who passed the MTT were randomised to treatment. Exclusion criteria DPM-CF-301 (Bilton 2011) Considered "terminally ill", listed for or had lung transplant Use of nebulised hypertonic saline was an exclusion criterion assessed at screening (visit 0). Significant episode of haemoptysis (>60mL) in the three months prior to enrolment Have had a myocardial infarction, cerebral vascular accident, major ocular, chest or brain surgery in the 3 months prior to enrolment Known cerebral, aortic or abdominal aneurysm			(21.63). Mean difference [95% CI]: -0.70 [-6.48, 5.08 Adverse events Adverse events: haemoptysis (mild) (n/N) at 6 months: Mannitol: 3/177 vs control: 2/118. Risk ratio: 4.62 [0.10, 224.14] Adverse events: bronchospasm (mild) (n/N) at 6 months: Mannitol: 0/177 vs control: 0/118. Risk ratio: Not estimable. Adverse events: haemoptysis (moderate) (n/N) at 6 months: Mannitol: 9/177 vs control: 1/118. Risk ratio: 6.00 [0.40, 89.09] Adverse events: bronchospasm (moderate) (n/N) at 6 months: Mannitol: 1/177 vs control: 0/118. Risk ratio: 2.01 [0.03, 133.11] Adverse events: haemoptysis (severe) (n/N) at 6 months: Mannitol: 1/177 vs control: 1/118. Risk ratio: 0.67 [0.02, 25.14] Adverse events: bronchospasm (severe) (n/N) at 6 months: Mannitol: 1/177 vs control: 0/118. Risk ratio: 2.01 [0.03, 133.11] Adverse events: bronchospasm in children and young people (N=105***), risk ratio: Not estimable because no events	(Described as double blind - mannitol and low-dose mannitol control administered and capsules identical in taste and appearance with identical methods of administration) Blinding (performance bias and detection bias) - clinicians: Low risk (Described as double blind - mannitol and low-dose mannitol control administered as capsules identical in taste and appearance and with identical methods of administration Pharmaxis confirmed investigators and study staff, including statisticians and all outcome assessors at investigator sites e.g. spirometry technicians were blinded. Both Bilton 2011 and Aitken 2012 used the same low-dose mannitol control that identical in taste and appearance to the 400mg mannitol active intervention) Blinding (performance bias and detection bias) - outcome assessors: Low risk (Described as double blind - mannitol and low-

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	Female subjects currently breast feeding or pregnant or using unreliable form of contraception if at risk of pregnancy) Participation in another investigative drug study parallel to, or within 4 weeks of study entry Known allergy to Bronchitol Use of beta-blockers Uncontrolled hypertension – systolic BP >190 and/or diastolic BP >100 Condition or situation which in the Investigator's opinion may put the subject at significant risk, may confound results or may interfere significantly with the subject's participation in the study MTT test positive DPM-CF-302 (Aitken 2012) Considered "terminally ill", listed for or had lung transplant Using nebulised hypertonic saline - can be eligible if 4 week			were reported among children and young people. Adverse events: bronchospasm in adults (N=190***), risk ratio [99% CI]: 3.35 [0.06 to 177.81], risk ratio [95%CI]: 3.35 [0.16 to 71.50]**** DPM-CF-302 (Aitken 2012)* Need for intravenous antibiotics for pulmonary exacerbations People needing additional IV antibiotics at 4 months follow-up (n/N): Mannitol: 63/177 vs control: 60/118. Risk ratio [95% CI]: 0.70 [0.54 to 0.91] People needing additional IV antibiotics at 6 months follow-up (n/N): Mannitol: 102/184 vs control: 74/121. Risk ratio [95% CI]: 0.91 [0.75 to 1.10] FEV1 % predicted Mean difference (SE) [95% CI] in change from baseline in FEV1 % predicted at 2 months, Mannitol (n=184) vs control (n=121): 3.89 (1.81) 3.89 [0.34, 7.44] Mean difference (SE) [95% CI] in change from baseline in FEV1 % predicted at 4 months, Mannitol (n=184) vs control (n=121): 2.34 (2.04) [-1.66, 6.34] Mean difference (SE) [95% CI] in change from baseline in FEV1 %	dose mannitol control administered as capsules identical in taste and appearance and with identical methods of administration. Pharmaxis confirmed blinding of investigators and study staff including statisticians and all outcome assessors. Incomplete outcome data (attrition bias): Low risk (Higher dropout rate with mannitol, 17% versus 12% for control, for adverse events and other reasons e.g. withdrawal of consent. However, paper provides flow diagram with timing and reasons for drop out and which group the participants were in. Sensitivity analyses conducted by Pharmaxis (methods of imputation of missing data for withdrawals) showed a consistent treatment effect in favour of mannitol andno change to conclusions)) Selective reporting (reporting bias): Low risk (Limited information was reported in the study publication; particularly HRQoL and lung function)

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	washout between screening and baseline visits Significant episode of haemoptysis (>60mL) in the three months prior to enrolment Have had a myocardial infarction, cerebral vascular accident, major ocular, chest or brain surgery in the 3 months prior to enrolment Known cerebral, aortic or abdominal aneurysm Female subjects currently breast feeding or pregnant or using unreliable form of contraception if at risk of pregnancy) Participation in another investigative drug study parallel to, or within 4 weeks of study entry Known allergy to Bronchitol Use of beta-blockers Uncontrolled hypertension – systolic BP >190 and/or diastolic BP >100 Condition or situation which in the			predicted at 6 months, Mannitol (n=184) vs control (n=121): 4.55 (2.03) [0.57, 8.53] Time to next exacerbation at 26 weeks** Hazard ratio [95% CI] for time to first protocol defined pulmonary exacerbation, Mannitol (n=184) v s control (n=121): 0.74 [0.41, 1.32]. log [hazard ratio] (SE): -0.3011 (0.2953) Quality of life Mean (SD) change in quality of life - respiratory at 4 months follow-up: Mannitol (n=164): -0.1 (17.58) vs control (n=114): 3.8 (21.89). Mean difference [95% CI]: -3.90 [-8.74, 0.94] Mean (SD) change in quality of life - vitality at 4 months follow-up: Mannitol (n=115): -1.9 (17.94) vs control (n=80): 5.4 (15.81). Mean difference [95% CI]: 3.50 [-1.27, 8.27] Mean (SD) change in quality of life - physical at 4 months follow-up: Mannitol (n=164): -0.1 (18.17) vs control (n=114): 2.3 (16.53). Mean difference [95% CI]: -2.40 [-6.52, 1.72] Mean (SD) change in quality of life - emotion at 4 months follow-up: Mannitol (n=164): 0.3 (14.35) vs control (n=114): 2.9 (12.64). Mean difference [95% CI]: -2.60 [-5.79, 0.59]	Additional data were provided by Pharmaxis on request for all primary outcomes of this review and many secondary outcomes Other bias: High risk (Participants underwent a mannitol tolerance test at screening; those who failed the test or in whom the test was incomplete were not entered into the study and thus, the participant population included only those with CF who passed the tolerance test and not all potential participants with CF. Sponsored by manufacturer of mannitol (Pharmaxis); authors or study staff worked for Pharmaxis or had financial interest). *Information on risk of bias extracted from Nolan 2015 Cochrane SR Other information

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	Investigator's opinion may put the subject at significant risk, may confound results or may interfere significantly with the subject's participation in the study MTT test positive or incomplete			Mean (SD) change in quality of life - eating at 4 months follow-up: Mannitol (n=164): -1.6 (17.29) vs control (n=114): -3.3 (16.39). Mean difference [95% CI]: 1.70 [-2.31, 5.71] Mean (SD) change in quality of life - health at 4 months follow-up: Mannitol (n=115): -0.1 (16.22) vs control (n=80): -1 (17.52). Mean difference [95% CI]: 0.90 [-3.95, 5.75] Mean (SD) change in quality of life - social at 4 months follow-up: Mannitol (n=164): -1.6 (13.66) vs control (n=114): 0.2 (15.55). Mean difference [95% CI]: -1.80 [-5.34, 1.74] Mean (SD) change in quality of life - body at 4 months follow-up: Mannitol (n=164): -2 (21.75) vs control (n=113): 1.5 (21.39). Mean difference [95% CI]: -3.50 [-8.66, 1.66] Mean (SD) change in quality of life - role at 4 months follow-up: Mannitol (n=115): -0.9 (13.93) vs control (n=79): -0.8 (17.33). Mean difference [95% CI]: -0.10 [-4.69, 4.49] Mean (SD) change in quality of life - weight at 4 months follow-up: Mannitol (n=115): 2 (32.23) vs control (n=80): 4.6 (27.94). Mean difference [95% CI]: -2.60 [-11.10, 5.90] Mean (SD) change in quality of life - digestion at 4 months	

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				follow-up: Mannitol (n=164): 0.1 (16.58) vs control (n=114): 2.1 (21.36). Mean difference [95% CI]: -2.00 [-6.67, 2.67] Mean (SD) change in quality of life - respiratory at 6 months follow-up: Mannitol (n=154): -1.4 (20.16) vs control (n=110): 5.6 (22.51). Mean difference [95% CI]: -7.00 [-12.28, -1.72] Mean (SD) change in quality of life - vitality at 6 months follow-up: Mannitol (n=107): -1.6 (20.48) vs control (n=76): -4.2 (17.72). Mean difference [95% CI]: 2.60 [-2.96, 8.16] Mean (SD) change in quality of life - physical at 6 months follow-up: Mannitol (n=155): -1.7 (18.85) vs control (n=110): 1.1 (18.2). Mean difference [95% CI]: -2.80 [-7.31, 1.71] Mean (SD) change in quality of life - emotion at 6 months follow-up: Mannitol (n=155): 0.4 (15.34) vs control (n=109): 2.1 (12.84). Mean difference [95% CI]: -1.70 [-5.11, 1.71] Mean (SD) change in quality of life - eating at 6 months follow-up: Mannitol (n=155): 155 -0.4 (18.37) vs control (n=110): -1.4 (17.3). Mean difference [95% CI]: 1.00 [-3.34, 5.34] Mean (SD) change in quality of life - health at 6 months follow-up: Mannitol (n=107): -1.5 (17.61) vs control (n=77): -0.9	

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				(18). Mean difference [95% CI]: -0.60 [-5.82, 4.62] Mean (SD) change in quality of life - social at 6 months follow-up: Mannitol (n=155): 3.3 (16.99) vs control (n=110): 0.9 (16.23). Mean difference [95% CI]: -4.20 [-8.24, -0.16] Mean (SD) change in quality of life - body at 6 months follow-up: Mannitol (n=155): 0.4 (20.29) vs control (n=109): 2.9 (20.86). Mean difference [95% CI]: -2.50 [-7.55, 2.55] Mean (SD) change in quality of life - role at 6 months follow-up: Mannitol (n=106): -2.3 (17.35) vs control (n=76): 1.1 (13.83). Mean difference [95% CI]: -3.40 [-7.94, 1.14] Mean (SD) change in quality of life - weight at 6 months follow-up: Mannitol (n=106): 4.1 (33.71) vs control (n=77): 7.8 (29.07). Mean difference [95% CI]: -3.70 [-12.83, 5.43] Mean (SD) change in quality of life - digestion at 6 months follow-up: Mannitol (n=154): 1.4 (20.47) vs control (n=110): 2.8 (23.48). Mean difference [95% CI]: -1.40 [-6.85, 4.05] Adverse events: Adverse events: haemoptysis (mild) (n/N) at 6 months: Mannitol: 3/184) vs control:	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				0/121. Risk ratio: 1.00 [0.10, 10.29] Adverse events: haemoptysis (moderate) (n/N) at 6 months: Mannitol: 1/184) vs control: 0/121. Risk ratio: 1.98 [0.03, 131.35] Adverse events: haemoptysis (severe) (n/N) at 6 months: Mannitol: 2/184) vs control: 0/121. Risk ratio: 3.30 [0.06, 176.31] Bilton 2011 and Aitken 2012 (data pooled by Cochrane SR Nolan 2015 across two studies, subgroup analysis by age): FEV1 % predicted in children and young people (N=258): Mean difference [95% CI] in FEV1 % predicted at 2 months, Mannitol vs control: 2.64 [-0.73 to 6.02] Mean difference [95% CI] in FEV1 % predicted at 4 months, Mannitol vs control: 1.34 [-2.42 to 5.10] Mean difference [95% CI] in FEV1 % predicted at 6 months, Mannitol vs control: 3.03 [-0.78 to 6.84] FEV1 % predicted in adults (N=317): Mean difference [95% CI] in FEV1 % predicted at 2 months,	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Mannitol vs control: 3.72 [0.82 to 6.64] Mean difference [95% CI] in FEV1 % predicted at 4 months, Mannitol vs control: 4.23 [0.98 to 7.48] Mean difference [95% CI] in FEV1 % predicted at 6 months, Mannitol vs control: 5.74 [2.36 to 9.13] Number of children and young people with protocol defined exacerbations at 6 months, mannitol (n=154***) vs control (n=105***), risk ratio [95% CI]: 0.62 [0.35 to 1.09] Number of adults with protocol defined exacerbations at 6 months, mannitol (n=207***) vs control (n=134***), risk ratio [95% CI]: 0.76 [0.52 to 1.13] Adverse events: haemoptysis in children and young people, mannitol (n=154***) vs control (n=105***), risk ratio [99%CI]: 5.48 [0.36 to 82.41], risk ratio [95%CI]: 5.48 [0.69 to 43.50]**** Adverse events: haemoptysis in adults at 6 months, mannitol (n=207***) vs control (n=134***), risk ratio [99% CI]: 1.83 [0.46 to 7.28], risk ratio [95%CI]: 1.83 [0.64 to 5.23]****	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				*Results extracted from Nolan 2015 Cochrane SR. ** Follow-up identified from primary study *** Number of participants identified from primary studies **** 95% CI calculated by the NGA technical team	
Full citation Skov, M., Pressler, T., Lykkesfeldt, J., Poulsen, H. E., Jensen, P. T., Johansen, H. K., Qvist, T., Kraemer, D., Hoiby, N., Ciofu, O., The effect of short-term, high-dose oral N-acetylcysteine treatment on oxidative stress markers in cystic fibrosis patients with chronic P. aeruginosa infection - A pilot study, Journal of Cystic Fibrosis, 14, 211-218, 2015 Ref Id 360293	Sample size N=21 Characteristics Gender: 12 males and 9 females Median age: 39 years (range 25–61 years) Baseline lung function of the patients in the NAC group was FEV1 (% predicted) mean (95% CI) 58.36% (46.26; 70.46) and of the patients in the control group 53.7% (37.6; 69.8). Inclusion criteria Adult patients with confirmed CF with chronic P. aeruginosa lung infection, at the end of a two-week intravenous antibiotic treatment. Exclusion criteria Hypersensitivity to N-acetyl cysteine, prior	Interventions NAC in a mean dose of 36 mg/kg/day (max 59 mg/kg/day and min 25.8 mg/kg/day). Duration: 4 weeks Comparison: Control group (no placebo)	Details Design: open-label, controlled, RCT Method of randomization: not reported Allocation concealment: not reported Blinding: open trial Procedure: the control group did not receive placebo medication and was therefore aware of the group to which they were assigned. Patients in the NAC group received oral treatment with N-acetylcysteine, tablets of 600 mg effervescent (Mucolysin ®600 produced by Sandoz A/S), 2 tablets twice a day (a	Results Change in FEV1 % predicted mean (95% CI) Intervention: +2.11 (−1.44; 5.66) Control: −1.4 (−4.7; 1.9)	Limitations Assessed with risk of bias Cochrane tool: Random sequence generation (selection bias): Unclear risk (method not reported) Allocation concealment (selection bias): Unclear risk (not reported) Blinding (performance bias and detection bias): high risk (open trial) Incomplete outcome data (attrition bias): Low risk (Intention-to-treat analysis was carried out) Selective reporting (reporting bias): low risk Other bias: Low risk (None identified) Other information None

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Denmark Study type Open-trial RCT Aim of the study This study was intended as a pilot study enabling proper power calculations necessary for number of CF patients to be included in a larger phase II clinical study in CF patients. Study dates March 2011 to August 2013 Source of funding The Mucolysin tablets were kindly provided by Sandoz A/S. The Novo Nordisk Foundation supported HKJ as a clinical research stipend.	lung transplantation or if on lung transplant waiting list Patients who received NAC in the last 30 days, patients with recent hemoptysis or an abnormal liver function test (ALAT) more than twice the normal range (10–70 U/L).		total daily dose of 2400 mg) for 4 weeks. All other medication was continued, including inhalation with pulmozyme, bronchodilators with β2 agonists and colistin and per oral treatment with ciprofloxacin and azithromycin. Analysis: not reported. Two of the patients belonging to the NAC group did not complete the trial (1 due to adverse events 1 due to lack of compliance). These two patients were excluded from the final analysis, thus the effect of the treatment with NAC was evaluated in 9 CF patients compared to 10 CF controls.		