NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Mannitol dry powder for inhalation for the treatment of cystic fibrosis

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List of abbreviations

Ab	Antibiotics
ABPI	Association of the British Pharmaceutical Industry
ACD	Appraisal Consultation Document
AE	Adverse event
ANCOVA	Analysis of covariance
ATC	Anatomical Therapeutic Chemical Classification System
Bcc	Burkholderia cepacia complex
BD	Bi-daily
BMI	Body mass index
BOCF	Baseline observation carried forward
BP	Blood pressure
BSC	Best Supportive Care
BTPS	Body temperature, ambient pressure, saturated with water vapour
CF	Cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire – Revised
CFRD	Cystic fibrosis related diabetes
CFTR	Cystic fibrosis transmembrane conductance regulator
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CRD	Centre for Reviews and Dissemination
DBP	Double Blind Phase
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ERG	Evidence Review Group
FAD	Final Appraisal Determination
FEF	Forced Expiratory Flow
FEV1	Forced Expiratory Volume in the first second
FVC	Forced Vital Capacity
GP	General practitioner
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQoL	Health related qualify of life
HS	Hypertonic saline
HTA	Health Technology Assessment
HUI	Health Utility Index
ICER	Incremental cost-effectiveness ratio

ITT	Intention-to-treat
I.v.	Intravenous
IVRS	Interactive Voice Response System
LOCF	Last observation carried forward
LoQ	List of questions
LSmean	Least Squares mean
LYG	Life years gained
MAA	Marketing Authorisation Application
MAR	Missing at random
MCID	Minimal Clinically Important Difference
MMRM	Mixed model repeated measures
MRSA	Methicillin-resistant Staphylococcus aureus
MTT	Mannitol Tolerance Test
NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Clinical Excellence
NS	Not significant
OD	Once daily
OLEP	Open Label Extension Phase
OLP	Open Label Phase
PA	Pseudomonas aeruginosa
PbR	Payment by Results
PCT	Primary Care Trust
PDPE	Protocol defined pulmonary exacerbations
PE	Pulmonary Exacerbations
PEF	Peak Expiratory Flow
PEFR	Peak Expiratory Flow Rate
PFTs	Pulmonary Function Tests
PP	Per-protocol
Pred	Predicted
PRO	Patient reported outcome
PSS	Personal Social Services
QALY	Quality-adjusted life year
QoL	Quality of Life
QWB	Quality of well-being
RCTs	Randomized Control Trials
Resp	Respiratory
rhDNase	Recombinant Human Deoxyribonuclease
RR	Relative risk
RTI	Respiratory tract infection

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SMC	Scottish Medicines Consortium
SOC	System Organ Class
SP	Safety population
SPC	Summary of Product Characteristics
STA	Single Technology Appraisal
TGA	Therapeutics Goods Administration
TIS	Tobramycin inhalation solution
Tx	Treatment
UK	United Kingdom
US	United States
USA	United States of America
VAT	Value Added Tax
VIF	Variance inflation factors
WHO	World Health Organization
WTP	Willingness to pay

Executive summary

Bronchitol™ (mannitol dry powder for inhalation) is an inhaled non-ionic osmotic, mucolytic agent designed to improve lung function by correcting the impaired mucociliary clearance characteristic of cystic fibrosis (CF). Bronchitol is administered by inhalation with a hand-held, breath activated device.

The marketing authorisation application (MAA) for Bronchitol was submitted by Pharmaxis via the centralised procedure in October 2009 and approval is expected in the third quarter of 2011.

The current proposed indication Pharmaxis have sought approval for is as follows:

- Bronchitol is indicated for the treatment of cystic fibrosis (CF) in adults aged 18 years and above as an add-on therapy to rhDNase, and in patients ineligible, intolerant, or inadequately responsive to rhDNase.*

Cystic fibrosis (CF) is an autosomal recessive transmitted fatal disease characterised by food malabsorption, steatorhoea, growth failure and pulmonary infection. Defect in the CF gene leads to decreased mucociliary transport resulting in a vicious circle of phlegm retention, infection, and inflammation. Pulmonary symptoms of CF include a chronic or persistent cough that is productive of purulent and/or bloody sputum, dyspnea, wheezing, and chest pain. Today, lung disease is the major cause of morbidity and mortality in CF. In more than 90% of CF patients chronic pulmonary infection is the cause of death.

Bronchitol is encapsulated in a size 3 hard gelatine capsules as 40 mg of spray-dried mannitol powder for inhalation with no excipients. The recommended dose of Bronchitol is 400 mg (i.e., 10 capsules) twice daily. Bronchitol is available as an initiation pack free of charge which includes 10 capsules and one inhaler device to be used for the first dose. In addition, Bronchitol is also available as a 14 day carton of 280 capsules and 2 inhaler devices. The cost of a 14 day carton pack is expected to be around £236.25.

Clinical evidence of Bronchitol comes primarily from two large pivotal double blind randomised controlled studies (DPM-CF-301 and DPM-CF-302). These studies were conducted with patients aged 7 years or older but included a high proportion of adult patients (DPM-CF-301: n=18 46.2%; DPM-CF-302: n=19, 39.6%), the target patient group for this submission.

Both studies assessed the incremental effect of Bronchitol 400mg BD in addition to best supportive care, with or without concurrent rhDNase use. Bronchitol was shown to significantly improve lung function over 26 weeks in patients with CF measured by change in FEV_1 from baseline. The positive effect of Bronchitol was already evident after 6 weeks of treatment and was maintained over the 26 week double blind phase. Responders are defined as patients

* The indication granted to Bronchitol is: “Bronchitol is indicated for the treatment of cystic fibrosis in adults aged 18 years and above as an add-on therapy to best standard of care”.

achieving ≥5% relative improvement in FEV_1 or an absolute improvement of ≥100 ml in FEV^1 measured at the 6 week-visit. Only those patients satisfying the definition of a responder are to continue with this treatment.

The rate of pulmonary exacerbations and associated antibiotic treatment was numerically reduced with Bronchitol treatment independent of concomitant rhDNase use. The consistency and effect size strongly suggest a meaningful effect of Bronchitol although statistical significance was not achieved.

Overall, the use of Bronchitol in the overall population (which included adult patients) shows positive results for Bronchitol therapy over Control and these effects were seen regardless of concomitant rhDNase use. Analyses of the key outcomes measures based on the target patient population of adult patients showed results which were very consistent with those of the overall study population; therefore, the conclusions drawn from the overall population appear to hold for the adult only population and Bronchitol treatment shows significant advantages in terms of pulmonary measures in both studies.

Open label extension phase data showed that there was a sustained clinically relevant improvement in FEV_1 for at least 18 months in patients receiving Bronchitol. Patients that switched from the control group to Bronchitol 400mg BD in the open label phase showed a similar improvement in FEV_1 and in exacerbation rates as that seen in the Bronchitol group during the double blind phase. These results held regardless of rhDNase use and were also seen in the adult only population.

In the safety evaluations of the pivotal trials, the most common treatment emergent adverse events were condition aggravated (CF exacerbation), cough, headache and pharyngolaryngeal pain.

Overall, these data show that Bronchitol is an effective treatment for patients with CF in addition to best supportive care and regardless of rhDNase use.

The cost-effectiveness of Bronchitol in adults with CF was compared with best supportive care. Best supportive care involves multiple medications and drug therapy. These often include inhaled antibiotics, anti-inflammatory agents, bronchodilators, vitamin supplements, pancreatic enzymes and antidiabetic agents for patients with diabetes. Bronchitol was trialled on top of these standard therapies and, as there were limited restrictions on the co-medications or treatment provided in the study, the Control arm can be considered as best supportive care in a real world setting.

For the purposes of this submission a de novo economic evaluation was conducted with the aim of investigating the impact of Bronchitol treatment on costs and outcomes in the adult CF population. The chosen structure of the model was a patient-level simulation model. Bronchitol was compared to best supportive care either as mono-therapy or as add-on therapy to rhDNase. The base case results are shown inTable 1.

Table 1 Base-case cost-effectiveness results

	Bronchitol	Control	Bronchitol + rhDNase	Control + rhDNase
Technology acquisition cost	38,498	0	112,433	69,284
Other costs	173,425	180,188	173,425	180,188
Total costs	211,923	180,188	285,858	249,472
Difference in total costs	N/A	31,735	N/A	36,386
LYG	12.10	11.40	12.10	11.40
LYG difference	N/A	0.70	N/A	0.70
QALYs	10.52	9.75	10.52	9.75
QALY difference	N/A	0.77	N/A	0.77
ICER	N/A	41,074	N/A	47,095

LYG, life years gained; QALY(s), quality-adjusted life year(s); ICER, incremental cost-effectiveness ratio

Section A – Decision problem

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Bronchitol™ (mannitol dry powder for inhalation) is a non-ionic osmotic, mucolytic agent that acts by inducing an influx of water into the airway lumen improving hydration of airway secretions, and increasing mucociliary clearance by reducing its viscosity and stimulating cough. Mannitol dry power is administered by inhalation with a hand-held, breath activated device.

WHO have assigned a new ATC code which classifies mannitol as a mucolytic agent RO5CB16.

1.2 What is the principal mechanism of action of the technology?

Bronchitol is an inhaled hyperosmotic medicinal product designed to improve lung function by correcting the impaired mucociliary clearance that is characteristic of cystic fibrosis. While the exact mechanism of action is unknown, inhaled mannitol is known to change the viscoelastic properties of mucus, increase the hydration of the periciliary fluid layer and contribute to increased mucociliary and cough clearance of the retained secretions. It can therefore be considered both mucoactive and mucolytic. The overall increase in mucociliary clearance improves lung function and reduces subsequent inflammation and infection.

Osmotic agents such as mannitol act on the underlying primary mechanism of mucociliary dysfunction rather than on secondary effects such as inflammation or infection and potentially represent a major advance for cystic fibrosis treatment. Mannitol was specifically selected because:

- It has a low molecular weight and can be formulated to deliver a high osmotic load in a relatively low dose.
- It is stable and non hygroscopic allowing formulation as a respirable dry powder that can be delivered in 2-5 minutes.
- Unlike other sugars or salts such as lactose or sodium chloride it crosses the intact epithelial barrier only very slowly and as such has a prolonged osmotic effect[1,2].

The above features are designed to confer advantages in both efficacy and ease of use compared to osmotic agents that take 20 minutes to be delivered by nebuliser and are rapidly absorbed through the hyperactive sodium channels that are a feature of CF airways[2].

Bronchitol has a different mode of action to rhDNase, which reduces the viscoelasticity of airway secretions by catalysing the hydrolytic cleavage of phosphodiester linkages in the DNA

backbone. RhDNase is an effective mucolytic but unlike Bronchitol has not been shown to increase mucociliary clearance.

There is therefore the potential for the two drugs to work together.

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Bronchitol does not have a UK marketing authorisation for the treatment of cystic fibrosis. Pharmaxis submitted a European Marketing Authorisation Application (MAA) via the centralised procedure for Bronchitol in October 2009. Approval is expected in the third quarter of 2011.

The inhalation device to be used and packed with the inhaled dry powder mannitol capsules is the high resistance RS01 Inhaler Model 7 from Plastiape S.p.A. The device is a Class I CE-marked device, with a conformity declaration of 10th June 2004.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the licence).

The marketing authorisation application (MAA) for Bronchitol was submitted by Pharmaxis via the centralised procedure in October 2009 and the CHMP Day 120 list of questions (LoQ) was received in March 2010. Pharmaxis submitted responses to this LoQ in July 2010 and await further feedback from the CHMP at the Day 180 clockstop. The main issues described here are those raised by the CHMP in the Day 120 LoQ.

The current proposed indication Pharmaxis have sought approval for is as follows:

- Bronchitol is indicated for the treatment of cystic fibrosis (CF) in adults aged 18 years and above as an add-on therapy to rhDNase, and in patients ineligible, intolerant, or inadequately responsive to rhDNase[†].

The indication sought differs from the population studied in DPM-CF-301 as this is focused on the adult (≥18 year) population. The paediatric population (aged 6-17 years) was excluded from the indication as the CHMP indicated that the benefit risk was difficult to assess at this time. This was due to the apparent efficacy noted with the (50mg) sub-therapeutic control which led the CHMP to question the ability to determine the safety of Bronchitol in this population when compared with control. This was not an issue for the adult population as data from both DPM-

[†] The indication granted to Bronchitol is: “Bronchitol is indicated for the treatment of cystic fibrosis in adults aged 18 years and above as an add-on therapy to best standard of care”.

CF-301 and DPM-CF-302 studies suggest that mannitol 50 mg is sub-therapeutic in this age group. Therefore the safety profile of Bronchitol, (mannitol 400 mg) BD can be assessed in the adult population as compared with the control group (50 mg mannitol).

Pharmaxis accepted that the determination of the benefit/risk in the 6-17 year age group is problematic due to the apparent control effect, despite there being a meaningful improvement from baseline with 400mg BD The population of children studied continue to have an important unmet need evidenced by impaired lung function (<90% predicted) at an early age placing these children in a population facing more rapid decline[3]. Pharmaxis intends to apply for an indication in younger patients in due course.

The CHMP queried the clinical relevance of the results due to the high drop-out rate noted in study DPM-CF-301. Pharmaxis performed multiple sensitivity analyses which demonstrated that the data and method of analysis are consistent, robust and not subject to introduction of any bias as a result of the high rate of dropouts. Further, the withdrawal of substantial numbers of patients in DPM-CF-301 does not appear linked to the overall acceptability of mannitol treatment in the majority of patients. The dropout rate in this study had no impact on the validity of the primary endpoint (change in FEV_1) and study outcomes.

The CHMP also queried the acceptability of Bronchitol to patients. Pharmaxis clarified that compliance was favourable in the DPM-CF-301 trial; 83.6% patients were acceptably compliant (≥ 60% compliance), and 64% of patients' compliance was at a level of 80% or more. Furthermore, the high proportion of patients (86%) who completed the six month study and subsequently elected to continue in to the open label phase of study DPM-CF-301 provides evidence of patient acceptance of inhaling 10 capsules of 40 mg mannitol twice a day. Although time consuming compared to some common asthma medications, inhaled mannitol is a significant advance over nebulised therapy for patients with CF, in overall ease of use, with relatively minimal additional burden. Evidence based on The Cystic Fibrosis Questionnaire – Revised (CFQ-R) which was used to assess the burden of treatment demonstrated that no meaningful change in treatment burden in either active or control arms resulting from the need to inhale the contents of 10 capsules twice daily.

As Bronchitol is an orphan designated product for the treatment of cystic fibrosis, the significant benefit of this treatment has been assessed in relation to rhDNase, the current approved mucolytic of choice. The demonstration of significant benefit with Bronchitol has been made for patients who were taking rhDNase (users) and for those whom rhDNase was unsuitable due to treatment ineligibility, tolerability issues or lack of efficacy (non-users).

The CHMP questioned efficacy noted in the rhDNase non-user population and also whether the non-user population described in the DPM-CF-301 study was appropriate. Pharmaxis acknowledged that the non-user population included in DPM-CF-301 was a broader cohort than the non-user population described in the original indication. Therefore a retrospective evaluation of benefit/risk in a defined non-user group in whom rhDNase use was unsuitable in study DPM-CF-301 was performed. Bronchitol has been shown to be a safe and well tolerated product in

this population over one year of use and the effect size estimate over 26 weeks in this defined subgroup (n=68) was 65.01 mL (p=0.056) and in adults (n=44) was 105.74 mL (p=0.032), this data strongly supports a positive benefit/risk profile for the proposed Bronchitol indication.

A further concern was raised by the CHMP regarding the potential deleterious effects of the combination of Bronchitol with rhDNase. However, Pharmaxis clarified that the rhDNase user population had more severe CF disease at baseline compared with non-users with lower mean % predicted FEV1 (58.7% versus 66.1% respectively). Baseline medical histories, concomitant medication use and exacerbation rates also indicated that rhDNase users had more severe disease. Hence, this subgroup was more likely to have a higher rate of adverse events (AE's) during the study. Due to this imbalance at baseline Pharmaxis clarified that it was not appropriate to compare rhDNase users with non-users. Furthermore, when compared against control, the safety profile of the Bronchitol treatment group is similar irrespective of rhDNase use.

In terms of the overall safety profile, the type and frequency of AEs in study DPM-CF-301 is consistent with the disease state and disease severity in cystic fibrosis patients. Overall there were no AEs of significant concern and the benefit risk profile is positive. Pharmaxis is investigating the collection of long term safety data via the UK CF Registry as one component of the risk management activities Pharmaxis will undertake for Bronchitol.

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

The proposed indication for Bronchitol is the following: "Bronchitol is indicated for the treatment of cystic fibrosis in adults aged 18 years and above as an add-on therapy to rhDNase and in patients ineligible, intolerant or inadequately responsive to rhDNase"[‡].

Pharmaxis intends to apply for an indication in younger patients in due course.

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

An open label extension (26 weeks) of long-term study DPM-CF-302, which is assessing efficacy and safety of Bronchitol in CF patients is currently ongoing in North America (United States of America (USA) and Canada). The last patient visit for this trial is planned for October 2010 and top line results will be available in December 2010.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

[‡] The indication granted to Bronchitol is: "Bronchitol is indicated for the treatment of cystic fibrosis in adults aged 18 years and above as an add-on therapy to best standard of care".

It is anticipated that Bronchitol will become available in the UK in October 2011 depending upon regulatory approval.

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

Regulatory approval has not been obtained outside the UK for Bronchitol.

Pharmaxis Pharmaceuticals Limited has filed for a European Marketing Authorisation via the centralised procedure for Bronchitol that will cover the 27 EU countries, Iceland, Liechtenstein, and Norway.

In addition, an MAA for Bronchitol in the treatment of CF was submitted to the Therapeutics Goods Administration (TGA) in Australia on the 15th of December 2009.

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

Scottish Medicines Consortium intends to appraise Bronchitol imminently. Appraisal is planned to be started in the first quarter of 2011.

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table 2 Unit costs of technology being appraised

Pharmaceutical formulation	*Bronchitol is encapsulated in a size 3 hard gelatine capsules as 40 mg of spray-dried mannitol powder for inhalation with no excipients.*
Acquisition cost (excluding VAT)	*The cost for 14 day carton of 280 capsules and 2 inhaler devices is expected to be around £236.25*.* *The initiation dose carton which contains 10 capsules and one inhaler device will be free of charge.*
Method of administration	*Inhalation*
Doses	*The recommended dose of Bronchitol is 400 mg*
Dosing frequency	*Twice a day*
Average length of a course of treatment	*Lifetime*
Average cost of a course of treatment	*Average daily cost (800 mg) is expected to be around £16.88.*
Anticipated average interval between courses of treatments	*N/A*
Anticipated number of repeat courses of treatments	*Treatment is for a chronic condition and is likely to be continuous*
Dose adjustments	*N/A*

** The NICE Single Technology Appraisal process triggered for Bronchitol precedes marketing authorization approval expected early next year. Pharmaxis has provided tentative costs of Bronchitol however the final acquisition costs are contingent on the final label text approved by EMA.*

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Cost of the inhaler device is included in the unit cost of Bronchitol.

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

In clinical practice, before commencing treatment with Bronchitol, all patients should be assessed for bronchial hyperresponsiveness to mannitol during administration of their initiation dose (10 capsules). The initial dose assessment entails 6 steps where lung function measurements are performed, so the patient is monitored whilst an increasing dose of Bronchitol up to 400 mg is inhaled.

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

The need for routine monitoring is not above usual practice for cystic fibrosis patients.

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

A bronchodilator must be administered 5-15 minutes before Bronchitol is used. Bronchitol inhalation is recommended before physiotherapy. The use of bronchodilators followed by physiotherapy is amongst the most frequently used therapies in patients with cystic fibrosis. Improving airway patency before physiotherapy may help in the clearance of secretions from the chest. Bronchodilators may be given before physiotherapy for this reason.

2 Context

In this background section the manufacturer or sponsor should contextualise the evidence relating to the decision problem.

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

Cystic fibrosis (CF) is an autosomal recessive transmitted fatal disease characterised by food malabsorption, steatorhoea, growth failure and pulmonary infection. The CF gene defect leads to an absent or malfunctioning CFTR protein, which results in abnormal chloride conductance on the apical membrane of the epithelial cell. In the lung this results in airway surface liquid depletion and, since airway surface liquid is essential to support ciliary stability and functioning, ciliary collapse and decreased mucociliary transport. The consequence of this is a vicious circle of phlegm retention, infection, and inflammation.

Pulmonary symptoms of CF include a chronic or persistent cough that is productive of purulent and/or bloody sputum, dyspnea, wheezing, and chest pain. Today, lung disease is the major cause of morbidity and mortality in CF. In more than 90% of CF patients chronic pulmonary infection is the cause of death.

Key aim in management of CF is clearance of airways from thickened sticky mucus thereby reducing the risk of infections and exacerbations and improving lung function.

2.2 How many patients are assumed to be eligible? How is this figure derived?

According to the Annual Data Report of UK CF Registry in 2008[4] the total number of adult patients diagnosed with CF and receiving treatment in the UK was 3651. The UK CF Registry tracks the health of people with Cystic Fibrosis throughout the UK. Clinical Data is collected in specialist CF Centres and network shared care clinics at the patient's Annual Review. According to CF Registry total number of CF patients was 8513. This registry includes CF patients from centres in Scotland and Northern Ireland who correspond to approximately 17.5% of all patients in the registry. Overall, 56% of UK CF Registry patients were aged over 16 years old and 44% over 20 years old. Using these cut-off numbers we estimated that approximately 52% of all patients were over 18 years old, i.e., 4427 patients in the UK. When adjusting this number for patients from centres in England and Wales only, the total number of CF adults is 3651.

2.3 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

Currently there are no NICE Guidelines for the treatment of cystic fibrosis.

2.4 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

In CF patient management is an integrated approach of prevention and symptomatic treatment. Multidisciplinary care for CF patients is considered essential.

Standards of care and guidelines for treatment include the following as part of standard treatment and best supportive care: pancreatic enzymes, antidiabetic agents for patients with diabetes, vitamin supplements, anti-inflammatory agents, inhaled bronchodilators, antibiotics and agents that assist in mucus clearance[5].

Airway-clearance therapies represent an important part of care of CF patients. Most patients have increased airway secretions, and enhancing mucus clearance with physical techniques (for example active cycle of breathing, positive pressure, and autogenic drainage) is a major goal of therapy.

The most common strategies are chest physiotherapy, or percussion and postural drainage, high-frequency chest-wall compression using an inflatable vest connected to an air compressor, hand-held expiratory vibratory devices, and acoustic waves to vibrate the mucus from the airway walls.

Airway clearance therapies are supported pharmacologically through different approaches: rhDNase reduces the viscoelasticity of airway secretions and improves their clearance; rehydration therapies increase the volume of airway surface liquid through osmotic forces thereby improving mucociliary clearance. Aerosolised antibiotics are used both for eradication of initial infection and for suppression of the chronic infection of the lung with P. aeruginosa.

Bronchitol would potentially provide an alternate or supplemental agent to other therapeutic or physical therapies for inducing airway clearance, leading to improved lung function, reduced rate of pulmonary exacerbations and associated antibiotic treatment.

2.5 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

Despite all progress in CF treatment over the last decades, CF still remains a fatal disease and life expectancy is still unacceptably short. The predicted median life span in 2009 was 37.4 years[6]; mean age at death in the UK was 27 in 2008[7].

Due to improved treatment, CF patients are able and wish to lead a productive life. This is at odds with the complex and time consuming treatment causing substantial burden.

The complexity and amount of time for daily treatment routines lead to non-adherence and subsequently to a deterioration of lung function. Several studies indicate a 30–70% therapeutic adherence in cystic fibrosis[8,9,10,11,12]. Adherence worsens with age and disease severity[13]. Non compliance in the treatment of patients with CF can lead to direct costs to the patient in terms of reduced quality of life and places pressure on healthcare systems because non-compliant patients may experience worsening of their condition and require more costly interventions.

Treatments currently used in CF have proven their value in clinical practice. However, a strong evidence base from rigorous controlled clinical trials is lacking to provide clear guidance on management of patients with cystic fibrosis. The issue of insufficient data to support use of current therapies especially for a long-term treatment of CF is described in literature, including several systematic reviews[14,15,16,17].

2.6 Please identify the main comparator(s) and justify their selection.

Current patient management involves the use of multiple therapies such as bronchodilators, steroids, physiotherapy, antibiotics, hypertonic saline and rhDNase.

In line with anticipated label indication of Bronchitol the main comparators would be:

- Best supportive care
- Best supportive care plus rhDNase

Mannitol is expected to work via a different mechanism of action to currently registered and available treatments (rhDNase and inhaled antibiotics) and as such Pharmaxis considers that best supportive care with or without rhDNase is the most applicable and clinically relevant comparator.

Best supportive care involves multiple medications and drug therapy. These often include inhaled antibiotics, anti-inflammatory agents, bronchodilators, vitamin supplements, pancreatic enzymes and antidiabetic agents for patients with diabetes. Bronchitol was trialled on top of these standard therapies and, as there were limited restrictions on the co-medications or treatment provided in the study, the control arm can be considered as best supportive care in a real world setting.

In addition hypertonic saline is used in about 80% of UK CF centres although usage in those centres is limited to the range of only 10-30% of patients[18], the dosages used are often below the 7% strength used in the only long term study, and also the frequency of dosage is normally once a day rather than the twice a day that was trialled. As no study has directly compared Bronchitol to hypertonic saline an assessment has to rely on indirect comparison.

2.7 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

Bronchodilators might be prescribed in case of hyper responsiveness.

2.8 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

The majority of patients are managed from a limited number of regional CF centres. Use of mucolytics is a common practice in the complex CF treatment. Therefore, no additional resources will be needed with regards to Bronchitol. The resource use associated with Bronchitol will mainly be unit cost of the medication.

Key cost drivers in CF management are pulmonary exacerbations and hospitalizations. As the disease progresses, up to 35% of patients with the severe form of the disease require multiple hospitalizations per year[5,19].

Long term value of Bronchitol is the slowdown in disease progression and lower rate of exacerbations, which translates in health gain and cost avoided.

Resource utilisation data were obtained from patient-level data of the double-blind randomised clinical trial DPM-CF-301.

2.9 Does the technology require additional infrastructure to be put in place?

Existing infrastructure will be sufficient and will not need to be changed. Treatment with Bronchitol fits with the current patient management practice in regional CF centres.

3 Equity and equality

NICE considers equity in terms of how the effects of a health technology may deliver differential benefits across the population. Evidence relevant to equity considerations may also take a variety of forms and come from different sources. These may include general-population-generated utility weightings applied in health economic analyses, societal values elicited through social survey and other methods, research into technology uptake in different population groups, evidence on differential treatment effects in different population groups, and epidemiological evidence on risks or incidence of the condition in different population groups.

3.1 Identification of equity and equalities issues

3.1.1 Please specify any issues relating to equity or equalities in NICE guidance, or protocols for the condition for which the technology is being used.

N/A.

3.1.2 Are there any equity or equalities issues anticipated for the appraisal of this technology (consider issues relating to current legislation and any issues identified in the scope for the appraisal)?

There are two issues that may prevent equal access to the technology:

- Once considered a childhood disease, cystic fibrosis is now also a disease of adults. Increased longevity has resulted in the aging of the cystic fibrosis population. Current label of Bronchitol is restricted to adults. In the clinical trials patients 6 years and older were included however as described in section 1.4, the determination of the benefit/risk in the 6-17 year age group is problematic due to the apparent control effect, despite there being a meaningful improvement from baseline at 400mg. The population of children studied continue to have an important unmet need, and Pharmaxis intends to apply for an indication in younger patients in due course.

- It is possible that patients with physical disabilities associated with impaired manual dexterity may find it difficult to load capsules into the inhaler, and might not be able to use Bronchitol without assistance.

3.1.3 How have the clinical and cost-effectiveness analyses addressed these issues?

Clinical analyses are performed on the whole trial population. Results can be additionally separated for paediatric, adolescent and adult populations. The cost-effectiveness analysis is a patient-level simulation Markov model, i.e. the progression of each individual patient is modelled, rather than the progression of a whole patient cohort at once. Data were obtained from patient-level data of the double-blind randomised clinical trials DPM-CF-301 and DPM-CF-302 which as

well as adults includes children aged over 6 years old as defined by the inclusion criteria of these trials. Outcomes will be calculated for various age groups.

There were no patients with physical disabilities included in the clinical trials.

4 Statement of the decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	*People with cystic fibrosis*	*Adults (18 years and above) with cystic fibrosis*	*Current label of Bronchitol is restricted to adults; hence the base case analysis will be performed on adults. The entire population (age 6>) as well as different age groups will be modelled as a separate scenario.*
Intervention	*Mannitol dry powder for inhalation*	*Mannitol dry powder for inhalation.* *Bronchitol is given in addition to best supportive care with or without rhDNAse.*	
Comparator(s)	*The following treatments used alone or in combination with each other:* • *Inhaled mucolytics: rhDNase* • *nebulised hypertonic saline* • *best supportive care (which may include a wide range of inhaled and oral active treatments)*	*The following comparators will be evaluated:* • *rhDNase plus best supportive care* • *best supportive care* • *nebulised hypertonic saline*	
Outcomes	*The outcome measures to be considered include:* • *mortality* • *lung function* • *respiratory symptoms* • *reduction in pulmonary exacerbations* • *exercise tolerance* • *adverse effects of treatment* • *health-related quality of life.*	*The following outcomes will be included:* • *mortality* • *lung function (decline in percentage predicted FEV1)* • *improvement in respiratory symptoms (respiratory domain CFQ-R)* • *rate of pulmonary exacerbations requiring hospitalisation* • *improvement in exercise tolerance (physical domain CFQ-R)* • *adverse effects of treatment* • *health-related quality of life*	
Economic analysis	*The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per*	*In line with the scope the incremental cost per quality-adjusted life year will be*	*To be earmarked as an exacerbation in the DPM-CF-301 and DPM-CF-302 study the patient had to be*

	quality-adjusted life year. *The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.* *Costs will be considered from an NHS and Personal Social Services perspective.* *Resource use should take account of any reduction in pulmonary exacerbations in both the primary and secondary care settings*	*calculated.* *The time horizon will be life-long.* *Costs will be considered from an NHS and Personal Social Services perspective.* *Resource use will be taken from the hospitalisations, hospital visits, community health care visits, and CF-related concomitant medication collected in the DPM-CF-301 and DPM-CF-302 study.*	*hospitalised. The number of exacerbations not requiring hospitalisation is unknown. Thus costs for exacerbations in the primary care setting cannot be identified separately, but will be included in the overall average cost per patient and hence consider any reduction in these exacerbations in the primary care setting.*
Subgroups to be considered	*If evidence allows, subgroups by lung function and prior treatment (including consideration of intolerance to treatments) should be considered.*	*Subgroups by lung function (ppFEV >80; 60-79; 40-59 and <40) will be considered.* *Prior treatment data will be used in the analysis which were collected retrospectively for DPM-CF-301 and prospectively for DPM-CF-302 study specifically for group of patients who were intolerant, failed or were not eligible for treatment with rhDNase.*	
Special considerations, including issues related to equity or equality	*Guidance will only be issued in accordance with the marketing authorisation.* *Details of the components of best supportive care should be clearly described.* *Consideration will be given to people with a disability who may not be able to manipulate inhaler devices.*	*In accordance with the expected marketing authorisation the base case analysis will be performed on adults.* *Best supportive care will reflect the control arm from the two phase III studies.*	*There were no patients with physical disabilities included in the clinical trials. It is expected that that patients with physical disabilities associated with impaired manual dexterity might need assistance in using Bronchitol but not more than with any other current inhaled treatment.*

Section B – Clinical and cost effectiveness

5 Clinical evidence

Summary

- Two large pivotal double blind randomised controlled studies (DPM-CF-301 and DPM-CF-302) were identified which provided relevant data on patients with CF who were treated with Bronchitol. Both studies had a high proportion of adult patients, the target patient group for this submission.
- Both studies assessed the incremental effect of Bronchitol 400mg BD in addition to best supportive care (BSC), with or without concurrent rhDNase use.
- The studies were of high quality and the study designs were very similar.
- Bronchitol was shown to significantly improved lung function over 26 weeks in patients with CF measured by change in FEV_1 from baseline
- The positive effect of Bronchitol was evident over the first 6 weeks of treatment and was maintained over the 26 week double blind phase.
- Additionally, these FEV_1 results showed consistency with the data seen in phase II studies which included adult patients in the study population and the treatment effect of Bronchitol is supported by the results seen in additional spirometry measures.
- The rate of pulmonary exacerbations and associated antibiotic treatment was numerically reduced with Bronchitol treatment independent of concomitant rhDNase use. The consistency and effect size strongly suggest a meaningful effect of Bronchitol although statistical significance was not achieved.
- Overall, the use of Bronchitol in the overall population (which included adult patients) shows positive results for Bronchitol therapy over BSC and these effects were seen regardless of concomitant rhDNase use.
- Analyses of the key outcomes measures based on the target patient population of adult patients showed results which were very consistent with those of the overall study population; therefore, the conclusions drawn from the overall population appear to hold for the adult only population and Bronchitol treatment shows significant advantages in terms of pulmonary measures in both studies
- Open label extension phase data showed that there was a sustained clinically relevant improvement in FEV_1 for at least 18 months in patients receiving Bronchitol. Patients that switched from the control group to Bronchitol 400mg BD in the open label phase showed a similar improvement in FEV_1 and in exacerbation rates as that seen in the Bronchitol group during the double blind phase. These results held regardless of rhDNase use and were also seen in the adult only population.
- In the safety evaluations of the pivotal trials, the most common treatment emergent adverse events were condition aggravated (CF exacerbation), cough, headache and pharyngolaryngeal pain. Haemoptysis occurred more frequently in the Bronchitol group than in the control group.

- Overall, these data show that Bronchitol is an effective treatment for patients with CF in addition to BSC and regardless of rhDNase use. Results seen in the overall study population also apply to the adult only population, the target patient groups for this submission.

5.1 Identification of studies

5.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 9.2, appendix2.

RCTs of Bronchitol as a treatment for patients with cystic fibrosis were identified from the published literature by searching a number of different sources. The first phase search was conducted on the complete cystic fibrosis population in order to identify all data which may be relevant to the adult-only population which is the focus of this appraisal. The second phase search (see 5.2.1) identified only the studies which provided data in an adult population, with doses and formulations in line with the anticipated licensed indication.

Full details of the search strategy are presented in Appendix 2.

5.2 Study selection

5.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below

The inclusion and exclusion criteria used for the first and second phases of the literature search are summarised in Table 3.

Table 3 Eligibility criteria used in search strategy

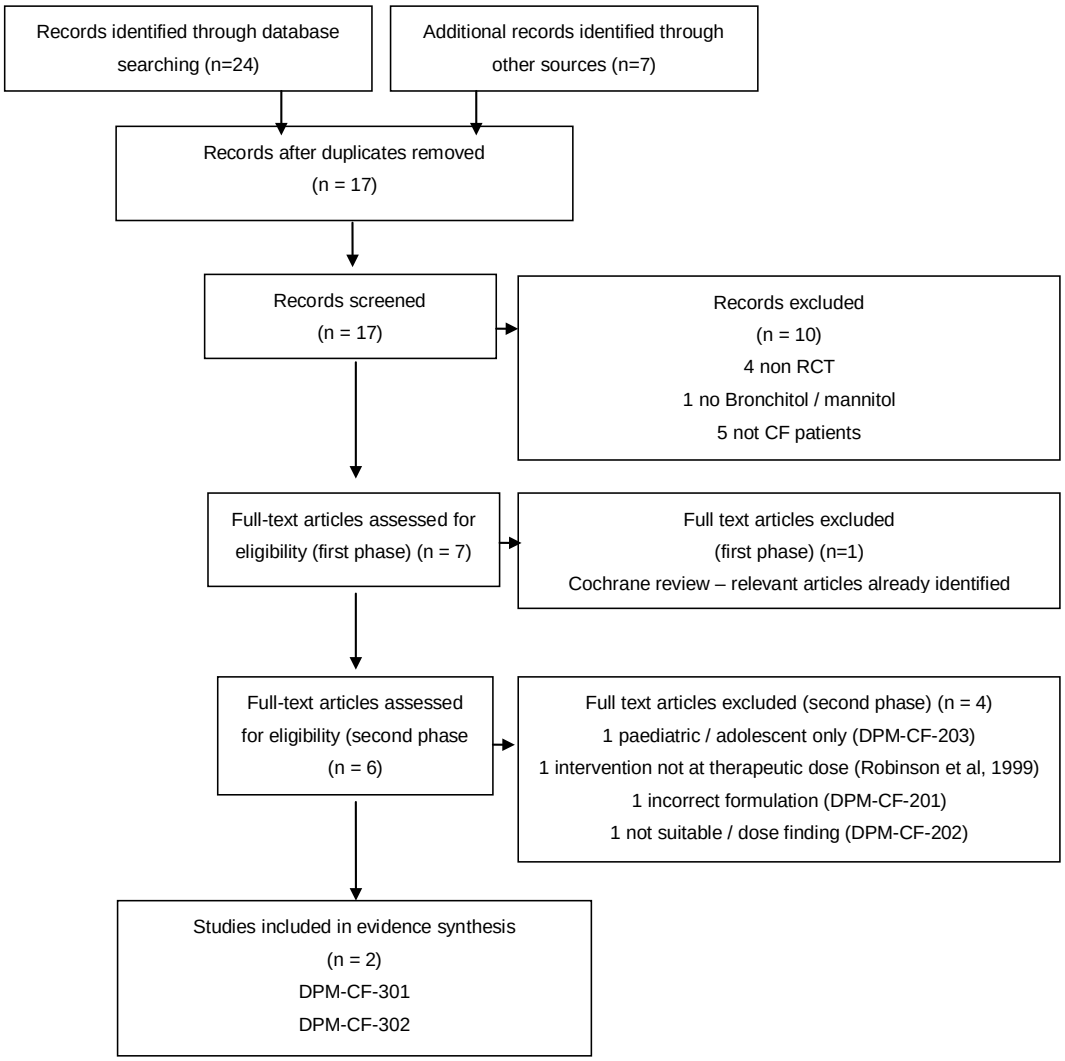
	Inclusion criteria	Exclusion criteria
First phase	Population: Patients with cystic fibrosis Interventions: Bronchitol or Bronchitol Study design: randomised clinical trial Language restrictions: English language only	
Second phase		Population: Paediatric or adolescent patients only Interventions: Doses of Bronchitol / Bronchitol not at therapeutic dose (i.e. not at ≈400mg BD); different formulation to that being licensed.

5.2.2 A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 5.2.4.

From the first phase literature search, a total of six studies were indentified for further consideration. These studies include three Phase II efficacy trials (DPM-CF-201, DPM-CF-202 and DPM-CF-203) and two Phase III trials (DPM-CF-301 and DPM-CF-302). These studies in the clinical development plan for Bronchitol treated patients ages 6 and up - in total, 113 patients in Phase II and 361 in Phase III. An additional study was carried out in Australia supported by the National Health & Medical Research Council of Australia and Australian Cystic Fibrosis Research Trust (Robinson et al. 1999) - this included 12 adult patients treated with Bronchitol.

Following the second stage review, the phase III Bronchitol clinical trials (DPM-CF-301 and DPM-CF-302) were identified as providing the most appropriate data Although studies DPM-CF-201 and DPM-CF-202 do provide data on both adult and paediatric/adolescent patients, the studies are too small to be able to extract meaningful data in the adult only population and only assess treatment effects over a 2 week period. In addition, DPM-CF-201 included a formulation of mannitol which is different to the one which has been submitted for regulatory approval and DPM-CF-202 was designed as a dose finding study. However these studies provide useful supporting data in the wider CF population (which includes adult patients) and therefore a summary of the study designs along with key outcomes data are presented in Appendix 18.

Figure 1 Flow diagram of included and excluded studies



5.2.3 When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

For the pivotal RCTs included in this review, the key source of evidence is the clinical study reports. However, data from these studies have been also been presented and the relevant articles are listed below (Table 4).

Table 4 List of relevant publications for pivotal RCTs of Bronchitol in adult patients

Study	Publications
DPM-CF-301	Inhaled dry powder mannitol in cystic fibrosis (CF): Microbiology results from the 6 month double-blind CF301 study. D. Bilton, P. Robinson, P. Cooper, J. Kolbe, C.G. Gallagher, H. Fox, B. Charlton. Abstract E3500 at ERS conference, September 2010 Randomized, Double Blind, Placebo-Controlled Phase III Study of Inhaled Dry Powder Mannitol (Bronchitol) in CF. Bilton, D.; Robinson, P.; Cooper, P.; Charlton, B. Pediatric Pulmonology 2009 Suppl. 286 (A216) Randomised, double-blind, placebo-controlled phase III study of inhaled dry powder mannitol in cystic fibrosis (CF). Diana Bilton, Phil Robinson, Peter Cooper, Brett Charlton. Eur Respir J 2009; 34 Suppl. 53 (A1619) Randomised, double blind, placebo-controlled Phase III Study of Bronchitol (inhaled dry powder mannitol) in Cystic Fibrosis (CF). D. Bilton, P. Robinson, P. Cooper, B. Charlton. J of Cystic Fibrosis 2009; Suppl. 25 (A95)
DPM-CF-302	Six-month administration of inhaled mannitol in cystic fibrosis - A safety and efficacy study. Aitken M.L., Flume P.A., Geller D.E., Lapey A., Zuckerman J., Fox H., Charlton B. Pediatric Pulmonology 2010; 45 SUPPL. 33: 299 (A225)

Complete list of relevant RCTs

5.2.4 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below

Both pivotal studies assess the safety and efficacy of Bronchitol 400mg BD over 26 weeks (Table 5). **This submission will focus on the adult only population from these two studies.** However, neither study was powered to specifically show efficacy in this patient group and therefore the data from the total population will be reported first then the adult only population will be reported. Both studies do include a high proportion of adult patients (DPM-CF-301: 64.4%, DPM-CF-302: 49.5%).

Table 5 List of relevant RCTs of Bronchitol in adult patients

Study	Intervention	Comparator	Study population	Primary study reference
DPM-CF-301	Bronchitol 400mg BD	Bronchitol 50mg BD (Control)	Subjects with CF, aged ≥6 with FEV_1 30-90% of predicted.	Clinical study report
DPM-CF-302	Bronchitol 400mg BD	Bronchitol 50mg BD (Control)	Subjects with CF, aged ≥6 with FEV_1 40-90% of predicted.	Clinical study report

ITT = intention to treat analysis population

5.2.5 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

As discussed in section 2.6, current patient management for CF involves the use of a number of therapies as part of the standard treatment and best supportive care (BSC). Bronchitol provides an alternative or supplemental agent to other therapeutic or physical therapies for airway clearance.

The anticipated licence is for patients who are currently taking rhDNase (rhDNase users) and for patients who are ineligible, intolerant in inadequately responsive to rhDNase (rhDNase non users)[§]. Therefore the clinical program has included the assessment of Bronchitol benefit in relation to two relevant comparators:

- rhDNase users: for those patients currently on rhDNase, the comparison will be: rhDNase + BSC vs. rhDNase + Bronchitol + BSC.
- rhDNase non-users: for patients who are ineligible, intolerant or inadequately responsive to rhDNase, the appropriate comparison will be Bronchitol + BSC vs. BSC

In order to carry out controlled clinical trials, a sub-therapeutic dose of Bronchitol was chosen to maintain study blinding (see 5.3.2 for details). Both of the key studies compared Bronchitol with a sub-therapeutic dose of Bronchitol and therefore have an appropriate comparator.

No RCTs were found which directly compared Bronchitol with hypertonic saline. Any such comparisons would therefore need to rely on indirect methods.

5.2.6 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

Both pivotal RCTs will be included in further discussion. In addition, supporting data in the overall CF population (including adults, adolescents and children) from studies DPM-CF-201 and DPM-CF-202 will be presented as supporting data in Appendix 18. Data for DPM-CF-203 will not be presented in this submission since the study included no adult patients.

[§] The indication granted to Bronchitol is: “Bronchitol is indicated for the treatment of cystic fibrosis in adults aged 18 years and above as an add-on therapy to best standard of care”.

List of relevant non-RCTs

5.2.7 Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 5.8 and key details should be presented in a table; the following is a suggested format.

No investigational product has been given to any investigators external to Pharmaxis; therefore the only non-randomised evidence for Bronchitol in the CF population will come from internal studies.

In both pivotal RCTs, an open label phase (OLP) followed the end of the double blind phase of the studies. This was an additional 26 weeks following the 26 week randomised double blind phase (DBP) of the study. In addition, DPM-CF-301 had a second 26 week open label extension phase (OLEP) giving the opportunity to collect up to78 weeks of data on patients initially randomised to Bronchitol 400mg BD and up to 52 weeks of Bronchitol therapy for those originally randomised to the sub-therapeutic dose of Bronchitol (see section 5.8.1).

All patients included in the OLP received Bronchitol 400mg BD. The OLP and OLEP for DPM-CF-301 completed in March 2010 and summary data are available. The last patient visit for DPM-CF-302 OLP was in October 2010. Only draft data on a small number of outcome measures are available at this stage and therefore are not included in this report. Relevant publications are listed in 0 but, as with the double-blind studies, the primary source of data is the clinical study report.

Table 6 List of relevant publications for non-RCT evidence of Bronchitol in adult patients

Study	Publications
DPM-CF-301 OLP / OLEP	Long term administration of inhaled dry powder mannitol in CF: Results from the open label phase III DPM-CF-301 study. Bilton D., Robinson P., Cooper P., Kolbe J., Gallagher C.G., Fox H., Charlton B. Pediatric Pulmonology 2010; 45 SUPPL. 33: 321 (A286) Phase III Study of Inhaled Dry Powder Mannitol (Bronchitol™) in Cystic Fibrosis – Results from the 6 month Open Label Phase. D. Bilton, MD, P. Robinson, MD, P. Cooper, MD, C. Gallagher, MD, J. Kolbe, MD, B. Charlton, MD PhD. Am J Respir Crit Care Med 2010; 181: Suppl. A2338 Phase III Study of Inhaled Dry Powder Mannitol (Bronchitol™) in Cystic Fibrosis – Results from the 12 month Open Label Phase. D. Bilton, P. Robinson, P. Cooper, CG. Gallagher, J. Kolbe, H. Fox, B. Charlton. J of Cystic Fibrosis 2010; 9: Suppl. 21

5.3 Summary of methodology of relevant RCTs

5.3.1 As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public

domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, the information should be tabulated.

The two pivotal RCTs are very similar in design and objectives and were designed to compare the efficacy and safety of Bronchitol 400mg BD as an addition to BSC in patients with CF (Table 7, Figure 2). The studies included both rhDNase users and non-users and therefore are a fair reflection of the currently treated CF population. These studies also contain a large proportion of adult patients.

Table 7 Background and objectives for pivotal RCTs

Study	Primary study objective	Study dates	Study population
DPM-CF-301	To determine the effect of Bronchitol compared to control on FEV1 in patients with CF	5 April 2007 to 31 March 2009	Subjects with CF, aged ≥6 with FEV1 >30 and <90% predicted; no concomitant hypertonic saline use; negative Bronchitol tolerance test (MTT)
DPM-CF-302	To determine whether inhaled Bronchitol compared to control improves FEV1 in patients with cystic fibrosis (CF).	3 September 2008 to 12 April 2010	Subjects with CF, aged ≥6 with FEV1 >40% and <90% predicted no concomitant hypertonic saline use; negative Bronchitol tolerance test (MTT).

This table includes items 2b, 14a and 14b from CONSORT checklist.

Figure 2 Study schema for pivotal studies

Study phase	Screening	26 week double blind phase		
Duration	2-5 weeks	6 weeks	8 weeks	12 weeks
Week	0	6	14	26
Visit	V0 V1	V2	V3	V4
Treatment	Screening MTT	Bronchitol 400 mg BD OR Control BD		

MTT = Bronchitol tolerance test

Mannitol tolerance test (MTT)

In both studies, a Bronchitol tolerance test (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 dry powder Bronchitol are administered in cumulative doses and lung function measurements are performed. Only patients who passed the MTT were randomised to treatment.

Changes to studies

After the start of patient recruitment in DPM-CF-301 a number of small changes to the study were made. These included increased study recruitment, clarifications to procedures and the addition of an interim safety analysis. The only protocol amendment of significance to this submission was the addition of the second open label phase (the OLEP) described in section 5.2.7 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.

No changes to the DPM-CF-302 protocol were made after subject recruitment had started.

Methods

5.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.

Both pivotal RCTs were multinational, multicentre randomised clinical trials including patients with CF. Some key aspects of the study methods are discussed below.

Treatments

Patients randomised to receive active Bronchitol received 400mg BD for 26 weeks. The Bronchitol dose of 400mg was chosen based on the results from the dose finding Phase II trial (DPM-CF-202), where 400mg showed the greatest improvement in FEV_1. With consideration that utilizing more than 10 capsules may overly compromise patient's compliance with treatment, the 400mg dose appeared to be the most appropriate balance between acceptability/tolerability and efficacy.

In both studies, Bronchitol was given as an inhaled dry powder where a dose of 400mg required the inhalation of the contents of ten x 40mg capsules of spray dried Bronchitol via RS01 dry-powder inhaler device. Treatment was taken twice a day, once in the morning and once in the evening, approximately two hours before sleep and ideally within 30 minutes before the subject's regular treatments (including premedication with 400mcg dose of salbutamol (or alternative)) but before physiotherapy or exercise. Capsules were loaded into the inhaler device, punctured, then inhaled in a deep, controlled manner; followed by a five second breath hold. Each consecutive capsule followed the previous immediately. The process was repeated until the contents of ten capsules had been inhaled. The initial treatment dose was administered in the clinic setting under medical supervision to ensure subject safety and good administration technique.

In both studies, the control group received 10 x spray dried Bronchitol 5mg per capsule, BD for 26 weeks and the dose was delivered as for the active treatment. The standard premedication was the same as described for the active study drug.

The study protocols included only limited restrictions on co-medications or treatment provided as part of BSC. In addition, subjects that were using rhDNase routinely prior to enrolment in this clinical trial continued to use rhDNase throughout the trial. Wherever possible rhDNase treatment was kept consistent throughout the study period and a record that reflected actual rhDNase use, rather than prescribed use, was maintained. Therefore, the control arms can be considered as the best supportive care in a real world setting and also in addition to existing rhDNase therapy if appropriate (see section 5.2.5 for details).

Hypertonic saline was excluded during the double blind treatment phase since it has a mode of action similar to that of Bronchitol which could confound the results. In addition, it is not standardised in either its formulation or administration.

Blinding

To maintain blinding in the phase III studies, the control had to be delivered across ten capsules and since 5mg was the smallest available fill, a final dose of 50mg (10 x 5mg) was selected. The emitted dose from 10 x5 mg capsules is similar to that from a single 40mg capsule (used in the DPM-CF-202 dose finding study) and therefore a dose of 50mg BD was chosen for the control (sub-therapeutic) treatment as agreed with the CHMP and the FDA.

Outcomes measurements

The primary outcomes for the two studies were identical and focus on measures of lung function. FEV_1 is the gold standard outcome for assessing pulmonary therapies in CF and it is important also since it is linked to mortality and quality of life (QoL) (see section 5.3.4). Frequency of post treatment FEV_1 measures was set at 6, 14 and 26 weeks to establish time to effect and duration of effect.

Baseline safety and efficacy measures were obtained at regular intervals throughout the treatment period, allowing direct comparisons from baseline to end of treatment period and between group differences.

Study duration

The duration of the double blind phase (26 weeks) was chosen as this was considered sufficient to prove the efficacy. However, in order to confirm the safety of the treatment, the additional open-label phases were offered to patients on completion of the initial double-blind study period.

Table 8 Comparative summary of methodology of pivotal RCTs

	Study 301	Study 302
Location	40 sites in 4 countries: Australia (10), New Zealand (2), United Kingdom (24), Ireland (4)	53 sites in 7 countries (USA 28; Canada 3; Argentina 8; Germany 3; Belgium 4; France 6; Netherlands 1)
Design	Randomised, multicentre, controlled, parallel group double-blind 26-week safety and efficacy phase followed by a 26-52 week open label safety phase	Randomised, multicentre, controlled, parallel arm, double blind 26-week treatment, followed by 26 weeks of open label treatment
Duration of study	26 weeks (blinded phase) and 26 weeks (open label phase) plus further 26 week open label extension phase (OLEP) in 23 study centres.	26 weeks (blinded phase) and 26 weeks open label phase
Method of randomisation	All subjects from a site were given consecutive enrolment numbers in successive order of inclusion. Enrolment numbers were generated electronically 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.	Subject identification numbers were generated electronically when 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.
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 indistinguishable taste. Several strategies were put in place to minimize the subject's association between MTT and study drug	The subjects, 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.
Intervention and comparator	Bronchitol 400mg BD vs. control (Bronchitol 50mg BD)	Bronchitol 400 mg BD vs. control (Bronchitol 50mg BD)
Primary outcomes	Change in absolute FEV1 over 26 weeks compared to control	Change in absolute FEV1 over 26 weeks compared to control
(Key) secondary outcome	• Change in FEV_1 in rhDNase users • FEV_1 "response"[a] • Other measures of lung function • Quality of life[a] • QOL "response"[b] • Pulmonary exacerbations[a] • Use of IV antibiotics, rescue oral or inhaled antibiotics • Hospital days due to pulmonary exacerbations • Safety profile: adverse events, haematology, biochemistry, change in bronchodilator response, sputum microbiology, physical examination	▪ Change in absolute FEV1 (rhDNase users) • FEV_1 "response"[a] ▪ Pulmonary exacerbations [a] ▪ Quality of life ▪ Use of IV antibiotics, rescue oral or inhaled antibiotics ▪ Days in hospital due to pulmonary exacerbations ▪ Improvements in other measures of lung function[d] ▪ Safety profile (adverse events, haematology, biochemistry, sputum microbiology (both qualitative and quantitative), physical examination, including vital signs)

	• • Hospital and community care costs[c]	▪ Hospital and community care costs[c] ▪ Sputum weight[b]
This table includes items 3a, 4b, 8a, 8b, 9, 10, 11a and 11b from CONSORT checklist a minor adjustment from protocol to include analyses for both rhDNase strata b additional item not in protocol however was included in the statistical analysis plan (SAP) c not addressed in this section d change in % predicted FEV_1 was not in protocol however was included in the statistical analysis plan (SAP)		

Participants

5.1.1 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.

Inclusion and exclusion criteria for the pivotal RCTs are very similar and the only differences between them are:

- Diagnosis requirements for CF were more specifically defined in DPM-CF-302
- The FEV_1 inclusion criteria was raised to $\geq$40% predicted in DPM-CF-302 (from $\geq$30% in DPM-CF-301)
- In DPM-CF-302 nebulised hypertonic saline could not be used in 4 weeks prior to visit 1 (i.e. could be stopped at visit 0 and with a 4 week gap to the baseline assessment at visit 1) but in DPM-CF-301 use of nebulised hypertonic saline is an exclusion criterion assessed at screening (visit 0).
- Differences in MTT protocol: the 35mg dose (administered as 5mg + 10mg + 20mg) in DPM-CF-301 was replaced with a single 40mg capsule in DPM-CF-302
- DPM-CF-302 specifically excludes patients if MTT is incomplete or positive whereas the wording in DPM-CF-301 only excludes patients for a positive test. However, the protocol for DPM-CF-301 also states that randomised therapy was only dispensed at Visit 1 to those with a negative MTT result. Therefore, despite wording differences these two exclusion criteria will have the same net effect.

Apart from the FEV_1 criteria, these inclusion and exclusion differences are unlikely to have any impact on treatment outcomes and therefore the study populations are very similar.

Table 9 Eligibility criteria in the pivotal RCTs

Study	Inclusion criteria	Exclusion criteria
DPM-CF-301	• Written informed consent • Confirmed diagnosis of cystic fibrosis • Subjects aged ≥6 years of age • FEV_1 >30% and <90% predicted • Able to perform techniques necessary to measure lung function	• Considered “terminally ill”, listed for or had lung transplant • Using nebulised hypertonic saline • 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 for of contraception 9if at risk of pregnancy) • Participation in another investigative drug study

Study	Inclusion criteria	Exclusion criteria
		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	• Written informed consent • Confirmed diagnosis of cystic fibrosis via sweat test and/or genotype • Subjects aged ≥6 years of age • FEV_1 >40 % and <90% predicted • Able to perform techniques necessary to measure lung function	• Considered "terminally ill", listed for or had lung transplant • Using nebulised hypertonic saline - can be eligible if 4 week 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 for of contraception 9if 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 or incomplete
This table includes items 4a from CONSORT checklist		

5.3.3 Describe the patient characteristics at baseline. Highlight any differences between study groups.

Table 10 Characteristics of participants in the pivotal RCTs across randomised groups – ITT population

Study 301	**Bronchitol (n=177)**	**Control; (n=118)**	**Total ITT (n=295)**
Age (years)			
Children (6-11 years)	31 (1.75%)	17 (14.4%)	48 (16.3%)
Adolescent (12-17 years)	32 (18.1%)	25 (21.2%)	57 (19.3%)
Adult (≥18 years)	114 (64.4%)	76 (64.4%)	190 (64.4%)
Mean (SD)	23.1 (11.7)	22.8 (10.8)	23.0 (11.3)
Gender - Female	71 (40.1%)	61 (51.7%)	132 (44.7%)
Race - Caucasian	169 (95.5%)	115 (97.5%)	284 (96.3%)
BMI (kg/m^2)	21.1 (4.0)	20.4 (3.6)	20.8 (3.8)
rhDNase use	96 (54.2%)	67 (56.8%)	163 (55.3%)
FEV_1 (L)			
Screening (L)[a]	2.08 (0.82)	1.95 (0.71)	2.03 (0.78)[c]
Screening - predicted (%)[a]	62.84 (15.79)	61.26 (15.76)	62.21 (15.79)[c]
Baseline (L)[b]	2.07 (0.82)	1.95 (0.69)	2.02 (0.77)
Baseline predicted (%)[b]	62.4 (16.45)	61.4 (16.13)	62.0 (16.30)
Study 302	**Bronchitol (n=184)**	**Control (n=121)**	**Total (n=305)**
Age (years)			
Children (6-11 years)	35 (19.0%)	24 (19.8%)	59 (19.3%)
Adolescent (12-17 years)	56 (30.4%)	39 (32.2%)	95 (31.1%)
Adult (≥18 years)	93 (50.5%)	58 (47.9%)	151 (49.5%)
Mean (SD)	19.6 (9.3)	20.4 (10.2)	19.9 (9.7)[c]
Gender - Female	90 (48.9%)	58 (47.9%)	148 (48.5%)
Race - Caucasian	182 (98.9%)	119 (98.3%)	301 (98.7%)
BMI (kg/m^2)	20.2 (4.12)	19.8 (3.70)	19.9[c]
rhDNase use	137 (74.5%)	92 (76.0%)	229 (75.1%)
FEV_1 (L)			
Screening (L)[a]	2.06 (0.71)	2.02 (0.72)	2.04 (0.71)[c]
Screening - predicted (%)[a]	65.24 (13.9)	64.35 (15.29)	64.89 (14.46)[c]
Baseline (L)[b]	2.06 (0.77)	1.96 (0.74)	2.02 (0.76)[c]
Baseline predicted (%)[b]	64.8 (15.7)	62.5 (16.0)	63.9 (15.82)[c]

Data are presented as n (%) for counts and mean (SD) for continuous variables

a FEV1 is the best value taken at week -2 (visit 0 = screening) pre-bronchodilator spirometry. FEV1 % predicted is estimated from this value

b FEV1 is the best value taken at week 0 (visit 1 = baseline) pre-bronchodilator spirometry. FEV1 % predicted is estimated from this value;

c Calculated as weighted mean of individual treatment groups

The demographic characteristics of the treatment groups in both studies appeared to be evenly represented although there were a lower proportion of female patients in the Bronchitol group (40.1%) than in the control group (51.7 %) in DPM-CF-301.

The two pivotal RCTs were relatively well matched on baseline characteristics. The majority of patients were Caucasian, the overall proportion of females was comparable and the mean BMI for the populations was around 20kg/m^2. Patients in DPM-CF-301 study were on average slightly older than in DPM-CF-302 study due to a higher proportion of adult patients (64.4% vs. 49.5%). Patients had moderately severe CF lung disease (approximately 65% predicted of normal FEV_1 for age, gender and height) but the range was wide. A high proportion of patients in each study were rhDNase users and the proportions were well balanced across the treatment groups. The FEV_1 and predicted FEV_1 values were comparable across the studies and also across treatment groups within studies.

Since the focus of this appraisal is adult patients, the demographic characteristics for the adult only population is also presented (Table 11).

Table 11 Summary of demographic and baseline characteristics of pivotal RCTs for adult patients only

DPM-CF-301 adult only	**Bronchitol (n=114)**	**Control (n=76)**	**Total (n=190)**
Age (years), Mean (SD)	29.6 (9.42)	28.8 (8.49)	29.3 (9.05)
Female, N (%)	43 (37.7%)	41 (53.9%)	84 (44.2%)
Caucasian, N (%)	111 (97.4%)	75 (98.7%)	186 (97.9%)
FEV_1			
Screening (L)[a]	2.32 (0.83)	2.07 (0.71)	2.22 (0.80)
Screening predicted (%)[a]	58.77 (15.59)	56.96 (16.67)	58.05 (16.01)
Baseline (L)[b]	2.30 (0.85)	2.07 (0.70)	2.21 (0.80)
Baseline predicted (%)[b]	58.1 (15.91)	57.3 (16.79)	57.8 (16.23)
rhDNase user	58 (50.9%)	44 (57/9%)	102 (53.7%)
DPM-CF-302 - adult only	**Bronchitol (n=93)**	**Control (n=58)**	**Total (n=151)**
Age (years), Median (range)	24.0 (18-48)	27.0 (18-53)	(18-53)
Female, N (%)	37 (29.8%)	22 (37.9%)	59 (39.1%)
Caucasian, N (%)	92 (98.9%)	58 (100%)	150 (99.3%)
FEV_1			
Screening (L)[a]	2.47 (0.7)	2.37 (0.66)	2.43 (0.68)[c]
Screening predicted (%)[a]	61.97 (13.46)	62.28 (13.89)	62.09 (13.62)[c]
Baseline (L)[b]	2.40 (0.74)	2.28 (0.69)	2.35 (0.72)[c]
Baseline predicted (%)[b]	61.9 (15.0)	59.8 (14.3)	61.1 (14.74)[c]
rhDNase user	64 (68.8%)	41 (70.7%)	105 (69.5%)

This table includes items 15 from CONSORT checklist
Data are presented as n (%) for counts and mean (SD) for continuous variables
a FEV_1 is the best value taken at week -2 (visit 0 = screening) pre-bronchodilator spirometry. FEV_1 % predicted is

estimated from this value
b FEV_1 is the best value taken at week 0 (visit 1 = baseline) pre-bronchodilator spirometry. FEV_1 % predicted is estimated from this value;
c Calculated as weighted mean of individual treatment groups

In DPM-CF-302, the Bronchitol group was slightly younger than the control group and females were represented equally across treatment groups, but were fewer females than males in both treatment groups. There was an equal distribution of rhDNase users and rhDNase non-users across treatment groups.

Outcomes

5.3.4 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life, and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice).

The key outcomes from the pivotal RCTs (Table 12) are discussed in more details below. Since CF cannot be cured; the goal of Bronchitol therapy is to clear the airways of mucus, improves respiratory function, reduce respiratory infections and slow long-term decline. FEV_1 change is a recommended primary endpoint because of the obstructive nature of CF lung disease (see Appendix 2 for further discussion).

Table 12 Primary and secondary outcomes of the pivotal RCTs

Study	Primary outcomes and measures	Secondary outcome(s) and measures
DPM-CF-301	Change in absolute FEV_1 over 26 weeks compared to control	• Change in FEV_1 by existing rhDNase treatment[a] • Proportion of subjects who "respond" on the basis of FEV_1 (overall and by rhDNase stratum)[b] • Proportion of subjects who "respond" on the basis of quality of life (overall and by rhDNase stratum)[b] • Reduction in pulmonary exacerbations (overall and by rhDNase stratum)[a] • Improvement in quality of life (overall and in each rhDNase stratum)[a] • Reduction in days on IV antibiotics, rescue oral or inhaled antibiotics • Reduction in hospital days due to pulmonary exacerbations • Other measures of lung function • Safety profile: adverse events, haematology, biochemistry, change in bronchodilator response, sputum microbiology, physical examination • • Reduction in hospital and community care costs[c]
DPM-CF-302	FEV_1 change from baseline (mL) compared to control	▪ Change in FEV_1 by existing rhDNase treatment ▪ Reduction in pulmonary exacerbations (overall and by rhDNase stratum)[a] ▪ Improvements in quality of life ▪ Reduction in days on IV antibiotics, rescue oral or inhaled antibiotics ▪ Reduction in days in hospital due to pulmonary exacerbations

Study	Primary outcomes and measures	Secondary outcome(s) and measures
		▪ Improvements in other measures of lung function[d] ▪ Safety profile (adverse events, haematology, biochemistry, sputum microbiology (both qualitative and quantitative), physical examination, including vital signs) ▪ Reduces hospital and community care costs[c] ▪ Sputum weight[b]
This table includes items 6a and 6b from CONSORT checklist a minor adjustment from protocol to include both strata b additional item not in protocol however was included in the statistical analysis plan (SAP) c not addressed in this section d change in % predicted FEV_1 was not in protocol however was included in the statistical analysis plan (SAP)		

Measures of pulmonary function

Assessment of all the pulmonary function tests (PFTs) was standardised by using a standard calibrated spirometer. Site staff were trained to perform these assessments according to a standard procedure. Wherever possible, pulmonary function testing was performed as close as possible to the same time of the day at each visit and coincided with the trough treatment effect since the previous Bronchitol/control dose – this was defined as at the number of hours since the last dose of Bronchitol or control and was least 12 hours in DPM-CF-301 and 6-12 hours in DPM-CF-302. The order and timing of all concurrent treatments (e.g. postural drainage and medications, and required withholding of concurrent medications) was the same for every visit. All pulmonary function testing was done in the sitting position and three manoeuvres were conducted with the best values reported according to ATS criteria[20].

Using published algorithms, the observed FEV_1 value at a given timepoint was used to calculate the % predicted FEV_1 value based on published algorithms[21,22] (see Appendix 17).

FEV_1 measures were obtained from the forced vital capacity (FVC) manoeuvre. The largest FEV_1 (at body temperature, ambient pressure, saturated with water vapour (BTPS)) was reported. A minimum of three acceptable and repeatable blows were performed.

Change from baseline in forced vital capacity (FVC) and forced expiratory flow in the middle half forced vital capacity (FEF_{25-75}) were captured using the same methodology. The largest FVC at BTPS was reported. FEF_{25-75} was obtained from the single acceptable 'best-test' curve (e.g. largest sum of FVC and FEV_1) and reported at BTPS.

In addition, FEV_1 responder analyses were carried out where responders were defined in three different ways:

- those achieving at least a 100mL increase in FEV_1 from baseline
- those achieving at least a 5% relative increase in FEV_1 from baseline
- those achieving at least a 5% increase in percent predicted FEV_1

Since there are no guidelines on a clinically meaningful threshold for FEV_1 change in CF, these definitions were defined in consultation with CF experts. Patients with missing values at week 26 were conservatively assumed to be non-responders.

An additional endpoint was considered where an overall FEV_1 responder was defined as patients achieving either an increase in FEV_1 from baseline to week 6 or week 14 which was ≥ 5% of the baseline value or an absolute increase of at least 100ml in FEV_1 from baseline to week 6 or 14. These timelines were considered relevant to a potential treatment stopping rule in clinical practice (see section 6).

Pulmonary Exacerbations (PDPE / PE)

The study considered "protocol defined" pulmonary exacerbations (PDPE) included events where patients were treated with intravenous antibiotics for four or more of the following listed twelve signs or symptoms:

- change in sputum production (volume, colour, consistency)
- dyspnoea
- new or increased haemoptysis
- malaise, fatigue or lethargy
- fever ($\geq 38^{o}$ C)
- anorexia or weight loss
- sinus pain or tenderness
- change in sinus discharge
- FVC or FEV_1 decreased by ≥10% from previous recorded value
- radiographic signs indicative of pulmonary infection
- increased cough
- changes in physical examination of the chest

Any respiratory event, irrespective of the number of presenting signs and symptoms, and which had associated antibiotic use (intravenous, oral or inhaled) were classified as pulmonary exacerbations (PE).

Sputum Weight

During and for the first 30 minutes following the initial administration of Bronchitol/control at Visit 1(week 0) and Visit 3 (week 14), all sputum produced was collected into a pre-weighed container. The entire sample was then weighed on study scales; the weight of the container subtracted and the result recorded.

Quality of life (CFQ-R)

The Cystic Fibrosis Questionnaire - Revised[23] (CFQ-R) is a disease specific, developmentally appropriate questionnaire designed to measure the physical, emotional and social impact of CF

on subjects and their families. This questionnaire was included in order to interpret the objective change in FEV_1. It was administered prior to the start of the study and then at weeks 14 and 26 in a quiet room prior to other study related procedures.

An additional analysis was carried out to determine whether a patient experience an improvement in respiratory symptoms or not. Since the respiratory scale of the CFQ-R for adolescents and adults contained six questions, using a minimal clinically important difference MCID of 4.0 points corresponds to a change of approximately one category on one question[24].

No total score exists for this instrument. The domains considered most relevant to this study are the respiratory, physical and vitality domains. In all cases, a higher score on the CFQ-R indicates a higher rating of patient QoL.

QOL – Health Utility Index HUI (DPM-CF-302 only)

The HUI is a generic, preference scored, comprehensive system for measuring health status, health related quality of life and producing utility scores. The HUI is self administered for subjects aged >12 years and proxy administered for children <12 years old. The HUI was administered in DPM-CF-302 only and measurements were undertaken at Visit 0 (Screening), Visit 3 (Week 12), Visit 4 (Week 26) and at termination visit in case of early withdrawal. These data were primarily collected to support economic modelling (see section 6). A HUI2 global utility score was determined for each patient (see Appendix 15 for details) – the utility score is defined for the interval -0.36 to 1.00 where negative scores represent states considered worse than death.

Rescue Antibiotic Use

The use of rescue antibiotics was monitored and documented. This data included all nebulised antibiotics, oral and intravenous use. Subjects kept a diary record of all antibiotic use while in the study including the antibiotic name, indication for use, the dose and the start and stop dates. Routine antibiotic use was carefully distinguished from rescue antibiotics.

Days in Hospital due to PE

At the time of hospital admission, the following information was recorded:

- physical examination and medical history
- signs and symptoms
- sputum microbiology results
- spirometry
- number of days since last hospital admission
- results of laboratory tests
- chest x ray report

In addition the medications administered during admission and the number of days in hospital was obtained at the time of hospital discharge.

Bronchodilator Response Test (DPM-CF-301 only)

To determine whether inhaled Bronchitol might sensitise the airways with chronic use, subjects had their bronchodilator response measured at visit 1 prior to receiving the initial dose of study medication. This test was repeated at visit 4. For those routinely taking bronchodilators, a 6-12 hour withholding period was imposed before the procedure. The test was considered invalid if compliance with the withholding periods was not 100%. This endpoint will not be reported in this submission.

Sputum microbiology

A sputum sample was collected at Visits 0 through 6 inclusive and cultured for qualitative assessment (presence/absence of bacteria). The Visit 0 microbiology sputum sample was taken before administration of the MTT procedure and represented the baseline sample. The sample was categorized as normal flora or no growth; or abnormal flora. If bacteria were grown then the type of organism was recorded and classified into the most common CF pathogens (*Pseudomonas aeruginosa, Staphylococcus aureus, Haemophilus influenzae, Aspergillus sp, Burkholderia cepacia, MRSA* or other). The amount of growth was also recorded (scanty, moderate, heavy or not specified).

In DPM-CF-302, sputum samples for quantitative microbiology were quantified for *Staphylococcus aureus* and *Pseudomonas aeruginosa* using a single standard operating procedure.

These data will not be reported in this submission.

Compliance

At each study visit, patients were prescribed enough medication to last until the next visit plus two weeks extra supply in the event of a delayed visit. All used and unused blister packs were to be returned at the next visit and, based on that count the level of compliance was determined. To be protocol complaint subjects were asked to be $\geq$80% complaint at each visit (i.e. returned medication is less than 20% of the prescribed medication) and a minimum compliance level of 60% over the 26 week period was specified in the SAP. Compliance was used as a means of defining the per protocol population in each study and only summary results will be reported in this submission.

Reliability/validity/current use in clinical practice

FEV_1 has been conventionally used as a primary outcome in CF clinical trials, in part, because it is linked to mortality and QOL - decline predicts mortality and correlates with survival in CF. FEV_1 is objective, easily performed in children over 6 years of age, repeatable, adjustable for

age, height and sex, and can be frequently measured. FEV1, therefore remains the gold standard for assessing pulmonary therapies in CF, and is a recognised primary variable in CHMP guidelines. Lung function as measured by FVC is also an important factor in measuring lung function[25,26,27].

Acute worsening of lung function can be captured as a pulmonary exacerbation. Exacerbations associated with infections typically worsen the progression of lung disease in these patients. No consistent standard definition criteria exist. Criteria defined in the protocol follow criteria that have been used in other pivotal phase III clinical trials with rhDNase and hypertonic saline[28,29].

The CFQ-R is a validated HRQoL measure designed to measure the physical, emotional and social impact of CF on subjects and their families.

In terms of outcomes, the differences between the studies were that DPM-CF-302 included an additional quantitative assessment of microbiology parameters but does not include the bronchodilator response test which was included in DPM-CF-301. Additionally, study DPM-CF-302 collected HUI data which was not included in DPM-CF-301.

Statistical analysis and definition of study groups

5.3.5 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.

The Intent-to-Treat (ITT) and safety (SP) populations included all subjects who received at least one dose of study medication. This is the population for the analysis of all safety data. The ITT population was the primary population for analyses.

Per-protocol (PP) included all patients in the ITT who had no major protocol violations, a minimum of 60% compliance with study treatment and at least two assessments of FEV_1 after receiving study treatment.

The primary endpoint and key secondary endpoints have been estimated using both the ITT and PP analysis sets while the secondary efficacy endpoints were analysed using the ITT analysis. In addition some of the secondary endpoints have been analysed using the PP analysis set. The results presented are those for the ITT population unless otherwise noted.

Table 13 Statistical analyses in the relevant RCTs

	DPM-CF-301	DPM-CF-302
Hypothesis objective	To determine the effect of Inhaled Dry Powder Mannitol compared to control on FEV_1 in subjects with Cystic Fibrosis (CF)	To determine whether inhaled mannitol compared to control improves FEV_1 in patients with cystic fibrosis (CF).
Statistical analysis for primary endpoint	Change from baseline in FEV_1 was assessed using mixed models repeated measures analyses (MMRM) in SAS. Change from baseline in FEV_1 values were the outcome variables. Included covariates were: Treatment group, rhDNase use, region (Europe vs. not), study week, disease severity (% predicted FEV_1 at screening), age, baseline spirometry value and gender.	FEV_1 was analysed using mixed model repeated measures (MMRM) methodology with subject fitted as a random effect and an unstructured variance-covariance structure. Two analyses were carried out: difference between treatments in change from baseline (across all timepoints) and difference between treatments in change from baseline to each timepoint. Included covariates were: Treatment group, rhDNase use, region (Argentina, Belgium/Netherlands, Canada, France, Germany, Netherlands, USA), study week, disease severity (% predicted FEV_1 at screening), age, baseline spirometry value and gender.
Sample size, power calculation	• A total sample size of 109 subjects in the Bronchitol arm and 73 subjects in the control arm taking concurrent rhDNase would give the study 80% power to detect a difference of 85mL in change from baseline of FEV1 between the Bronchitol and control arms at 26 weeks in this subgroup of subjects • with 50% more subjects in each arm of the study when not restricted to subjects currently taking rhDNase, the study has 80% power to detect a difference of 70mL in change from baseline of FEV_1 between the Bronchitol and control arms at 26 weeks. • The study also has more than 80% power to detect a difference in rates of pulmonary exacerbations over the course of a 26 week study, assuming pulmonary exacerbation rates of 0.42 events per subject-year in subjects treated with Bronchitol, and 0.96 events per subject-year in subjects in the control group.	• A total sample size of 300 subjects was planned with 180 randomised to Bronchitol and 120 to control. An estimated 65% of subjects were expected to be taking rhDNase. With a dropout rate of 30%, 126 subjects in the Bronchitol arm were expected to complete the study (84 taking rhDNase, 42 not taking rhDNase), and 84 subjects in the control arm were expected to complete the study.

Data management and patient withdrawals	Using a mixed model for analysis utilizes all data for all subjects and provided missing values can be viewed as missing at random missing data do not need to be imputed. The pattern of withdrawal was explored through Kaplan Meier plots. With no emphatic evidence to suggest that values are not missing at random and therefore the mixed model with no imputation can be considered unbiased.	All data contained in the database are listed. Using a mixed model for analysis utilizes all data for all subjects and provided missing values can be viewed as missing at random missing data do not need to be imputed. In order to address any impacts of missing data on the primary endpoint and the robustness of the primary endpoint estimate, sensitivity analyses (ANCOVA) using 2 different missing data imputation methods was carried out: • Carrying forward the last available post-baseline observation • Carrying forward the baseline observation for subjects who do not have a valid Visit 4/Week 26 FEV_1 measurement
This table includes items 6a and 6b from CONSORT checklist These analyses are in line with SAPs which were finalized before study unblinding.		

The analyses methods for the primary endpoints are described above in Table 13 and from these analyses, the least squares mean (LSmean) and associated 95% confidence interval (CI) were reported. The original models proposed for DPM-CF-301 included change from baseline across the 26 weeks (weeks 0, 6, 14 and 26); however as this analysis included week 0 in assessment of the treatment effect (a time when there is no difference between treatment groups), the effect size does not accurately reflect the treatment change by time-point. Therefore additional models were developed to include only change from baseline across the study period (weeks 6, 14 and 26 without week 0). The models specified for DPM-CF-302 included change from baseline across the study (weeks 6, 14 and 26). The primary results reported here will be those for change from baseline across the study (weeks 6, 14 and 26) to maintain consistency across studies.

In both studies, to obtain specific estimates for the rhDNase sub-groups, treatment group-by-rhDNase use interaction term and/or treatment group-by-treatment group-by-time on study interaction term were fitted to models in order to obtain least squares estimates. Details of the analyses of other endpoints are:

- FEV_1 responder analyses were undertaken using logistic regression models to estimate odds of responding with treatment, gender, age, rhDNase use, region/country, baseline FEV_1 and baseline disease severity (% predicted FEV_1) as covariates. The odds ratio of the two treatment groups and its 95% confidence interval were estimated. Patients without a Visit 4/Week 26 FEV_1 measurement were considered to be non-responders for the FEV_1 responder analysis of the ITT population but were excluded from the analyses based on the completer population
- Additional measures of pulmonary function were analysed as per the primary endpoint.
- Time to event data was summarized, where estimable, by the median time to event and the 95% confidence interval (Brookmeyer and Crowley method based). Comparison of the treatment groups was conducted using Cox's proportional hazards regression

analysis including treatment, gender (DPM-CF-302 only), age, rhDNase use, region/country, baseline disease severity (DPM-CF-302 only, % predicted FEV_1). In DPM-CF-302, historical rates of PE/PDPE were also included as appropriate. The hazard ratio, 95% CI and p-value are presented

- Rate analysis of pulmonary exacerbations, hospitalizations and antibiotic use were analysed using regression models (negative binomial in DPM-CF-301 and Poisson in DPM-CF-302) including covariate terms for treatment group, gender (DPM-CF-302 only), age, rhDNase use, region/country and baseline disease severity (DPM-CF-302 only, % predicted FEV_1). The rate ratio and associated 95% CI and p-value are presented
- Change in QoL symptom scores were analysed similarly to the primary endpoint, replacing the baseline spirometry covariate with baseline QoL symptom score (which was collected at the screening visit). In addition for DPM-CF-302, age group (6-11, 12-13, 14-adult) was included as a covariate to reflect the different CFQ-R questionnaires which are administered according to age group. QoL response was analysed similarly to FEV_1 response but included baseline respiratory score from the CFQ-R instead of baseline FEV_1.
- In DPM-CF-302, change in % predicted FEV_1 was analysed with analysis of covariance (ANCOVA) at week 26/visit 4
- In DPM-CF-302, multiple regression analysis was performed on the HUI data and the multivariate analysis used all variables significant at the 0.50 significance level in the univariate analyses (see Appendix 2 for details).

5.3.6 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

In studies DPM-CF-301 and DPM-CF-302, the randomisation was stratified on rhDNase use (Yes/No) and some specific endpoints (including FEV_1 and pulmonary exacerbations for both studies) were identified in the protocol to be analysed by rhDNase use.

For the rhDNase user and non-user subgroups, the data summaries will focus on the key parameters. These endpoints were summarized and analysed separately for the subset of patients who were taking rhDNase and those who were rhDNase non-users.

Analyses of the target patient population, adults only, are key to this submission and will be presented below.

RhDNase subgroups

The patient characteristics of the rhDNase subgroups for both studies are show in Table 14. As for the overall populations, there were differences between the studies in terms of mean age and proportion of females. These data also show that rhDNase non-users were slightly older on average than users, driven by a higher proportion of adult patients in the non-user groups. The other difference between users and non-users is in the lung function variables. FEV_1 and % predicted FEV were both higher in the non-users groups.

Table 14 Patient characteristics by rhDNase subgroups in the key RCTs

DPM-CF-301 – rhDNase users	Bronchitol (n=96)	Control (n=67)	Total (n=163)
Age (years)			
Children (6-11 years)	13 (13.5%)	8 (11.9%)	21 (12.9%)
Adolescent (12-17 years)	25 (26.0%)	15 (22.4%)	40 (24.5%)
Adult (≥18 years)	58 (60.4%)	44 (65.7%)	102 (62.6%)
Mean (SD)	21.9 (10.20)	22.5 (9.92)	22.1 (10.06)
Gender - Female	38 (39.6%)	37 (55.2%)	75 (46.0%)
Race - Caucasian	93 (96.9%)	66 (98.5%)	159 (97.5%)
BMI (kg/m^2)	20.78 (3.80)	20.09 (3.16)	20.50 (3.56)
FEV_1 (L)			
screening (L)[a]	1.98 (0.78)	1.86 (0.63)	1.93 (0.72)[c]
predicted (%)[a]	60.10 (16.74)	57.59 (15.65)	59.07 (16.30)[c]
baseline (L)[b]	1.958 (0.780)	1.866 (0.638)	1.920 (0.724)
predicted (%)[b]	59.2 (17.26)	57.9 (16.38)	58.7 (16.86)
DPM-CF-302 – rhDNase users	**Bronchitol (n=137)**	**Control (n=92)**	**Total (n=229)**
Age (years)			
Children (6-11 years)	16 (19.0%)	18 (19.6%)	21 (12.9%)
Adolescent (12-17 years)	47 (34.3%)	33 (35.9%)	40 (24.5%)
Adult (≥18 years)	64 (46.7%)	41 (44.6%)	102 (62.6%)
Mean (SD)	18.3 (8.14)	20.0 (10.26)	18.9 (9.0)[c]
Gender - Female	73 (53.3%)	47 (51.1%)	120 (52.4%)
Race - Caucasian	136 (99.3%)	90 (97.8%)	226 (98.7%)
BMI (kg/m^2)	19.7 (3.66)	19.7 (3.60)	19.7 (3.6)[c]
FEV_1 (L)			
screening (L)[a]	2.04 (0.70)	1.99 (0.72)	2.02 (0.71)[c]
predicted (%)[a]	64.80 (13.77)	64.03 (15.19)	64.5 (14.36)[c]
baseline (L)[b]	2.02 (0.75)	1.93 (0.73)	1.98 (0.74)[c]
predicted (%)[b]	64.1 (15.7)	62.2 (16.0)	63.33 (15.82)[c]
DPM-CF-301 - rhDNase Non-Users	**Bronchitol (n=81)**	**Control (n=51)**	**Total (n=132)**
Age (years)			
Children (6-11 years)	18 (22.2%)	9 (17.6%)	27 (20.5%)
Adolescent (12-17 years)	7 (8.6%)	10 (19.6%)	17 (12.9%)
Adult (≥18 years)	56 (69.1%)	32 (62.7%)	88 (66.7%)
Mean (SD)	24.6 (13.11)	23.2 (11.85)	24.1 (12.61)
Gender - Female	33 (40.7%)	24 (47.1%)	57 (43.2%)
Race - Caucasian	76 (93.8%)	49 (96.1%)	125 (94.7%)
BMI (kg/m^2)	21.42 (4.203)	20.75 (4.088)	21/16 (4.157)
FEV_1 (L)			
Screening (L)[a]	2.20 (0.84)	2.08 (0.78)	2.15 (0.82)[c]
Predicted (%)[a]	66.09 (14.00)	66.09 (14.69)	66.09 (14.67)[c]
baseline (L)[b]	2.195 (0.847)	2.064 (0.747)	2.144 (0.809)
predicted (%)[b]	66.2 (14.68)	66.1 (14.69)	66.1 (14.63)

DPM-CF-302 - rhDNase Non-Users	Bronchitol (n=47)	Control (n=29)	Total (n=76)
Age (years)			
Children (6-11 years)	9 (19.15%)	6 (20.7%)	15 (19.7%)
Adolescent (12-17 years)	9 (19.1%)	6 (20.7%)	15 (19.7%)
Adult (≥18 years)	29 (61.7%)	17 (58.6%)	46 (60.5%)
Mean (SD)	23.4 (11.29)	21.5 (10.25)	22.7 (10.9)[c]
Gender - Female	17 (36.2%)	11 (37.9%)	28 (36.8%)
Race - Caucasian	46 (97.9%)	29 (100%	75 (98.7%)
BMI (kg/m^2)	21.1 (5.11)	20.1 (4.04)	20.7 (4.73)[c]
FEV_1 (L)			
screening (L)[a]	2.14 (0.76)	2.11 (0.72)	2.13 (0.75)[c]
predicted (%)[a]	66.53 (14.33)	65.37 (15.85)	66.09 (14.92)[c]
baseline (L)[b]	2.17 (0.81)	2.05 (0.76)	2.12 (0.79)[c]
predicted (%)[b]	66.9 (15.7)	63.2 (16.2)	65.49 (15.89) [c]

Data presented as n (%) for counts and mean (SD) for continuous data
This table includes items 15 from CONSORT checklist and also addresses CONSORT item 12b
a FEV_1 is the best value taken at week -2 (visit 0 = screening). FEV_1 % predicted is estimated from this value;
b FEV_1 is the best value taken at week 0 (visit 1 = baseline) pre-bronchodilator spirometry. FEV_1 % predicted is estimated from this value;
c Calculated as weighted mean of individual treatment groups.

In the ITT population of DPM-CF-301 only 9 (2.8%) patients changed their rhDNase usage during the course of the study and only three of these were adult patients:

- One non-user in the Bronchitol ≥18 year age group initiated rhDNase use between visit 2 and visit 3 and continued rhDNase use up to visit 4.
- Two rhDNase users in the control group were in the ≥18 year age group. The first ceased rhDNase use between visit 3 and visit 4 and did not restart rhDNase for the remainder of the study. The second was assigned to the rhDNase user group, however initiated use between visit 3 and visit 4 and continued rhDNase use up to visit 4.

In the DPM-CF-302 ITT population, 12 (3.9%) subjects had changes to their routine of rhDNase use during the treatment period and only two of these were adult patients

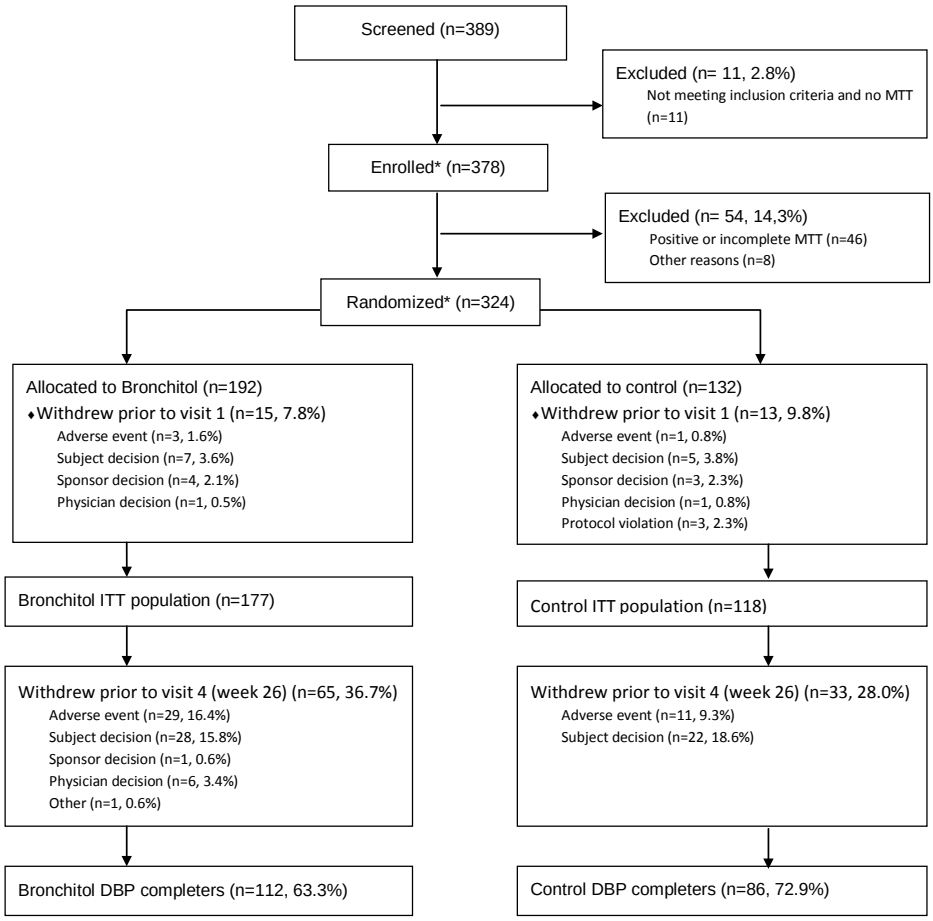
- One adult patient randomised to Bronchitol ceased their rhDNase treatment at screening –this subject was screened and randomised correctly as an rhDNase user. Due to unforeseen circumstances this subject was unable to attend visit 1 for several months, hence was re-screened but not re-randomised by the site. In the interim, the subject chose to cease rhDNase use. The subject was analysed in the correct treatment group (Bronchitol), but in the wrong stratum (rhDNase user). Subsequent examination of this subject's FEV_1 data showed that their FEV_1 had improved at every study visit.
- One adult patient randomised to the control group ceased rhDNase treatment at week 14. FEV_1 fell following cessation of rhDNase.

As the numbers of subjects affected are few, it appears that these changes in routine do not have a meaningful impact on the overall interpretation of the study.

Participant flow

5.3.7 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

Figure 3 Participant flow in DPM-CF-301



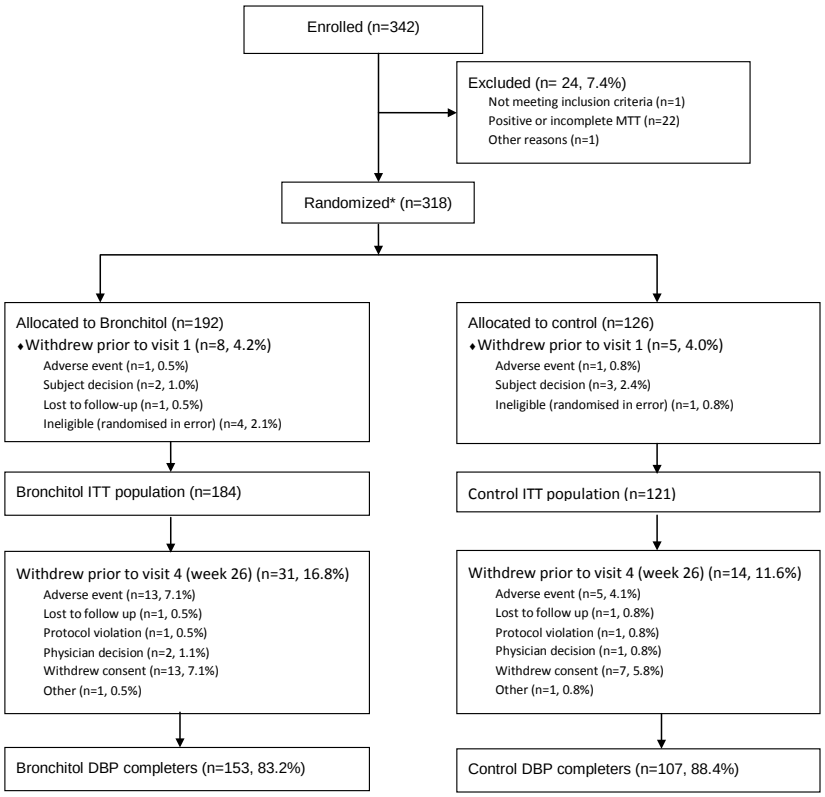
Note: * One randomised subject attended visit 1, but did not receive study drug and was not included in ITT
This addresses CONSORT item 13a.

In DPM-CF-301, 11 screened patients failed to meet the entry criteria for the study and also had no MTT and so were not enrolled to the study. Of the remaining 378 patients, 46 patients had a positive (failed) or incomplete MTT; five patients had a negative MTT but failed other eligibility criteria and were excluded; an additional three patients had a negative MTT but chose not to continue in the study. An additional patient was withdrawn at visit 1 prior to receiving study medication due to unstable lung function. Therefore the DPM-CF-301 ITT population consistent of 295 patients who were randomised and received at least one dose of randomised therapy.

Of the 342 patients enrolled in DPM-CF-302, one ineligible patient who did not have the MTT was mistakenly entered onto the cert. further patient had negative MTT but was withdrawn from the study prior to randomisation. After considering the other reasons for exclusion, 318 patients were randomised to treatment. Prior to the start of treatment a further 13 patients withdrew; therefore the ITT population for this study consisted of 184 patients in the Bronchitol group and 121 in the control group. Three patients randomised to control were not withdrawn as required by the protocol: 2 patients with a >20% FEV_1 fall post treatment and another with pancreatitis

In DPM-CF-302, there was differential withdrawal between baseline (week 0) and week 6 as follows: 14 Bronchitol subjects (7.6%) and 2 control subjects (1.7%). Nine (4.9%) of the Bronchitol withdrawals in this period were due to adverse events and only 1 (0.8%) control subject withdrew due to an adverse event prior to week 8. During the remainder of the study (week 8 to week 26), the drop-out rate was comparable with a 9.2% of the Bronchitol subjects and 9.9% control subjects withdrawing from the study

Figure 4 Participant flow in DPM-CF-302



This addresses CONSORT item 13a.

rhDNase use subgroups

A summary of the disposition of patients by rhDNase use is shown in Table 15.

Table 15 Disposition of patients by rhDNase groups

	Bronchitol	Control
rhDNase users		
DPM-CF-301		
Randomised and in ITT	96	67
Completers	60 (62.5%)	48 (71.6%)
Discontinued	36 (37.5%)	19 (28.4%)
DPM-CF-302		
Randomised and in ITT	137	92
Completers	112 (81.8%)	83 (90.2%)
Discontinued	25 (18.2%)	9 (9.8%)
rhDNase non users		
DPM-CF-301		
Randomised and in ITT	81	51
Completers	52 (64.2%)	38 (74.5%)
Discontinued	29 (35.8%)	13 (25.5%)
DPM-CF-302		
Randomised and in ITT	47	29
Completers	41 (87.2%)	24 (82.8%)
Discontinued	6 (12.8)	5 (17.2)

In DPM-CF-302, the pattern of completers and non-completers was similar in the two subgroups and in the two treatment groups although there are a higher proportion of completers in the Bronchitol group than in the control group within the rhDNase non-user subgroup.

Adult only population

A summary of the disposition in the adult only population is shown in Table 16. In DPM-CF-302, the results are very similar to those seen in the overall population although the completion rates are slightly lower.

Table 16 Disposition of adult patients

	Bronchitol	Control
DPM-CF-301		
Randomised and in ITT	114	76
Completers	71 (62.3%)	52 (68.4%)
Discontinued	43 (37.7%)	24 (31.6%)
DPM-CF-302		
Randomised and in ITT	93	58
Completers	70 (75.3%)	50 (86.2%)
Discontinued	23 (24.7)	8 (13.8)

5.4 Critical appraisal of relevant RCTs

5.4.1 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.

5.4.2 Please provide as an appendix a complete quality assessment for each RCT. See section 9.3, appendix 3 for a suggested format.

A complete quality assessment of the relevant RCTs can be found in Appendix 5.

5.4.3 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.

A summary of the critical appraisal of the key RCTs is presented in 0. Overall, the trials were of high quality.

Table 17 Quality assessment of key RCTs

Issue	Study 301	Study 302
Was randomisation carried out appropriately?	YES	YES
Was the concealment of treatment allocation adequate?	YES	YES
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	YES	YES
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	YES	YES
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	YES[a]	NO

Issue	Study 301	Study 302
Is there any evidence to suggest that the authors measured more outcomes than they reported?	NO	NO
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	YES	YES
Responses noted as Yes, No, Not clear or N/A. a unbalanced but additional analyses suggested no impact on primary outcomes		

5.5 Results of the relevant RCTs

5.5.1 Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given.

Key outcomes

The key outcomes of interest to the decision problem as defined in the scope are:

- mortality
- lung function
- respiratory symptoms
- reduction in pulmonary exacerbations
- exercise tolerance
- adverse effects of treatment
- health-related QoL

The majority of these outcomes were measured within the RCTs and will be reported here. However, mortality was not a measured outcome in the studies and any assumptions relation to mortality will be address only through the economic models in chapter 6. The use of formal exercise capacity or exercise tolerance as a clinical outcome in clinical trials is still in its infancy and there remains no clear guidelines on which methods should be utilised in clinical studies for CF patients. While exercise tolerance was not directly assessed in the Bronchitol phase III program, patients did report on their physical fitness through the Cystic Fibrosis Questionnaire-Revised (CFQ-R).

The key endpoints which will be reported here are:

- Change in FEV_1 from baseline (primary endpoint)
- Additional measures of pulmonary function (% predicted FEV_1, FEV_1 responders and FVC)
- Pulmonary exacerbations (and associated antibiotic use and hospitalisations)
- QoL (measured by CFQ-R)

Results for the overall population will be presented first followed by some key endpoints reported for the adult only population.

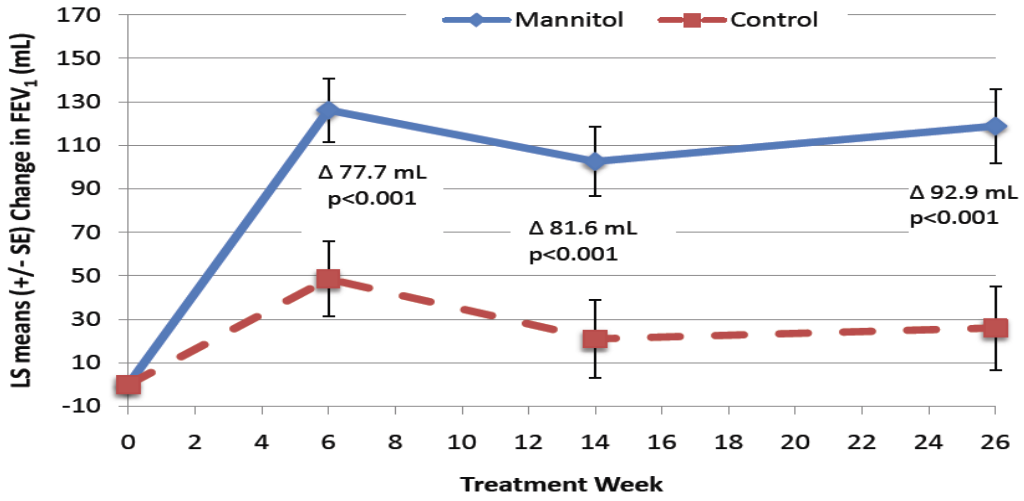
Primary efficacy outcome – change in FEV_1

In DPM-CF-301, 25 patients (19 (10.7%) Bronchitol and 6 (5.1%) control)) withdrew between week 0 and week 6. In the original MMRM model, these patients were included since they had a week 0 value and the primary analysis included change from baseline to each of weeks 0, 6, 14 and 26. However, analyses based on data from weeks 6-26 do not include these patients. In DPM-CF-302, 8 patients with no post-baseline FEV_1 values (8 Bronchitol and 1 control) were excluded from the MMRM analyses of pulmonary function.

When averaged across timepoints using a MMRM model, the estimated treatment effect for Bronchitol vs. control was 84.8mL over the post-randomisation visits (6-26 weeks) in DPM-CF-301. In study DPM-CF-302, the corresponding estimated treatment effect for Bronchitol vs. control was 54.1mL. The difference over weeks 0-26 and weeks 6-26 both showed a statistically significant advantage for Bronchitol in DPM-CF-301 ($p<0.001$ in both analyses) but the difference did not quite reach significance in DMP-CF-302 ($p=0.059$), possibly due to the greater responses seen in the control group in this study especially at the early assessment (Table 18).

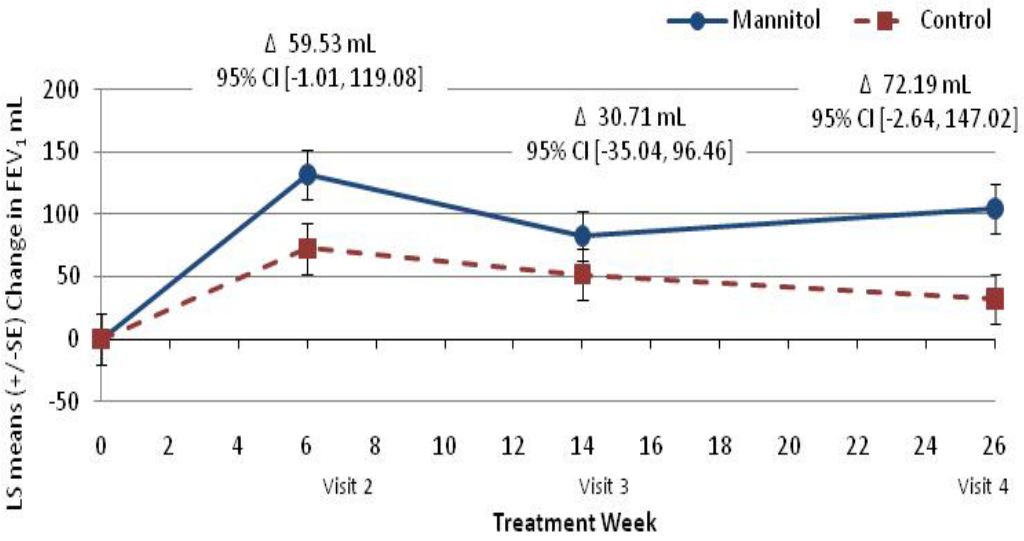
These unexpected results in DPM-CF-302 were explored further and the notable finding was a difference between treatment groups in the change from screening to baseline: the control group had a LSmean (SD) difference in FEV_1 of 59.3mL (215.1) while in the Bronchitol group FEV_1 difference was 8.6mL (232.9) (significant difference between treatments: $p=0.056$, Student's t-test). The analyses of change in FEV_1 over time in the control group may have been influenced by the instability in the baseline FEV_1. As this may have created bias, a post-hoc corrected baseline analysis (average of screening and baseline FEV_1) was conducted using the MMRM model. In the baseline corrected model, the absolute change from baseline for Bronchitol remained similar to the original analysis, however in the control group the change from baseline was much less (overall effect LSmean difference between treatments: 71.10mL ($p=0.008$)).

Figure 5 FEV_1 outcomes: DPM-CF-301 by timepoint



*p<0.001; MMRM model

Figure 6 FEV_1 outcomes: DPM-CF-302 by timepoint



MMRM model using screening FEV_1 value as covariate

This overall treatment effect is an average change from baseline across all post-baseline time points (weeks 6-26). The treatment change by time-point was determined with an additional interaction term in the model for each study:

- DPM-CF-301: mean change in FEV_1 was significantly greater at each timepoint for subjects treated with Bronchitol than for control subjects ($p<0.001$ at each timepoint), reinforcing the findings for overall change (Figure 5).
- DPM-CF-302: Bronchitol patients consistently improved FEV_1 at weeks 6, 14 and 26 but control patients also showed improvements and the treatment effect was not statistically significant ($p=0.050$ at week 6, p=NS at other timepoints) (Figure 6).

Post hoc analyses of % change in FEV_1 showed advantages for Bronchitol over control in both studies that was statistically significant (Table 18).

Overall, treatment with Bronchitol had an early and sustained improvement in lung function (FEV_1) over time and the effect was statistically significant in DPM-CF-301.

Table 18 FEV_1 efficacy data: Pivotal RCTs

Outcome	DPM-CF-301			DPM-CF-302		
	Bronchitol (N=177)	Control (N=118)	Difference	Bronchitol (N=184)	Control (N=121)	Difference
Treatment effect from baseline across the study (weeks 6-26) (mL)[a]						
Overall	-[b]	-[b]	84.8 [42.2,127.5] p<0.001	106.53 [62.43, 150.62]	52.38 [2.09, 102.68]	54.1 [-1.97;110.26] p=0.059
Change from baseline (mL) by timepoint						
Week 6	126.2 [97.5; 155.0]	48.5 [14.7; 82.3]	77.7 p <0.001	132.2 [86.30; 178.06]	72.6 [20.10;125.19]	59.53 p=0.050
Week 14	102.6 [71.4; 133.7]	21.0 [-14.2; 56.1]	81.6 p <0.001	82.7 [33.46; 132.02]	52.0 [-4.73; 108.79]	30.71 p=0.359
Week 26	118.9 [85.6; 152.2]	26.0 [-11.6, 63.6]	92.9 p <0.001	104.7 [50.33; 158.99]	32.5 [-30.47; 95.41]	72.19 p=0.059
% change in FEV_1 from baseline across the study (weeks 6-26) (%)[a]						
Overall	6.21 [4.64, 7.77]	2.61 [0.82, 4.39]	3.60 p=0.002	8.22 [5.57, 10.88]	4.47 [1.44, 7.50]	3.75 p=0.029

Data are presented as LSmeans and associated 95% CIs; differences are difference between LSmeans (95% CI)
a analyses are based on change from baseline to weeks 6-26 for both studies
b data not available from the analyses carried out

In order to address the impact of the withdrawals and missing data on the primary endpoint several single imputation methods were pre-specified in the SAP of DPM-CF-302. These included ANCOVAs at Visit 4/Week 26 with missing values being replaced by the last observation carried forward (LOCF) method and the baseline observation carried forward analysis (BOCF) methods. The LOCF method results in an estimate of treatment difference of 66.25 (95% CI -5.43, 137.94, p=0.070) and the BOCF methods results in an estimated treatment difference of 74.82 (95% CI 7.94, 141.70, p=0.028). Similar analyses were carried out for the DPM-CF-301 study and these sensitivity analyses demonstrated similar statistically significant results for both the original MMRM model and an ANCOVA model with multiple imputations.

Other key measures of pulmonary function

<u>% predicted FEV_1</u>

Table 19 % predicted FEV_1: Pivotal RCTs

Outcome	DPM-CF-301			DPM-CF-302		
	Bronchitol (n=177)	Control (n=118)	Difference	Bronchitol (n=184)	Control (n=121)	Difference
Change from baseline to week 26 (%)[b]						

Outcome	DPM-CF-301			DPM-CF-302		
	Bronchitol (n=177)	**Control (n=118)**	**Difference**	**Bronchitol (n=184)**	**Control (n=121)**	**Difference**
Change from baseline to week 26	2.64 (1.76, 3.53)	0.52 (-0.49, 1.53)	2.12 (0.81, 3.34) p=0.002	3.14 (1.49, 4.78)	0.72 (-1.18, 2.62)	2.42 (0.33, 4.51) p=0.024
a Data presented as mean (SD) b Based on ANCOVA model – LSmean + 95% CI c not calculated						

FEV_1 Responders

FEV_1 response was analysed using three different pre-defined definitions of response in the ITT and completer populations where patients had a week 0 and week 26 FEV_1 value. In DPM-CF-301, the proportion of subjects responding on Bronchitol treatment by meeting or surpassing clinically meaningful lung function thresholds is approximately twice that of the control group for all three definitions of FEV_1 responder (completers population) and favourable results are also see in the ITT population. Corresponding results from the ITT population in DPM-CF-302 showed significant advantages for Bronchitol in two of the three definitions with odds ratios of around 1.7-1.8. The third responder definition showed small advantages for Bronchitol which did not reach statistical significance (Table 20).

Table 20 FEV_1 responder analyses: Pivotal RCTs

	DPM-CF-301			DPM-CF-302		
ITT population	**Bronchitol (n=177)**	**Control (n=118)**	**Odds ratio**	**Bronchitol (n=184)**	**Control (n=121)**	**Odds ratio**
FEV_1 ≥100 mL[a]	62 (35.0%)	33 (28.0%)	1.31 [0.78, 2.21] p=NS	84 (45.7%)	43 (35.5%)	1.69 [1.02, 2.80], p=0.041
FEV_1 ≥5% [b]	64 (36.2%)	36 (30.5%)	1.24 [0.74, 2.09] p=0.026	86 (46.7%)	44 (36.4%)	1.85 [1.09, 3.13] p=0.023
% pred. FEV_1 ≥5%[c]	48 (27.1%)	22 (18.6%)	0.66 [0.37, 1.17] p=NS	52 (28.3%)	31 (25.6%)	1.20 [0.69, 2.10] p=NS
Completer population	**Bronchitol (n=116)**	**Control (n=89)**	**Odds ratio**	**Bronchitol (n=153)**	**Control (n=107)**	**Odds ratio**
FEV_1 ≥100 mL[a]	62 (53.4%)	33 (37.1%)	1.97 [1.08, 3.58] p=0.026	81 (52.9%)	42 (39.5%)	1.84 [1.09, 3.13][p=0.023
FEV_1 ≥5% [b]	64 (55.2%)	36 (40.4%)	2.00 [1.09, 3.66] p=0.026	83 (54.2%)	44 (41.1%)	1.87 [1.07, 3.24] p=0.027
% pred. FEV_1 ≥5%[c]	48 (41.4%)	22 (24.7%)	2.30 [1.20, 4.38] p=0.012	52 (34.0%)	31 (29.0%)	1.28 [0.73, 2.26] p=0.388
Data are presented as n (%) and differences are OR (95% CI) For the ITT population analyses, patients with no week 26 value are classified as non-responders.						

	DPM-CF-301			DPM-CF-302		
ITT population	**Bronchitol (n=177)**	**Control (n=118)**	**Odds ratio**	**Bronchitol (n=184)**	**Control (n=121)**	**Odds ratio**
a: patient classified as a responder if the absolute increase in FEV_1 from baseline to week 26 was ≥ 100mL. b: patient classified as a responder if the increase in FEV_1 from baseline to week 26 was ≥ 5% of the baseline value. c: patient classified as a responder if the increase in FEV_1 %predicted from baseline to week 26 was ≥ 5%.						

An additional analysis was carried out to look at a combined definition of response where patient classified as a responder if increase in FEV_1 from baseline to week 6 or week 14 was ≥ 5% of the baseline value or there was an absolute increase of at least 100ml in FEV_1 from baseline to week 6 or 14. In DPM-CF-301, 106 (59.9%) Bronchitol patients achieved this response and in DPM-CF-302 the rate was 111 (60.3%). The response rates seen in the control group were 63 (53.4%) for DP-CF-301 and 66 (54.5%) for DP-M-CF-302. These response rates can be compared with the responses rates to the two component parts of the definition (Table 20).

FVC

The effect of treatment on FVC was similar to that on FEV_1 in both studies. In DPM-CF-301, the absolute change in baseline over the post-randomisation period (6-26 weeks) for FVC was higher for Bronchitol (LSmean (SD): 130.77mL (20.5)) than for the control group (LSmean (SD): 21.99mL (23.3)). There was a statistically significant difference between treatments: LSmean difference 108.78mL (95% CI: 49.21, 168.35), $p<0.001$.) In DPM-CF-302, the corresponding mean overall effect on FVC was in favour of Bronchitol (mean difference 71.35mL, 95% CI [10.57, 132.13], $p<0.022$). In both the Bronchitol and control group, the overall absolute improvement from baseline was significant; however, the FVC improvement with Bronchitol treatment was twice that of control.

Summary of spirometry findings

The supportive spirometry findings seen in the overall ITT population reinforce the relevance of the FEV_1 spirometry results.

Further secondary efficacy results

Pulmonary Exacerbations – proportion of patients

The DPM-CF-301 study was not sufficiently powered to show a reduction in the secondary endpoint of exacerbations. Therefore, the incidence (proportion of subjects experiencing at least one exacerbation) was determined for PDPE and PE, but no statistical testing for exacerbation incidence differences was performed.

There were fewer subjects reporting at ≥1 PDPE event in the Bronchitol group (18.1%) than in the control group (28%) which was a reduction in incidence of 35.4%. Similarly, there were fewer

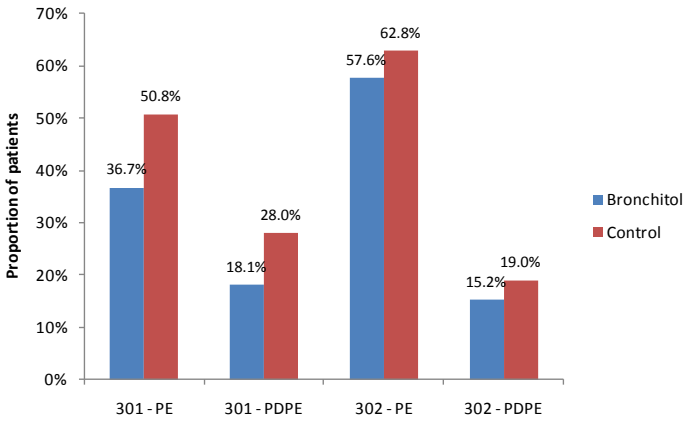
subjects reporting PE events in the Bronchitol group (36.7%) than in the control group (50.8%, reduction in incidence of 27.8%).

A sensitivity analysis was performed post-hoc and showed that in the population of subjects completing 26 weeks of treatment the rate of PDPE was 46.0% lower in the Bronchitol group than the control group (rate ratio 0.54 (0.29,1.01), p=0.0552)

In the DPM-CF-302 overall population, the incidence of subjects with ≥1 protocol defined PDPE was lower for Bronchitol than for control. A 15% reduction in the annualized rate of PDPE was observed for Bronchitol compared with control when adjusted for pre-specified covariates (rate ratio=0.85, 95% CI 0.51, 1.41, p=0.520). Patients with higher historical rates of PE (in the year preceding the participation in the study) had a higher rate of PDPEs (RR=1.59, p<0.001) and the mean number of PEs in the year preceding study participation was higher in the Bronchitol group (mean = 0.7 (SD=1.15)) versus the control group (mean = 0.6, (SD=0.94)).

As seen with PDPE's, the incidence of subjects with ≥1 PE was lower for Bronchitol than for control. A 7% reduction in the annualized rate of PE was observed for Bronchitol compared with control when adjusted for pre-specified covariates (rate ratio=0.93, 95% CI 0.74, 1.17, p=0.551). Also consistent with the findings in the PDPE analysis, subjects with higher historical rates of PE had a higher rate of PEs (RR=1.21, p<0.001)

Figure 7 Proportions of patients with PE and PDPE: Key RCTs



Rate of pulmonary exacerbations

In DPM-CF-301, the PE rate was 14% lower and the PDPE rate was 25% lower in the Bronchitol group compared with the control group although the differences were not significant. In DPM-CF-302, when adjusted for pre-specified covariates, the PE event rate was 7% lower for Bronchitol than for control and the PDPE event rate was 15% lower in the Bronchitol group. Neither of these differences were statistically significant (Figure 8).

In both studies, disease severity (baseline FEV_1% predicted) appeared to have a significant influence on the rate of PE (p<0.001) and on the rate of PDPE (p<0.001).

Figure 8 PE and PDPE event rates: Key RCTs

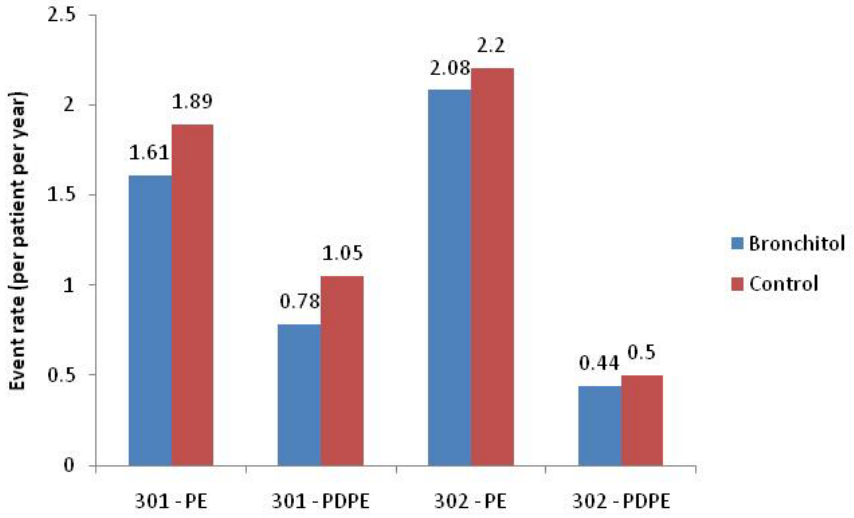


Table 21 PE and PDPE analyses: Key RCTs

Outcome	DPM-CF-301			DPM-CF-302		
	Bronchitol (N=177)	Control (N=118)	Difference	Bronchitol (N=184)	Control (N=121)	Difference
PDPE event rate per subject per year[a]			**Rate ratio**			**Rate ratio**
Overall	0.78 (1.976)	1.05 (2.148)	0.74 (0.47, 1.18) p=NS	0.44 [0.31, 0.60]	0.50 [0.35, 0.72]	0.85 (0.51, 1.41) p=NS
PE event rate per subject per year[a]			**Rate ratio**			**Rate ratio**
Overall	1.61 (2.799)	1.89 (2.522)	0.86 (0.64, 1.17) p=NS	2.08 [1.79, 2.42]	2.20 [1.85, 2.62]	0.93 (0.74, 1.17) p=NS
Median time to first PDPE[b]			**Hazard ratio**			**Hazard ratio**
Overall †	-	-	0.68 (0.42, 1.11) p=NS	-	-	0.74 (0.42, 1.32) p=NS
Median time to first PE[b]			**Hazard ratio**			**Hazard ratio**
Overall †	-	156 [116,-]	0.75 (0.53, 1.07) p=NS	4.05 [3.26; 5.43]	3.39 [2.83; 4.84]	0.87 (0.65, 1.18) p=NS

- median cannot be reported if fewer than 50% of subjects experienced a PE/PDPE
a presented as mean (SD) for DPM-CF-301 and Mean (95% CI) for DPM-CF-302
b presented in days for DPM-CF-301 and months for DPM-CF-302

Time to first PE/PDPE

In DPM-CF-301, the hazard ratio for time to first PDPE was lower for the Bronchitol group than for control but there were no significant differences between treatment groups in time to first PDPE. A similar result was seen for time to first PE (Table 21). However, the trends seen in the ITT population were significant in the PP population in favour of Bronchitol for both PE and PDPE

In DPM-CF-302, the median time to first PDPE was not estimable as less than half the subjects had a PDPE during the study. The median time to first PE overall was longer in the Bronchitol arm (4.05 months) than in the control group (3.39 months). The hazard ratio for Bronchitol compared with control for PDPE was 0.74 and the effect of historical rates of pulmonary exacerbations (HR=1.73, p<0.001), lung function at baseline (HR=0.98, p=0.020) and age (HR=0.96, p=0.054) on the hazard of PDPE was consistent with what was observed in the assessment of the rate of PDPE. Similarly, the hazard ratio (Cox proportional) for time to first PE for Bronchitol compared with control was 0.87 and the effect of historical rates of pulmonary exacerbations (HR=1.26, p<0.001), lung function at baseline (HR=0.99, p=0.013) and age (HR=0.97, p=0.003) on the hazard of PE was consistent with what was observed in the assessment of the rate of PE.

Use of Antibiotics

In both studies intravenous antibiotic use was a criterion for a PDPE, thus, all subjects experiencing a PDPE had rescue antibiotics.

In addition to the reduction in PDPE rates seen with Bronchitol in DPM-CF-301, Bronchitol treatment also reduced the mean days of antibiotic use for PDPEs, measured on a per patient per year basis, by 35.7% (Bronchitol mean 14.46 (SD=36.44) vs. control mean 22.50 (SD=50.14)). These findings were not statistically significant (rate ratio 0.66, 95% CI [0.25, 1.76]) but were consistent with other exacerbation related improvements.

The incidence of rescue antibiotic use for PE (by definition including PDPE) is reduced by treatment with Bronchitol (Bronchitol 35.6% vs. control 50.8%). The mean number of days of antibiotic use per patient per year was also reduced by Bronchitol treatment by 29.6% (mean (SD): Bronchitol: 26.76 (46.75) vs. control: 38.03 (56.71) days) but the difference was not statistically significant (rate ratio 0.73, 95% CI [0.39, 1.37]).

In DPM-CF-302, consistent with Bronchitol patients having a lower incidence of PDPEs, the incidence of rescue antibiotic use was lower for Bronchitol (15.2%) compared to control (19%). There was an 11% reduction in the mean number of days of rescue antibiotic use for PDPEs with Bronchitol (mean (SD): Bronchitol 10.5 (31.32) vs. control: 14.9 (41.25)) but this difference was not statistically significant (rate ratio 0.89, 95% CI [0.69, 1.15]).

Similarly, the use of rescue antibiotics all-cause PE was lower in the Bronchitol group (55.4%) than in the control group (61.2%), a 9.5% reduction. There was also a 9% reduction in the rate of antibiotic use for PE in the Bronchitol group compared with the control group when adjusted for covariates (rate ratio=0.91[95% CI 0.78, 1.07], p=0.266). The mean (SD) number of days of rescue antibiotic use for PE per patient per year was lower for Bronchitol (mean (SD) Bronchitol 32.4 (48.66) vs. control 38.1 (56.07)).

Hospitalisations for Pulmonary Exacerbations

The DPM-CF-301 results showed that 86% of the Bronchitol group and 82% of the control group did not experience any days in hospital due to PDPEs and 79% vs. 76% spent no days in hospital due to PEs. The average number of days of hospitalisation (normalised to days per patient per year) was slightly higher in the Bronchitol group than in the control group for PDPEs (mean (SD) days: 8.06 (23.88) vs. 7.11 (20.69)) and the regression model showed no significant differences between treatments (rate ratio: 0.94 95% CI [0.26, 3.42], p=NS). The treatment groups has very similar days of hospitalisation for PEs (mean (SD) days: 11.10 (25.89) vs. 11.50 (30.16)) and again there were no significant differences between treatments (rate ratio 0.88 95% CI [0.32, 2.39], p=NS).

The DPM-CF-302 results showed that 87% of the Bronchitol group and 84% of the control group did not experience any days in hospital due to PDPEs and 84% vs. 80% spent no days in hospital due to PEs. There was a 25% reduction in the rate of hospitalisations for PDPE (mean days per person per year: Bronchitol 0.33 vs. control mean 0.42; rate ratio 0.75, 95% CI [0.42, 1.33], p=NS). There was also a 25% reduction in the rate of hospitalisation for PEs for Bronchitol compared with control when adjusted for covariates (mean days per person per year: Bronchitol 0.45 vs. control 0.54; rate ratio 0.75, 95% CI 0.45, 1.25, p=NS).

Quality of life

The CFQ-R domains considered most relevant to assess a pulmonary directed therapy are respiratory, vitality and physical (Table 22).

In DPM-CF-301, Bronchitol improved the respiratory domain compared to control (mean 3.9 points) approaching the minimum clinically significant difference of 4 points for this domain in patients with stable disease (Quittner et al, 2009, see Appendix 18). Although the differences do not reach statistical significance, the other important domains achieved a treatment effect of 4.2 for physical and 7.2 for vitality. In DPM-CF-301, Bronchitol improved these domains compared to control (respiratory 3.9; physical 4.2; vitality 7.2) although the differences do not reach statistical significance. The mode of action of Bronchitol is to increase sputum production, thus, the standard respiratory domain incorrectly penalises this desired effect. When the sputum production question is removed from the respiratory domain the improvement in score compared to control exceeds the minimum clinically significant difference of 4 points).

The biggest positive treatment effect was observed in the vitality domain (effect size 1.8, p=0.146), and the largest negative treatment effect in the burden of treatment domain (effect size -1.61, p=0.1466).

In DPM-CF-302, there were no meaningful differences in mean change over baseline for either treatment group or between treatment groups for any of the QoL domains. The differences between Bronchitol and control group scores for both respiratory, physical domains of the CFQ-R were in favour of the control group. When excluding the mucus question from the respiratory domain, the difference between Bronchitol and control improved slightly but remained in favour

of the control group. Domain scores in favour of Bronchitol included vitality although the difference between Bronchitol and control was not clinically meaningful.

Table 22 Quality of life data (CFQ-R): Key RCTs

Outcome	DPM-CF-301		DPM-CF-302	
	Bronchitol (N=177)	Control (N=118)	Bronchitol (N=184)	Control (N=121)
Respiratory Domain				
Change pre-study – Week 26	1.3 (15.95)	-2.5 (17.55)	-1.4 (20.16)	5.6 (22.51)
Physical Domain				
Change pre-study – Week 26	-0.5 (16.22)	-4.7 (17.56)	-1.7 (18.85)	1.1 (18.20)
Vitality Domain				
Change pre-study – Week 26	2.1 (15.88)	-5.1 (18.13)	-1.6 (20.48)	-4.2 (17.72)

Data are presented as mean (SD)

The HUI utility values recorded at each timepoint are shown in Table 23.

Table 23 Utility values (HUI2): DPM-CF-302

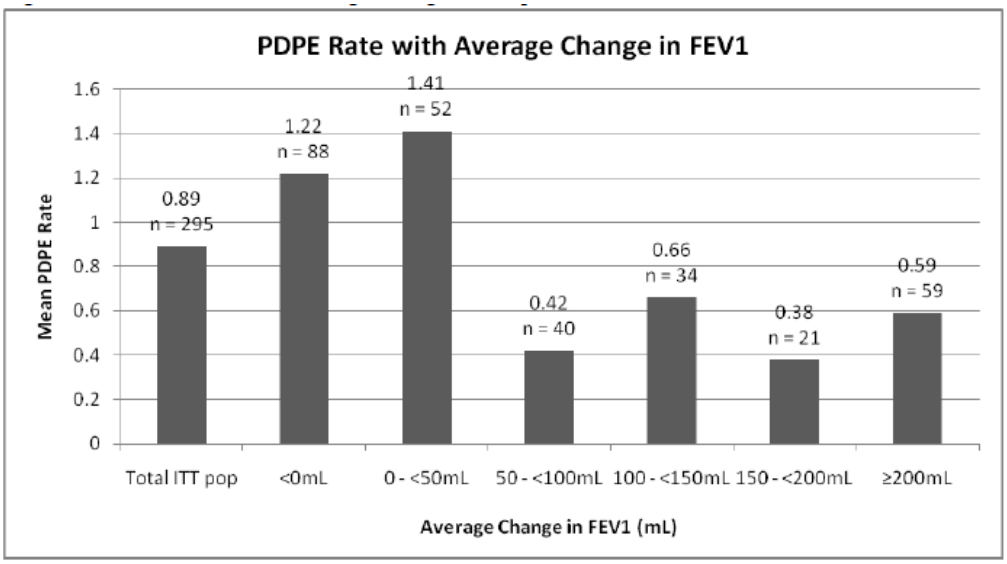
	Bronchitol (N=184)	Control (N=121)
Screening	0.915 (0.097)	0.919 (0.095)
Week 14	0.920 (0.099)	0.914 (0.085)
Week 26	0.909 (0.124)	0.917 (0.099)

Data are presented as mean (SD)

Additional analyses

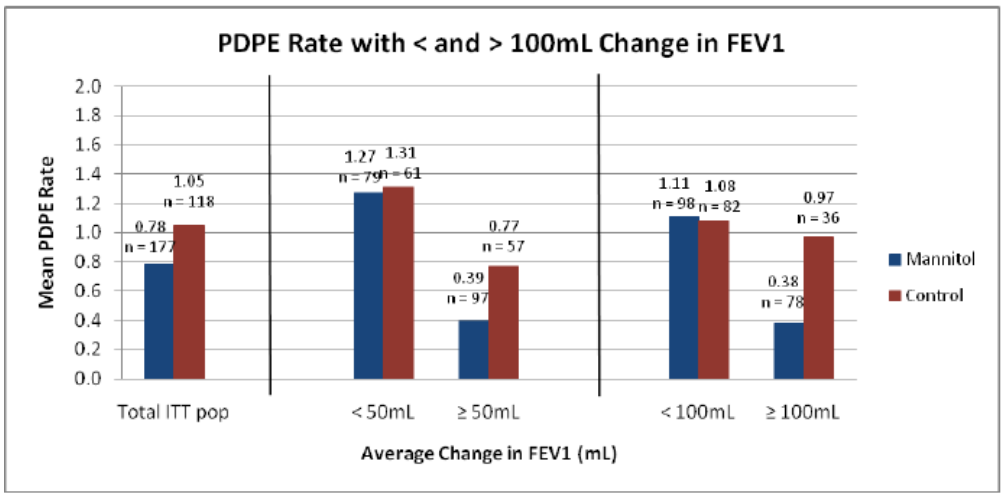
A post hoc analysis from DPM-CF-301 of FEV_1 responders shows that in those patients who have improvements in FEV_1, pulmonary exacerbations are reduced substantially (Figure 9,). Importantly, the reduction in exacerbation was most marked in the subjects from the Bronchitol group who had improved lung function. However exacerbations were not reduced in responders from the control group.

Figure 9 PDPE Rate with Average Change in FEV_1: DPM-CF-301



Source: EMEA Response Document Qu.1. Figure 5

Figure 10 Overall ITT PDPE Rate with < and > 50 & 100mL Change in FEV_1: DPM-CF-301



Source: EMEA Response Document Qu.1. Figure 6

Conclusions for overall population

Two large pivotal double blind randomised controlled studies evaluation the efficacy of Bronchitol in patients with CF. Bronchitol significantly improved lung function over 26 weeks in patients with CF measured by change in FEV_1 from baseline ($p<0.001$ compared to control; DPM-CF-301). In the DPM-CF-302 study, patients in the Bronchitol had a greater but not significant improvement in FEV_1 than subjects in the control group; however analyses which accounted for FEV1 changes seen between screening and baseline resulted in a significant treatment difference comparable to that seen in DPM-CF-301. The positive effect of Bronchitol

was evident over the first 6 weeks of treatment and was maintained over the 26 week double blind phase. Additionally, these FEV_1 results are very consistent with the data seen in phase II studies which include adult patients (Appendix 2).

The response to treatment with Bronchitol (defined by FEV_1 thresholds) was significantly greater for patients treated with Bronchitol compared to control in DPM-CF-302, and approximately twice that of the control group in the Bronchitol group in DPM-CF-301. The treatment effect of Bronchitol is supported by the results seen in additional spirometry measures.

The rate of pulmonary exacerbations and associated antibiotic treatment was numerically reduced with Bronchitol treatment independent of concomitant rhDNase use. The consistency and effect size strongly suggest a meaningful effect of Bronchitol although statistical significance was not achieved.

Overall, the use of Bronchitol in the overall population (which included adult patients) shows positive results for Bronchitol therapy over control (BSC).

Subgroup analysis – rhDNase use

Change in FEV_1 by rhDNase use

The results from DPM-CF-301 showed that regardless of concomitant rhDNase user there was an almost identical and significant improvement in FEV_1 from baseline over the 26 week double blind study period ($p<0.01$ for both sub-groups). There was no interaction between treatment and rhDNase use (Table 24).

In the rhDNase users group, analysis of the data at each time-point showed that the mean change in FEV_1 was significantly greater for patients treated with Bronchitol than it was for patients in the control group. Similarly, in the rhDNase non-user group, the mean change in FEV_1 was significantly greater at weeks 6 and 14 for patients treated with Bronchitol than it was for patients treated with control. At week 26, the difference was not considered statistically significant.

Additional analyses of % change from baseline in FEV_1 showed that there were significant advantages for Bronchitol at weeks 14 and 26 in the rhDNase user group and at weeks 6 and 14 in the non-user group.

Overall in DPM-CF-302, Bronchitol significantly improved FEV_1 compared with control in the ITT population when adjusted for rhDNase use at baseline (LSmean difference 65mL). The change from baseline to post-baseline (weeks 6-26) was significant in the Bronchitol arms irrespective from rhDNase use. Using the corrected baseline FEV_1 model, the overall treatment effect in rhDNase users was 56.89mL ($p=0.057$) and 105.63mL ($p=0.043$) in non-users. At all time points the treatment effect was greater in the Bronchitol group than the control group for rhDNase users and non-users in this study.

Analyses based on % change from baseline in FEV_1 by rhDNase use groups were generally consistent with those reported above for absolute change in FEV_1, and favoured Bronchitol overall.

These results confirm the efficacy of Bronchitol regardless of the rhDNase use at the start of therapy.

Table 24 Overall change in FEV_1 by rhDNase use: pivotal RCTs

Outcome	DPM-CF-301			DPM-CF-302		
	Bronchitol	**Control**	**Difference**	**Bronchitol**	**Control**	**Difference**
Average change from baseline across the study (weeks 6-26) (mL)						
rhDNase Users	**N=96**	**N=67**		**N=137**	**N=92**	
	85.22 [43.30; 127.14]	11.40 [-37.47; 60.26]	73.82 [12.04, 135.61] p=0.019	78.6 [27.64, 129.56]	35.11 [-20.99, 91.21]	43.49 [-19.80, 106.78] p=NS
rhDNase non-Users	**N=81**	**N=51**		**N=47**	**N=29**	
	152.80 [106.87; 198.73]	48.46 [-4.35; 101.27]	104.34 [36.08; 172.61] p=0.003	142.3 [69.62, 215.00]	55.8 [-32.86, 144.48]	86.5 [-23.78, 196.79] p=NS

Data presented as LSmean (95% CI)
This analysis was based on an MMRM model with term for treatment x rhDNase use together with all two way interactions

Other pulmonary endpoints

% predicted FEV1, response

In DPM-CF-301, analyses based on the combined response definition showed higher response rates for Bronchitol than control in the rhDNase user subgroup and similar rates in the non-user subgroup. In DPM-CF-302 the results seen by rhDNase use groups were also generally consistent with those reported above for absolute change in FEV_1, and favoured Bronchitol overall. Among rhDNase users the overall treatment effect favoured the Bronchitol group; 3.45% (95% CI 0.91 to 5.99), p = 0.008. In the Bronchitol group the mean change from baseline was 2.41% (95% CI 0.46 to 4.36) while it was -1.04% (95% CI-3.26 to 1.99) in the control group. Among rhDNase non-users the overall treatment effect favoured the Bronchitol group; 2.41% (95% CI –2.36 to 7.18), p = 0.320. In the Bronchitol group the mean change from baseline was 5.55% (95% CI 2.46 to 8.64) while it was 3.14% (95% CI-0.65 to 6.92) in the control group.

FEV_1 response

In DPM-CF-302, Analyses based on the three definitions of FEV_1 response showed numerical advantages for Bronchitol in the rhDNase user group (all odds ratios >1.8 for Bronchitol vs. control) and in the rhDNase non-user group the treatment groups were very similar. Analysis based on the combined response also showed generally higher response rates in rhDNase

users vs. non users but for both subgroups and the response rates were higher with Bronchitol in the rhDNase user group.

Pulmonary Exacerbations

In the rhDNase user group in DPM-CF-301, there were a lower proportion of subjects reporting at least one PDPE event in the Bronchitol group (22.9%) than the control group (31.3%, 26.8% lower for Bronchitol). Correspondingly, the PDPE mean event rate (per patient per year) was 24% lower in the Bronchitol group than in the control treatment group, however this was not significant (Table 25).

Amongst rhDNase users, there were a lower proportion of subjects reporting PE events in the Bronchitol group (40.6%) than the control group (55.2%, 26.4% lower for Bronchitol). The PE mean rate was lower in the Bronchitol group than in the control group corresponding to a non-significant 22% lower incidence. FEV_1% predicted appeared to have a significant impact on PE in this population ($p<0.001$).

In the rhDNase non-users population there was also a lower proportion of subjects reporting PDPE events in the Bronchitol group (12.3%) than the control group 23.5%, 47.7% lower for Bronchitol). The PDPE event rate per patient per year was 32% lower in the Bronchitol group than in the control group (p=NS).

In the rhDNase non-users population there was also a lower proportion of subjects reporting PE events in the Bronchitol group (32.1%) than the control groups (45.1%, 28.8% lower for Bronchitol). The PE rate was lower in the Bronchitol treatment group than in the control treatment group (9.3% lower incidence), however this was not significant. Again, disease severity did appear to have a significant impact on PE in this population, p=0.007.

In DPM-CF-302, the incidence of PDPE was similar for both treatment groups in the rhDNase user group (17.5% vs. 17.4%). The annualised rate of PDPE in this group increased by 9% in the Bronchitol group compared with control. Amongst the rhDNase users, similar proportions of patients had ≥1 PE (Bronchitol 62.8% vs. control 63%) and this was also reflected in the annualised rate of PE. The annualised rate of PDPE in the rhDNase users increased by 9% in the Bronchitol group compared with control.

Among non-rhDNase users, the incidence of subjects who had ≥1 PDPE was lower for Bronchitol (8.5%) than control group (24.1%). The annualised rate of PDPE was reduced by 66% for Bronchitol compared with control. Consistent with the finding for PDPE among rhDNase non-users, the incidence of subjects with ≥1 PE was lower for Bronchitol than control (42.6% vs. 62.1%) but there were no significant differences between treatments in the annualised rate of PE.

In DPM-CF-302, the overall trend in exacerbation reduction in Bronchitol group is driven in part by the lower PDPE rate in rhDNase non-users in the Bronchitol group, where the PDPE rate was

less than 25% of that seen in the control group. The small numbers of subjects in each subgroup, however, preclude any meaningful conclusions.

Table 25 Pulmonary exacerbations in the rhDNase subgroups: Key RCTs

Outcome	DPM-CF-301			DPM-CF-302		
	Bronchitol	**Control**		**Bronchitol**	**Control**	
rhDNase Users	n=96	n=67		n=137	n=92	
rhDNase non-Users	n=81	n=51		n=47	n=29	
PDPE event rate per patient per year[a]			**Rate ratio**			**Rate ratio**
rhDNase Users	1.05 (2.288)	1.19 (2.303)	0.76 (0.45, 1.27) p=NS	0.53 [0.37, 0.75]	0.43 [0.27, 0.67]	1.09 (0.61, 1.95) p=NS
rhDNase Non-Users	0.47 (1.479)	0.86 (1.932)	0.59 (0.24, 1.47) p=NS	0.18 [0.07; 0.49]	0.74 [0.40, 1.37]	0.34 (0.10, 1.09) p=NS
PE event rate per patient per year[a]			**Rate ratio**			**Rate ratio**
rhDNase Users	1.82 (2.803)	2.18 (2.746)	0.76 (0.55, 1.06) p=NS	2.36 [2.00; 2.78]	2.20 [1.80, 2.68]	1.00 (0.77, 1.30) p=NS
rhDNase Non-Users	1.37 (2.792)	1.51 (2.161)	0.94 (0.95, 1.56) p=NS	1.33 [0.92; 1.91]	2.22 [1.55; 3.17]	0.69 (0.41, 1.16) p=NS

a presented as mean (SD) for DPM-CF-301 and Mean (95% CI) for DPM-CF-302

As for the overall populations, analyses of antibiotic use and hospitalisation days both reflect the patterns seen in the rate of PE/PDPE for each study.

Efficacy conclusions by rhDNase use

All main analyses in both studies included rhDNase stratum as a covariate in the models and this was not found to be a factor which influences the results. Therefore, from these analyses, it did not appear that the effect of Bronchitol on key outcomes of interest would be expected to differ in the rhDNase user and non-user groups.

Data analyses of both pivotal studies were carried out for the rhDNase strata separately. Analyses of FEV_1 in DPM-CF-301 showed that regardless of concomitant rhDNase user there was an almost identical and significant improvement in FEV_1 from baseline over the 26 week double blind study period. Similar analyses in DPM-CF-302 also showed a consistent effect for Bronchitol regardless of rhDNase use.

Analyses of PDPE / PE data showed a generally lower rate of events for patients in the rhDNase non-user group. In all cases in DPM-CF-301, the incidence rates reported for Bronchitol patients were lower than for control patient although there were no significant differences between treatments. In DPM-CF-302, the overall trend in exacerbation reduction in Bronchitol group is driven in part by the lower PDPE rate in rhDNase non-users in the Bronchitol group, where the

PDPE rate was less than 25% of that seen in the control group. Analyses of antibiotic use and hospitalisation days both reflect the patterns seen in the rate of PE/PDPE for each study (as seen in the overall population analyses).

These results confirm the efficacy of Bronchitol regardless of the rhDNase use at the start of therapy.

Adult only population

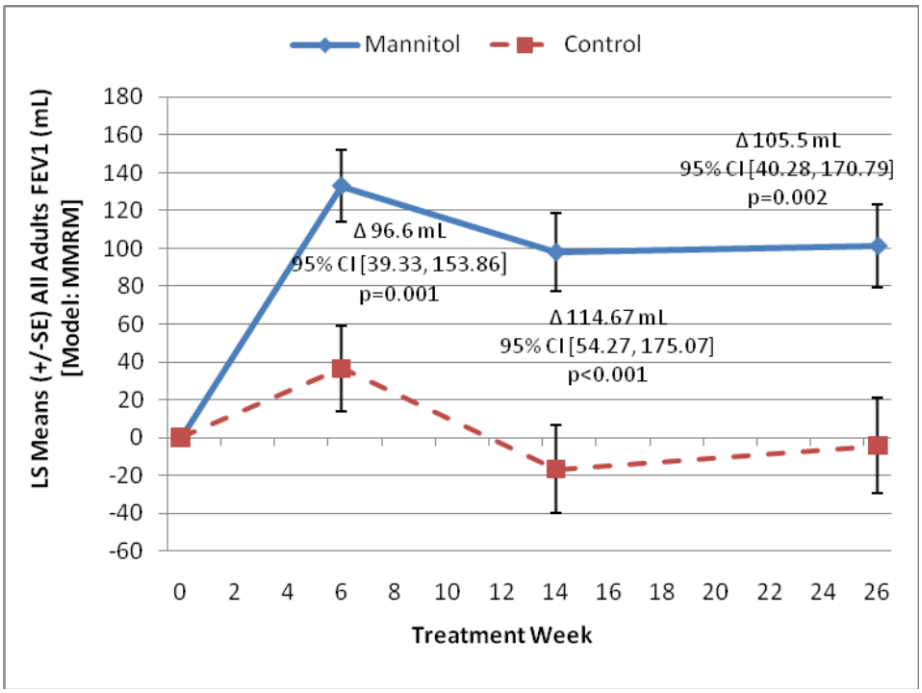
The adult only population is the patient population which is the focus on the anticipated product licence. Study DPM-CF-301 was not designed specifically to generate analyses in this patient group but the primary endpoint has been analysed separately for this population. In DPM-CF-302, analyses by age subgroups were pre-defined and will be summarised below.

In the analyses of the study endpoints for the overall population, the majority of the statistical models have included an adjustment factor for age. This has not been reported as a significant factor impacting the results or conclusions so it would therefore be expected that the results seen in the overall study populations above would be reflected in the adult only population.

For DPM-CF-301, a post-hoc analysis of the change in FEV_1 from baseline was carried out for the overall effect and at the different timepoints for the adult only population. These data show significant advantages for Bronchitol overall (6-26 weeks) (mean difference between treatments: 103.09mL, 95% CI [61.96, 144.24], p<0.0001] and at each timepoint in this patient population (Figure 11). The change in % predicted FEV_1 showed a similar pattern with statistically significant advantages for Bronchitol across 6-26 weeks (mean difference between treatment: 2.59%, 95% CI [1.11, 4.08], p=0.001) and at all timepoints. Analyses based on ANCOVA models also had similar results showing the robust nature of this endpoint in the adult only population in DPM-CF-301.

For DPM-CF-301, a post-hoc analysis of the change in FEV_1 from baseline was carried out at the different timepoints for the adult only population. These data show significant advantages for Bronchitol at each timepoint in this patient population. The change in % predicted FEV_1 showed a similar pattern with statistically significant advantages for Bronchitol at all timepoints. Analyses based on ANCOVA models also had similar results showing the robust nature of this endpoint in the adult only population in DPM-CF-301.

Figure 11 FEV_1 change from baseline in adult only population: DPM-CF-301 at each timepoint



Additional analyses by rhDNase subgroup showed similar results to those seen in the overall population analysis by rhDNase subgroup. In both rhDNase subgroups there were advantages for Bronchitol at all timepoints for the FEV_1. In the rhDNase user group, the differences were statistically significant at weeks 14 and 26 while in the non-user group the differences were statistically significant at weeks 6 and 14. Analyses of change in % predicted FEV_1 reflected those of FEV_1 in both rhDNase subgroups.

These analyses based on DPM-CF-301 show that the effects seen in the overall population in terms of FEV_1 outcomes are consistently reflected in the adult only population and show significant advantages for Bronchitol.

Several key outcomes have been analysed in the adult only population and these are discussed in more detail below. Subgroup analysis by age was generally consistent with overall ITT population and favoured Bronchitol in the adult only population (≥18 years of age). Further spirometry measure support the favourable effect of Bronchitol in this adult subpopulation (Table 26). Overall, the data in the adult only population show a pattern of results that is very consistent with that seen in the overall population.

Table 26 Key pulmonary outcomes in the adult only population: Pivotal RCTs

Outcome	DPM-CF-301			DPM-CF-302		
	Bronchitol (N=114)	Control (N=76)	Difference	Bronchitol (N=93)	Control (N=58)	Difference
Treatment effect from baseline across the study (weeks 6-26) (mL)[a]						
Overall	-[b]	-[b]	103.09 [61.96,144.24] p=0.001	113.51 [44.38, 182,64]	27.57 [-47.96, 103.1]	85.94 [4.63, 167.26] p=0.038
Change in FEV_1 (mL) from baseline at each timepoint						
Week 6	133.8 (227.02)	36.7 (185.25)	96.6 [39.33, 153.86] p=0.001	116.1 (252.70)	41.4 (221.67)	85.94 [-0.5, 172.38] p=0.051
Week 14	100.3 (266.91)	-11.8 (227.58)	114.67 [54.27, 175.07] p<0.001	57.5 (261.11)	4.7 (233.59)	53.37 [-42.3, 149.05] p=0.273
Week 26	115.6 (255.62)	-29.0 (254.32)	105.5 [40.28, 170.79] p=0.002	57.8 (260.33)	-64.7 (364.43)	118.52 [10.35, 226.68] p=0.032
% change in FEV_1 from baseline across the study (weeks 6-26) (%)[a]						
Overall	5.04 [3.12, 6.95]	0.71 [-1.49, 2.91]	4.33 [1.50, 7.17] p=0.003	6.41 [2.22, 10.59]	1.27 [-3.30, 5.84]	5.14 [0.23, 10.05] p=0.040
Change in % predicted FEV_1 from baseline to week 26 (%)						
Overall	2.76 [1.74, 3.78]	0.20 [-0.97, 1.38]	2.55 [1.04, 4.06] p=0.001	2.87 [0.85, 4.89]	0.54 [-1.8, 2.88]	2.33 [-0.4, 5.06] p=NS
Change in FVC from baseline across the study (weeks 6-26)						
Overall	105.61 [48.11, 163.12]	-6.99 [-72.56, 58.57]	112.60 [28.29, 196.92] p=0.009	154.56 [80.7, 228.4]	40.79 [-40.6, 122.2]	113.77 [26.14, 201.4] p=0.011

Data are presented as mean (SD) or LSmeans and associated 95% CIs; differences are difference between LSmeans (95% CI)
a analyses are based on change from baseline to weeks 6-26 for both studies
b data not available from the analyses carried out

In adults (≥18 years of age), the incidence of patients ≥1 PPE was lower for Bronchitol than control in DPM-CF-301 but slightly higher for Bronchitol in DPM-CF-302. In DPM-CF-302, the mean (SD) number of pulmonary exacerbations in the year preceding study participation was higher in the Bronchitol group [0.8 (1.33)] versus the control group [0.6 (0.84)] for adults age ≥ 18 years of age which may have influenced the results seen in this study. The incidence of those adults with ≥1 PE was lower among subjects in the Bronchitol group than in the control group for both studies These data are reflected in the event rates which are similar for the treatment groups for PE and slightly higher for Bronchitol in terms of PDPE events. Therefore, as seen in the overall population, the annual rate of PE and PDPE per patient in the adult only population is higher in the Bronchitol group than in the control group (Table 27).

Table 27 Pulmonary exacerbations in the adult population: Pivotal RCTs

	DPM-CF-301			DPM-CF-302		
Outcome	**Bronchitol (N=114)**	**Control (N=76)**	**Rate Ratio**	**Bronchitol (N=93)**	**Control (N=58)**	**Rate ratio**
Proportion of patients with PDPE	26 (22.8%)	27 (35.5%)	-	15 (16.1%)	8 (13.8%)	-
PDPE event rate (per patient per year)	1.05 (2.295)	1.43 (2.501)	0.77 [0.47, 1.25] p=NS	0.46 [0.29, 0.72]	0.29 [0.15, 0.58]	1.39 [0.59, 3.31] p=0.454

- not applicable
Data reported as mean (SD) for DPM-CF-301 and mean (95% CI) for DPM-CF-302; rate ratio reported as rate (95% CI)

In terms of quality of life impact, in the adult subpopulation of DPM-CF-302, the physical and vitality domain of the CFQ-R were in favour of Bronchitol compared to control (Table 28). In the respiratory domain, the score was lower in the Bronchitol group than in the control group. However, as seen in the overall population, the desired effect of Bronchitol to increase sputum may penalise this subdomain of the CFQ-R.

Table 28 Quality of life data (CFQ-R) in adult population: DPM-CF-302

	Bronchitol (N=93)	**Control (N=58)**
Respiratory Domain		
Change Weeks 0-26	-1.3 (20.65)	2.2 (21.16)
Physical Domain		
Change Weeks 0-26	-1.4 (15.62)	-2.0 (17.13)
Vitality Domain		
Change Weeks 0-26	-0.6 (21.35)	-5.0 (17.70)

Data are presented as mean (SD)

Based on DPM-CF-302, analyses of the HUI data in the adult only population showed that the mean values of change from baseline were similar for the two treatment groups (mean (SD) – Bronchitol: 0.8743 (0.1284) vs. control: 0.8756 (0.1547) and there was no significant difference between treatments.

Several of the pulmonary measures were also analysed for the adult rhDNase user and non-user subgroups (Table 29).

Table 29 Key pulmonary outcomes in rhDNase subgroups of the adult only population: pivotal RCTs

	DPM-CF-301			DPM-CF-302		
Outcome	**Bronchitol (n=114)**	**Control (n=76)**	**Difference**	**Bronchitol (n=93)**	**Control (n=58)**	**Difference**
Change in FEV_1 from baseline across the study (weeks 6-26) (mL)						
rhDNase users	-[a]	-[a]	109.27 [52.77, 165.77] p<0.001	106.27 [27.16, 185.38]	17.82 [68.02, 103.66]	88.45 [-8.46, 185.36] p=0.073
rhDNase non-users	-[a]	-[a]	96.92 [37.72, 156.12] p=0.002	92.57 [-9.49, 194.62]	7.17 [-115.60, 129.94]	85.39 [-58.80, 229.59] p=0.245
% change in FEV_1 from baseline across the study (weeks 6-26) (%)						
rhDNase users	2.85 [0.17, 5.54]	-1.34 [-4.33, 2.67]	4.19 [0.31, 8.07] p=0.034	5.94 [1.14, 10.74]	0.51 [-4.71, 5.72]	5.43 [-0.44, 11.31] p=0.07
rhDNase non-users	7.22 [4.61, 9.84]	2.74 [-0.46, 5.93]	4.49 [0.42, 8.56] p=0.031	4.89 [-1.31, 11.09]	0.11 [-7.35, 7.57]	4.78 [-3.98, 13.54] p=0.283
Change in % predicted FEV_1 baseline across the study (weeks 6-26)						
rhDNase users	1.65 [0.22, 3.08]	-1.01 [-2.62, 0.59]	2.66 [0.59, 4.73] p=0.012	1.98 [-0.59, 4.55]	-0.96 [-4.00, 2.07]	2.95 [-0.61, 6.50] p=0.104
rhDNase non-users	3.87 [2.47, 5.26]	1.43 [-0.28, 3.13]	2.44 [0.27, 4.61] p=0.028	2.61 [-0.89, 6.11]	1.17 [-3.33, 5.67]	1.44 [-3.96, 6.84] p=0.600
Change in FVC from baseline across the study (weeks 6-26)						
rhDNase users	81.35 [0.65, 162.05]	-36.07 [-126.4, 54.29]	117.42 [1.00, 233.85] p=0.048	147.58 [62.86, 232.29]	50.64 [-42.78, 144.06]	96.94 [-7.68, 201.55] p=0.069
rhDNase non-users	129.77 [50.90, 208.64]	22.52 [-72.61, 117.65]	107.25 [-14.17, 228.67] p=NS	155.83 [46.51, 265.16]	-0.57 [-131.08, 129.94]	156.41 [0.82, 312.00] p=0.049

Data are presented as LSmean (SD) or LSmean (95% CI) and are based on change from baseline to post baseline (weeks 6-26)
a not available

Among adult rhDNase users in DPM-CF-302, the mean change from baseline in FEV_1 was higher for Bronchitol than for control although the mean treatment difference was not significant. Using the corrected baseline FEV_1 model for DPM-CF-302, the overall treatment effect in adult rhDNase users was 135.22mL (p=0.003).

Among adult rhDNase non-users similar results were seen for the overall analysis. Using the corrected baseline FEV_1 model for DPM-CF-302, the overall treatment effect in adult rhDNase non-users was 114.08mL (p=0.091). At all time points the treatment effect was greater in the Bronchitol group than in the control group although none of the differences were statistically significant.

Therefore, FEV_1 results for the rhDNase subgroups are consistent with the overall results in the adult population and the pattern of results is similar to that seen in the overall ITT population.

Conclusions of adult only population

In DPM-CF-301 the analyses of the primary outcome showed very consistent FEV_1 results to the overall population. The MMRM models predicted significant advantages at each timepoint for change from baseline in both FEV_1 and % predicted FEV_1. Subgroup analysis by age was generally consistent with overall ITT population and in the adult only population the results favoured Bronchitol. This supports the fact that all primary analyses (on the overall ITT populations) were adjusted for age and therefore the results should apply to the adult population too. Analyses of key endpoints for the rhDNase subgroups of the adult population showed no unexpected findings compared with what was seen in the overall population. Data on additional outcomes measures (pulmonary exacerbations, QOL) also show consistent results in the adult population compared with the overall ITT population.

Based on these results, the conclusions drawn from the overall population appear to hold for the adult only population and Bronchitol treatment shows significant advantages in terms of pulmonary measures in both studies.

5.6 Meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.9 to 5.3.12.

A total of two key RCTs were identified from the literature and have been discussed above. Data from the adult only population of the two key RCTs (DPM-CF-301 and DPM-CF-302) were combined in order to provide an overall estimate of treatment effect. The endpoints analysed were those relevant for the economic model:

- % predicted FEV_1
- FEV_1 responder
- Per patient per year rate of PDPE

Although the impact of Bronchitol treatment on patient QoL is of importance in the assessment of treatment effectiveness, no significant differences were seen between treatment in any of the domains of the CFQ-R. Therefore these data have not been combined for analysis. The HUI2 data are relevant to the target patient population but were only collected in DPM-CF-302 and have been reported above.

The methodology used to analyses the specific endpoints followed that described in the individual studies but including data from the adult only populations from each of the two studies.

The results based on the final model for % predicted FEV_1 are presented in Table 30 below and details are given in Appendix 17. Advantages were seen in the combined adult only population in line with treatment differences seen in the adult only populations (Figure 11, Table 26).

Table 30 % predicted FEV_1 adult only population: combined DPM-CF-301 and DPM-CF-302

	Bronchitol	Control	Difference between treatments
DPM-CF-301			
Overall adult only Baseline predicted (%) Change from baseline to week 26[a]	N=114 58.1 (15.91) 2.76 [1.74, 3.78]	N=76 57.3 (16.79) 0.20 [-0.97, 1.38]	2.59 [1.11, 4.08] p=0.001
Adult only rhDNase users Change from baseline to week 26[b]	N=58 1.65 [0.22, 3.08]	N=44 -1.01 [-2.62, 0.59]	2.66 [0.59, 4.73] p=0.012
Adult only rDNase non-users Change from baseline to week 26[b]	N=56 3.87 [2.47, 5.26]	N=32 1.43 [-0.28, 3.13]	2.44 [0.27, 4.61] p=0.028
DPM-CF-302			
Overall adult only Baseline predicted (%) Change from baseline to week 26 [b]	N=93 61.9 (15.0) 2.87 [0.85, 4.89]	N=58 59.8 (14.3) 0.54 [-1.8, 2.88]	2.33[b] [-0.4, 5.06] p=0.095
Adult only rhDNase users Change from baseline to week 26[b]	N=64 1.98 [-0.59, 4.55]	N=41 -0.96 [-4.00, 5.67]	2.95 [-0.61, 6.50] p=0.104
Adult only rDNase non-users Change from baseline to week 26[b]	N=29 2.61 [-0.89, 6.11]	N=17 1.17 [-3.33, 5.67]	1.44 [-3.96, 6.84] p=0.600
Combined			
Overall adult only Baseline predicted (%)[c] Change from baseline in %predicted FEV_1 [d]	N=207 59.82 (15.51) 2.55 [1.73, 3.67]	N=134 58.38 (15.76) -0.02 [-1.36, 1.31]	2.55 [0.91, 4.18] p=0.002
Adult only rhDNase users Change from baseline in %predicted FEV_1 [d]	N=122 1.72 [0.24, 3.21]	N=85 -0.64 [-2.32, 1.04]	2.36 [0.27, 4.46] p=0.027
Adult only rDNase non-users Change from baseline in %predicted FEV_1 [d]	N=85 3.29 [1.61, 4.98]	N=49 0.40 [-1.67, 2.48]	2.89 [0.29, 5.50] p=0.030

Data presented as mean (SD) and 95% CI
a data calculated based on baseline values
b calculated based change from baseline to post baseline values (weeks 6-26) using a mixed model repeated measures analysis

c calculated as weighted mean of DPM-CF-301 and DPM-CF-302
d calculated using mixed model repeated measures analysis of DPM-CF-301 and DPM-CF-302 using imputed height.

Analyses were also carried out based on the FEV_1 responder definition described earlier (a relative increase of at least 5% or an absolute increase of at least 100ml in the FEV_1 at week 6 from baseline) in order to assess the early response to Bronchitol (Table 31).

Table 31 FEV_1 responders, adult only population: combined DMP-CF-301 and DMP-CF-302

	Bronchitol (n=207)	Control (n=134)
Baseline to week 26		
FEV_1 ≥100 mL[a]	72 (34.8%)	30 (22.4%)
FEV_1 ≥5% [b]	68 (32.9%)	30 (22.4%)
% pred. FEV_1 ≥5%[c]	48 (23.2%)	19 (14.2%)
Baseline to week 6		
Combined Responder at week 6[d]	100 (48.3%)	46 (34.3%)

a: patient classified as a responder if the absolute increase in FEV_1 from baseline to week 26 was ≥ 100mL.
b: patient classified as a responder if the increase in FEV_1 from baseline to week 26 was ≥ 5% of the baseline value.
c: patient classified as a responder if the increase in FEV_1 %predicted from baseline to week 26 was ≥ 5%.
d relative increase of at least 5% or an absolute increase of at least 100ml in the FEV_1 at week 6 from baseline

The results of the combined pulmonary exacerbations data are show in Table 32 and show very similar results to those seen in the overall study populations from DPM-CF-301 and DPM-CF-302. It should be noted that when the data from the two studies were combined, no adjustment was made for historical exacerbation rates and therefore the combined data may appear lower than for the individual studies.

Table 32 Pulmonary exacerbations in adult only population: combined DMP-CF-301 and DMP-CF-302

Outcome	Bronchitol (n=207)	Control (n=134)
Incidence of PDPE	41 (19.8%)	35 (26.1%)
Event rate per patient per year	0.63 [0.48, 0.82]	0.75 [0.56, 1.00]

These analyses again support the robust nature of the data from these two studies – results seen in the overall population are generally reflected in the adult only population and results seen when combining the two studies are consistent with those results.

5.7 Indirect and mixed treatment comparisons

Data from head-to-head RCTs should be presented in the reference-case analysis, if available. If data from head-to-head RCTs are not available, indirect treatment comparison methods should be used. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.13 to 5.3.22.

In order to compare Bronchitol with BSC in rhDNase users and non-users, direct head-to-head clinical trials provided the best source of evidence and no indirect comparisons were necessary.

Hypertonic saline was included in the scope of this appraisal as an alternative comparator to Bronchitol. A feasibility study was carried out in order to determine whether Bronchitol could be compared with hypertonic saline via indirect comparison.

A literature search was carried out to identify studies which would potentially be relevant for an indirect comparison and which met the following criteria:

- Patients with CF diagnosed clinically or by sweat and genetic testing, including all degrees of disease severity
- Treatment with hypertonic saline or Bronchitol (~400mg BD)
- Prospective randomised controlled trials (RCTs)

Of the 919 articles were identified:

- 267 were duplicates and were removed
- 603 were excluded based on abstract review
- 40 were excluded based on full text review
- One further study was added based on hand searches

Therefore a total of 10 studies (Bronchitol vs. control n=2, hypertonic saline vs. control: n=8) were included for further consideration. A list of all identified studies is given in Appendix 4.

The main limitation of preparing an indirect comparison between Bronchitol and hypertonic saline is the absence of a common control arm between the respective randomised controlled trials. The low dose formulation of Bronchitol (control as used in DPM-CF-301 and DPM-CF-302) may show some degree of clinical activity which would preclude its use as a common link to the hypertonic sale RCTs (control reported to be 0.9% saline (isotonic saline) as in 7/8 studies). Other limitations which were observed were differences in inclusion/exclusion criteria and baseline study characteristics between trials.

Indirect comparisons are not randomised comparisons, but are essentially observational findings across trials, and may suffer the biases of observational studies, for example due to confounding

by study-level characteristics such as setting, enrolled populations and permitted concomitant medication. As in this situation, indirect comparisons where only a small number of studies are available are low in power and frequently lead to indeterminate results with wide confidence intervals. Robust conclusions that can be drawn from such findings may be limited. Subgroup analysis and meta-regression are commonly used methods to assess or improve trial similarity for adjusted indirect comparison. However, subgroup analysis and meta-regression would not be possible in the current analysis because the number of potential trials involved in an adjusted indirect comparison would be too small. The internal validity of the trials involved in the adjusted indirect comparison should be examined because biases in trials will inevitably affect the validity of the adjusted indirect comparison.

Based on this feasibility study, an indirect comparison of Bronchitol and hypertonic saline was not felt to be an appropriate analysis in this situation.

5.8 Non-RCT evidence

Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3.2.8 to 3.2.10.

5.8.1 *If non-RCT evidence is considered (see section 5.2.7), please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 9.6 and 9.7, appendices 6 and 7.*

Relevant non-RCT data come for this appraisal come from the open label extension phase of one of the pivotal clinical trials.

Upon completion of the double blind phase of the two key RCTs described above (DPM-CF-301 and DPM-CF-302), a 26 week open label phases (OLP) was offered to patients. In both studies, patients completing the 26 week double blind phase were then entered into the open label phase where all patients received Bronchitol 400mg BD in line with the previously described study plans (section 5.2.7). The only finalised data available are from the DPM-CF-301 study and these will be discussed in more detail.

In addition, DPM-CF-301 had a second 26 week open label phase which was offered at 23 of the 40 study sites following completion of the first OLP. The submission of this protocol amendment occurred during the last months of study conduct and therefore it only became applicable to these studies sites. Overall, this additional extension phase gave the opportunity to collect up to78 weeks of data on patients initially randomised to Bronchitol 400mg BD and up to

52 weeks of Bronchitol therapy for those originally randomised to the sub-therapeutic dose of Bronchitol. The OLP data are valuable since they give an insight into the longer term efficacy safety of Bronchitol which is important for chronic disease management.

Since the overall design of this study has previously been described, the methodology review will focus on items specific to the OLP and OLEP.

Comparators

This open label phase study had no active comparator and was designed to collect longer term data on the safety of Bronchitol.

Methods

Following successful completion of the initial 26-week DBP, a 2-visit, 26-week, open label phase (OLP) was offered to all patients participating in the DBP of DPM-CF-301 and patients had to provide informed consent for this phase of the study. Following completion of the first OLP, patients at 23 sites were offered the chance to participate in a further 26 week open label extension phase (OLEP). All patients in the OLP and OLEP of DPM-CF-301 received Bronchitol 400mg BD. Patients who were in the control group during the DBP and decided to continue in the open label phases also received 400 mg BD. A total of 37 or the original 40 sites continued in the first open label phase (OLP) and 23 into the second open label phase (OLEP) (Figure 12).

Data capture included lung function, concomitant medication use, pulmonary exacerbations and adverse events, physical examination, blood test results and sputum microbiology using methods defined for the DBP.

The primary objective was to determine if long term use of Bronchitol demonstrated an appropriate safety profile in patients with CF. Secondary objectives were to determine if Bronchitol improved lung function following long term Bronchitol use.

Figure 12 Study Schema for DPM-CF-301 OLP and OLEP

Study phase	**Screening**	**26 week double blind phase**			**Open label phase**		**Open label extension phase**	
Duration	2-5 weeks	6 weeks	8 weeks	12 weeks	12 weeks	14 weeks	12 weeks	14 weeks
Week	0	6	14	26	38	52	64	78
Visit	V0	V1	V2	V3	V4	V5	V6	V7	V8
Treatment	Screening MTT	Bronchitol 400 mg BD[a] OR Control BD[a]			Bronchitol 400 mg BD			

MTT = mannitol tolerance test
a randomisation is 3:2 Bronchitol : control

The primary objective of long term safety of Bronchitol was assessed by the following:

- Incidence, severity, and relationship to treatment of treatment emergent adverse events. AE collection and assessment was the same in the OLP as in the DBP
- Changes in laboratory (haematology and biochemistry) parameters
- Changes in sputum microbiology data
- Changes in physical examination results
- Changes in vital signs

The secondary objectives of the study were assessed by the following:

- the absolute and percent change from baseline in FEV_1, overall and by rhDNase use.
- the absolute change from baseline in FEV_1 % predicted, overall and by rhDNase use.
- the absolute and percent change from baseline in other lung function measures, i.e. FVC, FEF_{25-75}, PEF, FEV_1/FVC ratio, overall and by rhDNase use.
- reduction in pulmonary exacerbations determined by:
    - rates of protocol defined pulmonary exacerbations (PDPE) overall and by use of rhDNase
    - time to first PDPE.
    - rates of all pulmonary exacerbation (PE) overall and by use of rhDNase
    - time to first PE.
- reduction in rescue antibiotic usage as measured by the:
    - number of patients receiving rescue antibiotic agents (irrespective of route)
    - number of courses of rescue antibiotic agents (irrespective of route)
    - number of days of exposure to rescue antibiotic agents (irrespective of route) per person year of observation
- reduction in the duration of hospitalisations due to pulmonary exacerbations as determined by:
    - number of hospital admissions due to PDPE
    - duration (days) of hospital admissions due to PDPE
    - number of hospital admissions due to PE
    - duration (days) of hospital admissions due to PE

All primary and secondary endpoints were assessed at weeks 26 (Visit 4 – part of the DBP), 38 (visit 5 - OLP), week 52 (visit 6 – OLP), week 64 (visit 7 – OLEP) and week 78 (visit 8 – OLEP).

Data capture included lung function, concomitant medication use, pulmonary exacerbations and adverse events, physical examination, blood test results and sputum microbiology.

Four weeks into the open label phase of the study, the investigator or designate, called the participant to enquire as to their health with particular regard to response to the open label medication. If problems were noted and an unscheduled visit was deemed necessary, this was arranged.

Participants

At study visit 4 of (i.e. the last visit in the double-blind phase) the patients in participating centres had the option of continuing on the study medication for an additional 26 weeks providing the patient:

1. had given written consent to continue on study medication
2. was without any clinical reasons to be withdrawn from the treatment as judged by the Investigator, and when applicable
3. was not pregnant or planning to become pregnant in the next 6 months

There were no specific exclusion criteria for the open label phase of the study apart from current pregnancy or planned pregnancy within the next 6 months.

Similarly, patients completing the OLP were offered the option of continuing into the OLEP if they met the same criteria.

Patient characteristics at baseline

A majority (55.3%) of the patients participating in the OLP were male and the average age of the participants was 23.2 years in the Bronchitol and 22.8 years in the ex-control groups. The majority of patients in both treatment groups were adults. The use of rhDNase use at screening was 52.6%, in Bronchitol and 56.2% in patients originally randomised to control. Patients randomized to Bronchitol had a slightly higher mean FEV_1 % predicted at screening compared with those randomized to control in the DBP. At the start of the OLP, the ex-control group had a starting FEV_1 of 28.9ml (2.9%) above the original baseline value.

Table 33 Patient characteristics – DPM-CF-301 OLP

DPM-CF-301 Safety OLP1 population	Bronchitol (n=97)	Patients initially randomised to Control (n=73)
Age (years)		
Children (6-11 years)	21 (21.6%)	14 (19.2%)
Adolescent (12-17 years)	16 (16.5%)	15 (20.5%)
Adult (≥18 years)	60 (61.9%)	44 (60.3%)
Mean (SD)	23.2 (12.5)	22.8 (12.0)
Gender - Female	40 (41.2%)	36 (49.3%)
Race - Caucasian	94 (96.9%)	71 (97.3%)
BMI (kg/m^2)	21.1 (3.82)	20.0 (3.70)

DPM-CF-301 Safety OLP1 population	Bronchitol (n=97)	Patients initially randomised to Control (n=73)
FEV_1 baseline (SD) baseline (L)[a] baseline predicted (%)[a]	 2.11 (0.85) 65.5 (15.11)	 1.83 (0.66) 60.4 (15.24)

Outcomes measured and statistical analyses

No comparisons of the randomised treatment groups will be conducted in the OLP of the study. Inferential analysis of changes in FEV_1 at selected time points will be presented for the subjects randomised to control. All other summaries will be descriptive. Sample sizes for the OLP of this study are not based on power considerations but rather on subjects consenting to continue in the OLP.

The following changes were made to the analysis for OLP and OLEP initially proposed in the protocol:

- Vital signs to be evaluated as a safety endpoint.
- Subgroup analysis by rhDNase use at baseline
- Further secondary efficacy endpoints to be included (change in FEV_1 % predicted, PEF, FEV_1/FVC)
- Inclusion of time to protocol defined pulmonary exacerbations (PDPE) and pulmonary exacerbations (PE)
- Covariates for analysis. None of the inferential analyses based on models requiring covariate adjustment were conducted.
- Analysis of the number of PDPEs and PEs
- Analysis of the number of days of rescue antibiotic usage
- Analysis of the number of hospitalisations due to pulmonary exacerbations

Subsets of the DBP ITT population were defined for the open label phase analyses as:

- ITT OLP1: The subset of the ITT population who consented to participating in the open label phase (OLP) of this study.
- ITT OLEP: The subset of the ITT population who consented to participating in the open label extension phase (OLEP) of this study
- Safety OLP1: The subset of the safety population who consented to participating in the OLP of this study
- Safety OLEP: The subset of the safety population who consented to participating in the PLEP of this study

Data are presented for patients according to the treatment group to which they were randomised in the DBP, i.e. Bronchitol group and control group (since they have had different lengths of exposure to Bronchitol).

Events which commenced before visit 4/week 26 were included in the DBP and have already been reported. The events that started on the date of visit 4/week 26 are reported in the OLP of the study for patients electing to participate in the OLP. The events that commenced on the date of visit 4/week 26 for patients who completed the study on that day, that is, elected not to continue in the OLP of the study, or who withdrew from the study at visit 4/week 26 after having consented to participating in the OLP, but prior to receiving study treatment in the clinic at Visit 4/Week 26, the event is considered to have occurred in the DBP of the study. Summaries of data for the patients electing to participate in the OLP include data collected in the DBP for selected endpoints for comparative purposes were included in the analyses.

As with the DBP of this study, data were also reported for the rhDNase subgroups defined at study baseline (rhDNase users / non-users) (Table 34). As expected, measures of lung function at the start of the OLP were less favourable in the patients initially randomised to control group than to Bronchitol.

Table 34 Patient characteristics by rhDNase subgroup – DPM-CF-301 OLP

DPM-CF-301 Safety OLP1 population - rhDNase users	**Bronchitol (n=51)**	**Patients initially randomised to Control (n=41)**
Age (years) - Mean (SD)	22.6 (11.91)	22.3 (11.24)
Gender - Female	17 (33.3%)	23 (56.1%)
Race - Caucasian	49 (96.1%)	40 (97.6%)
BMI (kg/m^2)	20.9 (4.09)	19.7 (3.41)
FEV_1 baseline (SD) baseline (L)[a] baseline predicted (%)[a]	 2.01 (0.86) 61.9 (17.66)	 1.75 (0.59) 57.7 (16.14)
DPM-CF-301 Safety OLP1 population - rhDNase non-users	**Bronchitol (n=46)**	**Patients initially randomised to Control (n=32)**
Age (years) - Mean (SD)	23.9 (13.15)	23.4 (12.99)
Gender - Female	23 (50.0%)	13 (40.6%)
Race - Caucasian	45 (97.8%)	31 (96.9%)
BMI (kg/m^2)	21.3 (3.52)	20.3 (4.09)
FEV_1 baseline (SD) baseline (L)[a] baseline predicted (%)[a]	 2.19 (0.83) 69.3 (13.65)	 1.99 (0.76) 65.8 (15.70)

Data are also reported for the adult only population which is the focus of this submission (Table 35).

Table 35 Patient characteristics for adult only population – DPM-CF-301 OLP

DPM-CF-301 Safety OLP1 population	Bronchitol (n=97)	Patients initially randomised to Control (n=73)
Age (years)- Mean (SD)	30.7 (9.87)	30.3 (9.26)
Gender - Female	23 (38.3%)	23 (52.3%)
Race - Caucasian	59 (98.3%)	43 (97.7%)
BMI (kg/m^2)	23.0 (3.18)	21.7 (3.46)
FEV_1 baseline (SD) baseline (L)[a] baseline predicted (%)[a]	 2.38 (0.88) 61.0 (16.21)	 2.03 (0.69) 56.7 (17.10)

Participant flow

Of the 295 patients randomised and included in the ITT population for the DBP phase of DPC-CF-301, 198 completed this phase and 170 (85.9%) entered the OLP. Of those 170 starting the OLP, 130 (76.5%) completed; 64 went on to enter the OLEP of whom 57 (89.1%) completed this study phase.

Table 36 Patient disposition: DPM-CF-301 OLP

	DBP treatment: Bronchitol	DBP treatment: Control	Total
ITT population DBP[a]	177	118	295
Completed DBP	112 (63.3%)	86 (72.9%)	198 (61.1%)
Entered OLP[b]	97	73	170
Completed OLP[c]	81 (83.5%)	49 (67.1%)	130 (76.5%)
Withdrew during OLP[c]			
Patient withdrew consent	10 (10.3%)	11 (15.1%)	21 (12.4%)
Adverse event	3 (3.1%)	10 (13.7%)	13 (7.6%)
Related to treatment[d]	3 (3.1%)	6 (8.2%)	9 (5.3%)
Protocol violation	1 (1.0%)	1 (1.4%)	2 (1.2%)
Sponsor decision	0	1 (1.4%)	1 (0.6%)
Other	2 (2.1%)	1 (1.4%)	3 (1.8%)
Entered OLEP[e]	42	22	64
Completed the OLEP[f]	38 (90.5%)	19 (86.4%)	57 (89.1%)
Withdrew during OLEP[f]	4 (9.5%)	3 (13.6%)	7 (10.9%)
Patient withdrew consent	1 (2.4%)	1 (4.5%)	2 (3.1%)
Adverse event	2 (4.8%)	2 (9.1%)	4 (6.3%)
Related to treatment[d]	0 (0.0%)	1 (4.5%)	1 (1.6%)
Lost to follow-up	1 (2.4%)	1 (4.5%)	2 (3.1%)

a based on 40 study sites
b based on 37 study sites
c percentage based on number consenting to participate in the OLP.
d Definitely, probably or possibly related to study treatment in the assessment of the Investigator
e based on 23 study sites

Critical appraisal

Several tools exist for the quality assessment of non-randomised studies but none have been fully validated. According to the CRD (ref CRD systematic review guide), quality assessment of any study is likely to consider the following areas, each of which will be discussed in relation to the OLP and OLPE of DPM-CF-301:

- Appropriateness of study design to the research objective – the study was designed to assess long term data on the safety of Bronchitol. As such the study design is appropriate.
- Risk of bias – the open label phases of this study (OLP and OLEP) are non comparative and therefore there is no risk of bias in any treatment comparisons.
- Other issues related to study quality – the study was conducted to similar standard as the double blind phase of the study which was of high quality. The safety assessment procedures remained the same as in the DBP of the study and the procedure to capture the efficacy data remained the same as in the DBP of the study. Only administrative and typographical updates were implemented during the open label phases of the trial and following the finalization of the previous CSR and did not affect the conduct of the trial or any study procedures.
- Choice of outcome measure – the outcomes measures were aligned with those already discussed for the double blind portion of the trial. Measures were all considered appropriate and clinically relevant.
- Statistical issues – no formal statistical analyses were planned for the data from the OLP and OLEP. Additional analyses were added after the study protocol was completed (see above) but none of these are comparative in nature.
- Quality of reporting – the reporting of the OLP and OLEP data is as presented in the appropriate sections of the study protocol and SAP.
- Quality of the intervention – all patients in the OLP and OLEP phases of the study continued the treatment with inhaled Bronchitol 400mg BD, including the patients who were on control during the DBP of the study. The patients continued to administer the treatment, including the premedication with 400µg salbutamol, in the same manner as in the DBP of the study
- Generalisability – the patients in these open label phases represent patients who continue with Bronchitol medication over the longer term. The results of the DBP Bronchitol group show the safety and efficacy of continued use of Bronchitol up to 72 weeks while the data from the DBP control group show the impact of switching to Bronchitol from standard care and the impact of that switch over a period of up to 52 weeks. In all cases, Bronchitol is given in addition to standard care.

The more formal quality assessment presented below was undertaking using guidelines from the CRD quality assessment tool (Chambers 2009) (Table 37).

Table 37 Critical appraisal of open label extension phases of DPM-CF-301

Critical appraisal criterion	Assessment
Were selection / eligibility criteria adequately reported?	Yes – see above text (and 0)
Was the selected population representative of that seen in normal practice?	Yes – patients were recruited in line with anticipated use of Bronchitol as an addition to standard care for patients who are currently taking rhDNase and for patients for whom rhDNase is unsuitable due to treatment ineligibility, tolerability issues or lack of efficacy. Both patient groups are represented in the OLP and OLEP.
Was an appropriate measure of variability reported?	Yes
Was follow up adequate and was loss to follow up reported or explained?	Yes – see 0
Were at least 90% of those included at baseline followed up?	No – over 80% patients originally randomised to receive Bronchitol and who entered the OLP completed the first 26 weeks of the OLP.
Were patients recruited prospectively?	Yes – patients in the DBP of this study were recruited prospectively and those patients who completed the DBP were eligible to enter the OLP if they provided consent and met the entry criteria.
Were patients recruited consecutively?	Yes – patients in the DBP of this study were recruited consecutively (see 0) and of those completing the DBP, all patients were eligible to enter the OLP if they provided consent and met the entry criteria.
Did the study report relevant prognostic factors?	Yes

Overall, the OLP and OLEP phases of study DPM-CF-301 are well conducted and provide important safety (and efficacy) data over a longer treatment period making the results relevant to clinical practice.

Clinical Efficacy Results

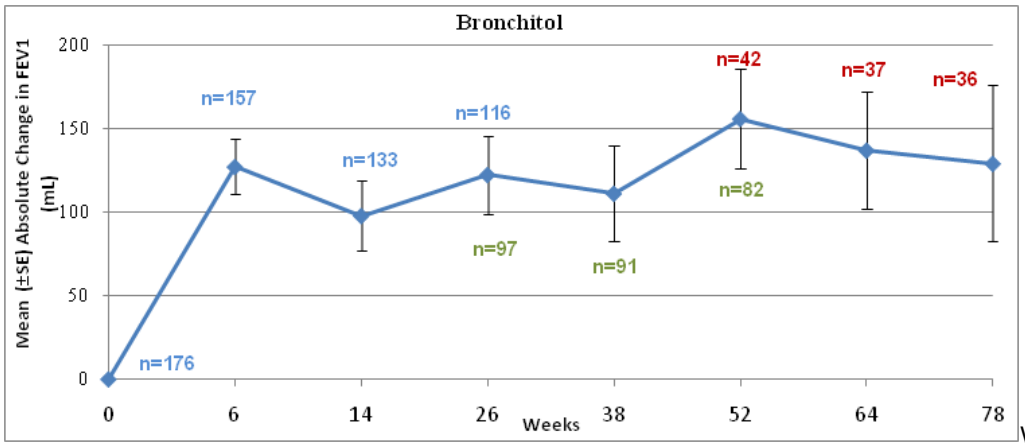
Efficacy

As with the reporting of the pivotal RCTs, the reporting of endpoints will focus on key endpoints only

FEV_1

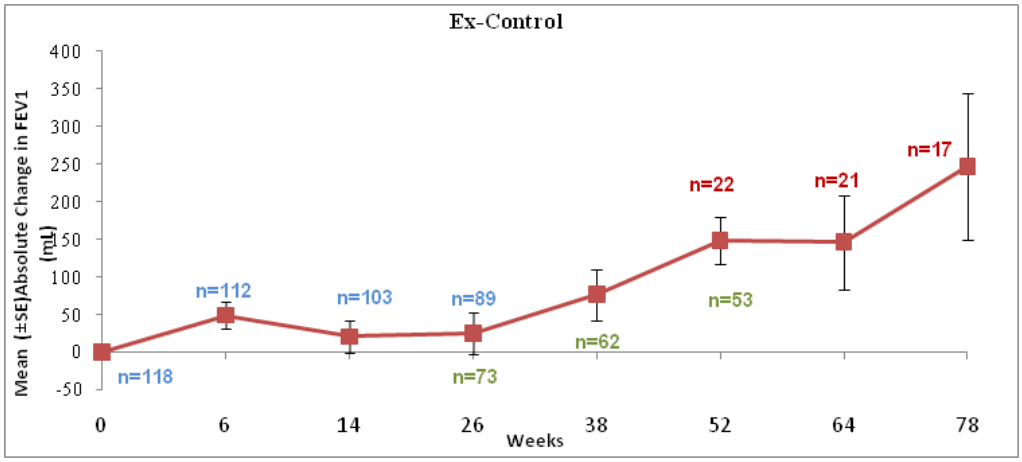
In this study, inhaled Bronchitol demonstrated clinically meaningful improvements in lung function of CF patients which was observed across the DBP and was sustained over 12 and 18 months when assessed by the absolute change (mL) in FEV_1 from baseline (Figure 13). Furthermore, patients who initially received control in the DBP of the study, and subsequently switched to receive Bronchitol 400mg BD in the open label phase experienced similar significant improvements in lung function after crossing over to 400mg Bronchitol (Figure 14).

Figure 13 Change in FEV_1 from baseline for Bronchitol group over DBP, OLP and OLPE – DPM-CF-301



Week 26 – start of OLP (n=116 patients completed the DBP and n=97 patients started the OLP)
Week 52 – start of OLEP (n=82 patients completed the OLP and n=42 patients started the OLEP)

Figure 14 Change in FEV_1 from baseline for ex-control group over DBP, OLP and OLPE – DPM-CF-301



Week 26 – start of OLP (n=89 patients completed the DBP and n=73 patients started the OLP)
Week 52 – start of OLEP (n=53 patients completed the OLP and n=22 patients started the OLEP)

At week 52 of treatment a significant ($p<0.001$) improvement from baseline (week 0) of 148.5mL in FEV_1 was achieved by those commencing on Bronchitol in the OLP – this corresponded to a significant 10.1% increase from baseline ($p<0.001$). Those patients who had already been on Bronchitol during the DBP continued to maintain an improvement in FEV_1. The % predicted FEV_1 was also improved at week 52 vs. Week 0 (Bronchitol 1.8%, control 2.6%). The increase in FEV_1 % predicted was noted irrespective of rhDNase use (Table 38).

Table 38 FEV_1 change over the OLP - DPM-CF-301

	Change from baseline to week 52 for patients who completed the OLP	
	Bronchitol	**Ex-control**
Overall population Mean (95% CI)	n=82 155.7 (97.0, 214.5)	n=53 148.5 (84.5, 212.5)
rhDNase users Mean (95% CI)	n=44 138.9 (52.3, 225.4)	n=29 107.2 (6.3, 208.2)
rhDNase non-users Mean (95% CI)	n=38 175.3 (93.7, 256.9)n	N=24 198.3 (123.4, 273.2)

These improvements appeared to be sustained in the population who continued to the OLEP. At week 78 of treatment the improvement of in FEV_1 was sustained in both those commencing on Bronchitol in the OLP, and also who had already been on Bronchitol during the DBP (247.1mL and 128.9mL respectively). However, only a small number of patients were available for analysis at week 78 (17 and 36, respectively) (Figure 13, Figure 14).

Consistent with the overall population, the adult Bronchitol population also had a similar sustained effect for the additional 26 weeks of treatment (at week 52 an improvement of 169.2mL from baseline was noted) and the patients originally randomised to the control group also showed an improvement from week 26 (39.3mL at week 52) (Table 39).

Table 39 FEV_1 change in the OLP: adult only population - DPM-CF-301

	Bronchitol			Ex-control		
	Absolute Value (L)	**Change from Baseline (mL)**	**% change from baseline (%)**	**Absolute Value (L)**	**Change from Baseline (mL)**	**% change from baseline (%)**
Baseline						
N Mean (SD)	60 2.4 (0.88)			44 2.0 (0.69)		
Week 26						
N Mean (SD) 95% CI[a]	60 2.5 (0.92)	60 117.7 (257.89) (51.0, 184.3)	60 5.5 (11.72) (2.5, 8.5)	44 2.017 (714.06)	44 -13.0 (210.00) (-76.8, 50.9)	44 -0.6 (11.29) (-4.0, 2.9)
Week 52						
N Mean (SD) 95% CI[a]	49 2.6 (1.03)	49 169.2 (265.67) (92.9, 245.5)	49 7.1 (10.87) (4.0, 10.3)	28 2.1 (0.70)	28 39.3 (185.95) (-32.8, 111.4)	28 281.8 (11.27) (-2.6, 6.2)
Week 78						
N Mean (SD) 95% CI[a]	25 2.3 (1.05)	25 29.2 (233.15) (-67.0, 125.4)	25 1.5 (12.06) (-3.4, 6.5)	10 2.044 (655.09)	10 53.0 (216.54) (-101.9, 207.9)	10 3.1 (12.80) (-6.0, 12.3)

[a]Based on a Student's t-distribution (one sample).
Data are reported based on number of patients with available data at each timepoint.

% predicted FEV_1

Analyses of change in % predicted FEV_1 showed that changes observed across the DBP were also sustained over the 12 month open label phases. The patients originally randomised to the

control group had an increase of 2.6% from baseline at week 52 (p=0.012), an improvement on the level (0.2%) at week 26. In the Bronchitol group the change in FEV_1 % predicted was maintained at similar level. The increase in FEV_1 % predicted was noted irrespective of rhDNase use. Consistent with the overall population, the adult Bronchitol population also had an increased improvement in FEV_1% predicted over the additional 26 weeks of treatment (4.3% at week 52 vs. 2.9% at week 26) and the patients originally randomised to the control group also showed a 1.1% improvement from week 26 (0.8% at week 52 vs. -0.3% at week 26).

Other spirometry measures

Other spirometry measures (FVC and PEF) support the effectiveness of Bronchitol. The overall increase in FVC at 52 weeks was 224.8mL and 162.1mL, for Bronchitol group and patients originally randomised to the control group respectively. The improvement in other spirometry parameters was seen irrespective of rhDNase use. In line with the overall population, these parameters showed similar patterns of change in the adult only population.

PDPE / PE

The incidence of patients with ≥1 protocol defined pulmonary exacerbation (PDPE) and/or PE was similar in both groups. However, the median time to first PE in was longer in patients on Bronchitol throughout the study as compared to patients originally randomised to the control group (9.2 months vs. 5.8 months).

The time to first PDPE for patients on their first 6 months of active Bronchitol (i.e. either receiving Bronchitol in the DBP, or patients originally randomised to the control group switched to Bronchitol in the OLP) demonstrated a similar trend, further confirming the efficacy of inhaled Bronchitol therapy in reducing exacerbations in patients with CF. The percentage of patients who were exacerbation free after 12 months on active Bronchitol remained higher than those exacerbations free in patients originally randomised to the control group at 6 months.

Hospitalizations and antibiotic use associated with PDPE showed that 84.5% of the Bronchitol group and 80.8% of the patients originally randomised to the control group did not experience any days in hospital due to PDPEs during the OLP/OLEP of the study.

Due to the small numbers of events, these data were not analysed separately for the adult only population.

Summary of results

Data from the open label phases of Study DPM-CF-301 (during which all patients received Bronchitol 400mg BD irrespective of their original treatment allocation) support the long-term safety of Bronchitol 400mg BD. In the overall safety population, there was no increase in the overall proportions of patients experiencing adverse events following long-term treatment. For both rhDNase users and non-users, generally similar results were reported compared to the

overall safety population. Similarly, the results in adult patients (aged ≥18 years) were consistent with those in the overall population.

The open label phase of study DPM-CF-301 demonstrated a sustained clinically relevant improvement in FEV_1 for at least 18 months in patients receiving Bronchitol. Patients that switched from the control group to Bronchitol 400mg BD in the open label phase showed a similar improvement in FEV_1 and in exacerbation rates as that seen in the Bronchitol group during the double blind phase. Overall, the data from study DPM-CF-301 demonstrate a sustained and important clinical benefit supporting the use of Bronchitol in clinical practice for the treatment of adult patients with CF.

5.9 Adverse events

This section should provide information on the adverse events experienced with the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator, or the occurrence of adverse events is not significantly associated with other treatments.

5.9.1 If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 9.8 and 9.9, appendices 8 and 9.

None of the main trials were designed primarily to assess safety outcomes although safety endpoints were secondary outcomes in both of the key RCTs. As described in section 5, the pivotal trials for this submission are DPM-CF-301 and DPM-CF-302. These provide the most appropriate source of comparative safety data for Bronchitol vs. standard care (BSC) in rhDNase users and non-users. Additional safety data for Bronchitol is available from the phase II studies identified in section 5 (See Appendix 4). Data from these studies will be included to provide an overall assessment of the safety of Bronchitol. Since the two pivotal studies for the safety assessment are the same pivotal studies as previously described, no further review of study methodology is given.

Additional data on the safety of Bronchitol in the adult CF population can be found in the OLP and OLEP phases of the DPM-CF-301 study. As before, the methodology of this study has already been discussed and will not be reviewed further.

5.9.2 Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below

Overall safety summary

The overall summary of safety for Bronchitol can be summarised based on the program of trials carried out in the CF population. The most commonly observed adverse reaction associated with the use of Bronchitol is cough. This was the only adverse event considered to be “very common” (i.e. occur with frequency ≥1/10). Although reported as a common adverse reaction, productive cough is a beneficial component of mucus clearance. Some patients also experienced a severe cough which led to cessation of treatment.

Other adverse events which were considered to be “common” (i.e. occur with frequency ≥1/100 to <1/10) were decreased appetite, headache, haemoptysis, bronchospasm, wheezing, asthma, condition aggravated, pharyngolaryngeal pain, productive cough, chest discomfort and bacteria sputum identified. Of those events, three (wheezing, asthma and bacteria sputum identified) were noted to occur less frequently in the Bronchitol group than in the control group.

The clinically most important adverse reaction associated with the use of Bronchitol is haemoptysis based on the potential severity.

Safety results from pivotal RCTs

Where not specified, AE refers to all treatment emergent adverse events (i.e. which occurred after the start of treatment with Bronchitol / control) regardless of causality. No statistical analysis of AEs was performed.

<u>Overall AEs</u>

In both studies, the occurrence of adverse events was similar in both treatment groups and similar across studies (Table 40). Likewise, the incidence of serious adverse events was similar in both groups in each study although the rates were higher in DPM-CF-301 than in DPM-CF-302.

In DPM-CF-301, the proportion of patients experiencing treatment related AEs (having been assessed as possibly, probably of definitely related to treatment) was approximately double in the Bronchitol group compared with the control group and less than double in DPM-CF-302.

Table 40 Summary of adverse events from pivotal studies

	DPM-CF-301		DPM-CF-302	
	Bronchitol (N=177)	**Control (N=188)**	**Bronchitol (N=184)**	**Control (N=121)**
Patients with at least one event (n (%)):				
Adverse event	154 (87.0%)	109 (92.4%)	165 (89.7%)	106 (87.6%)
Serious adverse event	46 (26.0%)	35 (29.7%)	31 (16.8%)	30 (24.8%)
Severe adverse event	42 (23.7%)	27 (22.9%)	29 (15.8%)	19 (15.7%)
Treatment-related adverse event[a]	72 (40.7%)	26 (22.0%)	44 (23.9%)	20 (16.5%)
Adverse event leading to withdrawal	28 (15.8%)	10 (8.5%)	13 (7.1%)	5 (4.1%)
Adverse event resulting in death	0	0	0	1 (0.8%)
Number of events				
Al adverse events	822	541	702	435
Serious adverse events	65	49	44	41
Treatment related adverse event[a]	129	58	88	36
Adverse event resulting in death	0	0	0	1

a possibly, probably or definitely causally related to treatment

Common AEs

In DPM-CF-301, the proportion of patients who experienced ≥ 1 TEAE was similar between the treatment groups. The most common AEs were respiratory, thoracic and mediastinal disorders which were more common with Bronchitol (Bronchitol 51.4% vs. control 45.8%). Other common events were related to general disorders and administration site conditions (42.9% vs. 45.8% respectively) and infections and infestations (39.0% vs. 47.5% respectively). The most common AEs were condition aggravated (CF exacerbation), cough and headache. In DPM-CF-301, the most significant AE of greater frequency in the Bronchitol group was haemoptysis; other more frequent events were minor in nature.

Table 41 Most common adverse events: Pivotal RCT DPM-CF-301

	Bronchitol (N=177)	**Control (N=118)**
Respiratory, thoracic and mediastinal disorder		
Cough	45 (25.4%)	24 (20.3%)
Haemoptysis	21 (11.9%)	10 (8.5%)
Pharyngolaryngeal pain	24 (13.6%)	5 (4.2%)
Productive cough	12 (6.8%)	7 (5.9%)
General disorders and administration site conditions		
Condition aggravated	57 (32.2%)	42 (35.6%)
Infections and infestations		
Nasopharyngitis	25 (14.1%)	17 (14.4%)
Lower respiratory tract infection	15 (8.5%)	20 (16.9%)
Upper respiratory tract infection	14 (7.9%)	8 (6.8%)
Gastrointestinal disorders		
Abdominal pain upper	12 (6.8%)	7 (5.9%)
Vomiting	13 (7.3%)	4 (3.4%)

	Bronchitol (N=177)	Control (N=118)
Abdominal pain	6 (3.4%)	8 (6.8%)
Toothache	9 (5.1%)	3 (2.5%)
Diarrhoea	9 (5.1%)	1 (0.8%)
Nervous system disorders		
Headache	38 (21.5%)	28 (23.7%)

All adverse events reported with a frequency of ≥5% in either treatment group are summarised.

A very similar pattern was seen in DPM-CF-302. The most frequently reported adverse events were general disorders and administration site conditions in similar proportions in both the Bronchitol group (50.5%) and the control group (51.2%). Both groups also showed similar frequency of infections and infestations (Bronchitol 43.5% vs. control. 41.3%) which were the next most frequently reported type of AEs. The Bronchitol group experienced a slightly higher frequency of respiratory, thoracic and mediastinal disorders (38.0% v 28.9%), and a slightly lower frequency of gastrointestinal disorders (28.3% v. 35.5%) and nervous system disorders (15.2% v 24%) than the control group.

As seen in DPM-CF-301, the most common event in both the Bronchitol and control groups in DPM-CF-302 was condition aggravated, which was seen slightly less frequently in the Bronchitol group than in the control group. Other common AEs were headache, cough, pharyngolaryngeal pain, and pyrexia occurring with similar frequency in both groups. Haemoptysis occurred more frequently in the Bronchitol group than in the control group.

Table 42 Most common adverse events: Pivotal RCT DPM-CF-302

	Bronchitol (N=184)	Control (N=121)
Respiratory, thoracic and mediastinal disorder		
Cough	28 (15.2%)	16 (13.2%)
Haemoptysis	13 (7.1%)	3 (2.5%)
Pharyngolaryngeal pain	19 (10.3%)	13 (10.7%)
General disorders and administration site conditions		
Condition aggravated	76 (41.3%)	54 (44.6%)
Pyrexia	17 (9.2%)	13 (10.7%)
Infections and infestations		
Nasopharyngitis	11 (6.0%)	6 (5.0%)
Upper respiratory tract infection	10 (5.4%)	11 (9.1%)
Gastrointestinal disorders		
Abdominal pain upper	6 (3.3%)	7 (5.8%)
Abdominal pain	14 (7.6%)	8 (6.6%)
Nervous system disorders		
Headache	26 (14.1%)	22 (18.2%)
Sinusitis	8 (4.3%)	7 (5.8%)

All adverse events reported with a frequency of ≥5% in either treatment group are summarised

Treatment-related AEs

In DPM-CF-301, treatment-related AEs were more commonly reported in the Bronchitol group compared with the control group and the most common events were respiratory, thoracic and

mediastinal disorders (Bronchitol 29.4% vs. control 15.3%) and the most common treatment-related AEs were cough, haemoptysis, and pharyngolaryngeal pain (Table 43).

Table 43 Treatment-related adverse events: Pivotal RCT DPM-CF-301

	DPM-CF-301	
	Bronchitol (N=177)	**Control (N=188)**
Cough	26 (14.7%)	8 (6.8%)
Haemoptysis	13 (7.3%)	4 (3.4%)
Pharyngolaryngeal pain	9 (5.1%)	0
Condition aggravated	6 (3.4%)	3 (2.5%)
Chest discomfort	5 (2.8%)	2 (1.7%)
Headache	5 (2.8%)	1 (0.8%)
Vomiting	4 (2.3%)	2 (1.7%)
Wheezing	2 (2.1%)	4 (3.4%)

Only includes adverse events which were considered possibly, probably or definitely causally related to treatment - all such adverse events reported with a frequency of ≥2% in either treatment group are summarised.

In DPM-CF-302, treatment-related AEs were reported by a greater proportion of patients in the Bronchitol group than in the control group. As with DPM-CF-301, the most common category of events was respiratory, thoracic and mediastinal disorders and the most common events were cough, haemoptysis, condition aggravated and pharyngolaryngeal pain (Table 44).

Table 44 Treatment-related adverse events: Pivotal RCT DPM-CF-302

	Bronchitol (N=184)	**Control (N=121)**
Cough	11 (6.0%)	4 (3.3%)
Condition aggravated	9 (4.9%)	4 (3.3%)
Haemoptysis	6 (3.3%)	0
Pharyngolaryngeal pain	5 (2.7%)	4 (3.3%)
Headache	5 (2.7%)	1 (0.8%)
Post-tussive vomiting	4 (2.2%)	0

Only includes adverse events which were considered possibly, probably or definitely causally related to treatment - all such adverse events reported with a frequency of ≥2% in either treatment group are summarised.

Severe AEs

In DPM-CF-301, the proportion of patients reporting adverse events of severe intensity was similar in both treatment groups and the most commonly reported were condition aggravated (Bronchitol 6.8% vs. control 8.5%) and cough (Bronchitol 4.0% vs. control 3.4%). The proportion of patients with severe haemoptysis was similar in both groups (Bronchitol 0.6% vs. control 0.8%).

A similar pattern was seen in DPM-CF-302 where the majority of adverse events were mild or moderate. The frequency of severe adverse events was similar in both the Bronchitol and control groups, and the most commonly reported events were condition aggravated which was reported

less frequently in the Bronchitol group (3.8%) than in the control group (6.6%). Severe haemoptysis was reported by three (1.6%) patients in the Bronchitol group only. Severe pharyngolaryngeal pain and headache were also reported in the Bronchitol group in two (1.1%) patients.

Serious AEs

In both studies, the proportion of patients reported SAEs was lower in the Bronchitol group than in the control group, with the difference most notable in DPM-CF-302. The most commonly reported events in both studies were in the general disorders and administration site conditions category, all of those events being condition aggravated: DPM-CF-301: Bronchitol 18.6% vs. control 21.2%; DPM-CF-302: Bronchitol 14.7% vs. control 16.5%.

In DPM-CF-301, the other notable SAEs were haemoptysis (Bronchitol 3.4% vs. control 1.7%) and lower respiratory tract infection (Bronchitol 2.3% vs. control 1.7%), no other events occurring in more than 2% patients overall. In DPM-CF-302, no other serious were reported by more than 2 patients except haemoptysis (Bronchitol 1.1% vs. control 0). The frequency of the infections and infestations category of SAEs was lower for Bronchitol (0.5%) than control (5.8%) in DPM-CF-302 mostly due to the higher rate of lower respiratory tract infections in the control group (Bronchitol 0 vs. control 2.5%).

In DPM-CF-302, one patient in the control group experienced an adverse event that was serious and resulted in death approximately three months after withdrawal from the study. This was not related to study treatment.

Withdrawal due to adverse events

In DPM-CF-301, the proportion of patients who withdrew due to AEs was greater in the Bronchitol group than in the control group but in DPM-CF-302, the Bronchitol rate was a little lower than for the control group. In DPM-CF-301, the most common reasons for withdrawal were cough (Bronchitol 6.2% vs. 3.4% control), condition aggravated (Bronchitol 4.0% vs. 1.7% control) and haemoptysis (Bronchitol 2.8% vs. 0 control), respectively. Although cough is a component of the therapeutic effect some patients experience cough of sufficient severity to warrant stopping treatment. All of these cough and haemoptysis events in both treatment groups were considered treatment related.

In DPM-CF-302, a slightly higher proportion of patients in the Bronchitol group than the control group withdrew due to adverse events. Twelve of the 13 patients in the Bronchitol group had events which were considered treatment-related, while in the control group two out of the five patients' events leading to withdrawal were considered treatment-related. As expected, cough was more frequently reported in the Bronchitol group (3.8%) than in the control group (1.7%) – the majority of these events were treatment related in the Bronchitol group.

Summary of safety by rhDNase subgroup

In both studies, the proportion of patients experiencing any adverse event among rhDNase users and non-users was similar to the overall safety population. In DPM-CF-302, the proportions of all adverse events were in general similar in both the rhDNase users and rhDNase non-users, and similar when compared to the overall safety population. Slight variations in proportions of subjects experiencing AEs are seen in the rhDNase non-users, particularly in the control group, when compared to the rhDNase users and the overall population, however the numbers of subjects in this group are small thus it is difficult to make meaningful comparisons.

In both studies and in both the Bronchitol and control groups, more rhDNase users than non-users reported condition aggravated, cough and haemoptysis. This was not entirely unexpected as the rhDNase users are a more severe disease group. Of interest, 12 of the 13 Bronchitol patients in DPM-CF-302 who had haemoptysis recorded as an adverse event were rhDNase users. In DPM-CF-302, rhDNase non-users had slightly different frequencies of some adverse events, when compared to the rhDNase users group and the overall population; however the number of subjects in each treatment group of this subgroup was small and thus it is difficult to make meaningful comparisons

In both studies, more rhDNase users than non-users experienced serious adverse events and the difference between rhDNase subgroups is greatest for Bronchitol group. In general, AEs and subsequent study withdrawal were more common in rhDNase users than non-users, independent of study treatment arm. The reason may be a less severe disease in non-users. The rhDNase users subgroup had similar adverse events and similar frequencies of adverse events to those seen in the overall safety population.

Table 45 Summary of adverse events by rhDNase subgroup: pivotal RCTs

	DPM-CF-301		DPM-CF-302	
rhDNase users	**Bronchitol (N=96)**	**Control (N=67)**	**Bronchitol (N=137)**	**Control (N=92)**
Patients with at least one (n (%)):				
Adverse event	85 (88.5%)	61 (91.0%)	121 (88.3%)	83 (90.2%)
Serious adverse event	31 (32.3%)	22 (32.8%)	27 (19.7%)	23 (25.0%)
Treatment-related adverse event[a]	40 (41.7%)	17 (25.4%)	34 (24.8%)	17 (18.5%)
Adverse event leading to withdrawal	17 (17.7%)	7 (10.4%)	19 (13.9%)	14 (15.2%)
Adverse event resulting in death	0	0	0	1 (1.1%)
Number of events				
All adverse events	482	335	551	324
Serious Adverse events	43	28	29	27
Treatment related adverse event[a]	77	47	72	32
Adverse event resulting in death	0	0	0	1
rhDNase non-users	**Bronchitol (N=81)**	**Control (N=51)**	**Bronchitol (N=47)**	**Control (N=29)**
Patients with at least one (n (%)):				
Adverse event	69 (85.2%)	48 (94.1%)	44 (93.6%)	23 (79.3%)
Serious adverse event	15 (18.5%)	13 (25.5%)	4 (8.5%)	7 (24.1%)
Treatment-related adverse event[a]	32 (39.5%)	9 (17.6%)	10 (21.3%)	3 (10.3%)
Adverse event leading to withdrawal	11 (13.6%)	3 (5.9%)	3 (6.4%)	3 (10.3%)
Adverse event resulting in death	0	0	0	0

	DPM-CF-301		DPM-CF-302	
Number of events				
Al adverse events	340	206	151	111
Serious Adverse events	22	21	4	7
Treatment related adverse event[a]	52	11	16	4
Adverse event resulting in death	0	0	0	0

a possibly, probably or definitely causally related to treatment

Table 46 Most common adverse events by rhDNase subgroups:DPM-CF-301

rhDNase users	**Bronchitol (N=96)**	**Control (N= 67)**
Condition aggravated	36 (37.5%)	27 (40.3%)
Cough	31 (32.3%)	15 (22.4%)
Bacteria sputum identified	20 (20.8%)	11 (16.4%)
Headache	21 (21.9%)	15 (22.4%)
Nasopharyngitis	15 (15.6%)	9 (13.4%)
Lower respiratory tract infection	7 (7.3%)	11 (16.4%)
Pharyngolaryngeal pain	17 (17.7%)	2 (3.0%)
Haemoptysis	13 (13.5%)	7 (10.4%)
Upper respiratory tract infection	6 (6.3%)	6 (9.0%)
Productive cough	9 (9.4%)	5 (7.5%)
Abdominal pain upper	7 (7.3%)	7 (10.4%)
Arthralgia	7 (7.3%)	3 (4.5%)
Vomiting	9 (9.4%)	3 (4.5%)
rhDNase nonusers	**Bronchitol (N=81)**	**Control (N=51)**
Condition aggravated	21 (25.9%)	15 (29.4%)
Cough	14 (17.3%)	9 (17.6%)
Bacteria sputum identified	13 (16.0%)	11 (21.6%)
Headache	17 (21.0%)	13 (25.5%)
Nasopharyngitis	10 (12.3%)	8 (15.7%)
Lower respiratory tract infection	8 (9.9%)	9 (17.6%)
Pharyngolaryngeal pain	7 (8.6%)	3 (5.9%)
Haemoptysis	8 (9.9%)	3 (5.9%)
Upper respiratory tract infection	8 (9.9%)	2 (3.9%)
Productive cough	3 (3.7%)	2 (3.9%)
Abdominal pain upper	5 (6.2%)	0
Arthralgia	5 (6.2%)	4 (7.%8)
Vomiting	4 (4.9%)	1 (2.0%)

All adverse events reported with a frequency of ≥5% overall in the rhDNase subgroup are summarised

Table 47 Most common adverse events by rhDNase subgroups: DPM-CF-302

rhDNase users	**Bronchitol (N=137)**	**Control (N=92)**
Condition aggravated	63 (46.0%)	41 (44.6%)
Cough	24 (17.5%)	12 (13.0%)
Headache	20 (14.6%)	16 (17.4%)
Pyrexia	13 (9.5%)	10 (10.9%)
Haemoptysis	12 (8.8%)	3 (3.3%)
Pharyngolaryngeal pain	12 (8.8%)	9 (9.8%)
Abdominal pain	9 (6.6%)	5 (5.4%)
Upper respiratory tract infection	9 (6.6%)	8 (8.7%)
Vomiting	8 (5.8%)	1 (1.1%)
Pharyngitis	7 (5.1%)	2 (2.2%)
Sinusitis	7 (5.1%)	6 (6.5%)
Bronchitis	4 (2.9%)	5 (5.4%)

Fatigue	3 (2.2%)	5 (5.4%)
rhDNase non-users	**Bronchitol (N=47)**	**Control (N=29)**
Condition aggravated	13 (27.7%)	13 (44.8%)
Pharyngolaryngeal pain	7 (14.9%)	4 (13.85)
Headache	6 (12.8%)	6 (20.7%)
Abdominal pain	5 (10.6%)	3 (10.3%)
Nasopharyngitis	5 (10.6%)	2 (6.9%)
Cough	4 (8.5%)	4 (13.8%)
Pyrexia	4 (8.5%)	3 (10.3%)
Bronchitis	3 (6.4%)	0
Influenza	3 (6.4%)	2 (6.9%)
Influenza like illness	3 (6.4%)	0
Malaise	3 (6.4%)	0
Nasal congestion	3 (6.4%)	0
Pain in extremity	3 (6.4%)	1 (3.4%)
Abdominal pain upper	2 (4.3%)	3 (10.3%)
Diarrhoea	2 (4.3%)	2 (6.9%)
Toothache	2 (4.3%)	2 (6.9%)
Upper respiratory tract infection	1 (2.1%)	3 (10.3%)
Dizziness	0	2 (6.9%)
Gastrooesophageal reflux disease	0	2 (6.9%)
Procedural pain	0	2 (6.9%)
Stomach discomfort	0	2 (6.9%)

All adverse events reported with a frequency of ≥5% overall in the rhDNase subgroup summarised

Summary of safety for adult only population

In the DPM-CF-301, the safety data were analysed by age subgroups and the relevant results for the adult only population, the focus of this submission, are reported in Table 48. In the adult only population of this study, the most serious AE was condition aggravated (Bronchitol 19.3% vs. control 22.4%), followed by Respiratory, thoracic and mediastinal disorders (5.3% of patients on Bronchitol vs 2.6% in the control arm) and infections and infestations (4.4% of patients on Bronchitol vs 5.3% in the control arm). Haemoptysis was experienced by 3.5% of patients on Bronchitol compared with 1.3% in the arm control.

Table 48 Most common adverse events (>3%) in the adult only population: DPM-CF-301

	Number (%) of patients	
	Mannitol 400 mg BD (n=114)	Control (n=76)
At least one SAE	**32 (28.1)**	**24 (31.6)**
General disorders and administration site conditions	**22 (19.3)**	**17 (22.4)**
Condition aggravated	**22 (19.3)**	**17 (22.4)**
Respiratory, thoracic and mediastinal disorders	**6 (5.3)**	**2 (2.6)**
Haemoptysis	**4 (3.5)**	**1 (1.3)**
Infections and infestations	**5 (4.4)**	**4 (5.3)**
Lower respiratory tract infection	**4 (3.5)**	**2 (2.6)**
Gastroenteritis	0 (0.0)	0 (0.0)
Gastroenteritis viral	0 (0.0)	0 (0.0)

Gastrointestinal disorders	**2 (1.8)**	**3 (3.9)**
Hepatobiliary disorders	0 (0.0)	0 (0.0)
Cholecystitis	0 (0.0)	0 (0.0)
Surgical and medical procedures	**4 (3.5)**	0 (0.0)
Injury, poisoning and procedural complications	0 (0.0)	**1 (1.3)**
Immune system disorders	0 (0.0)	0 (0.0)
Investigations	**1 (0.9)**	0 (0.0)
Musculoskeletal and connective tissue disorders	0 (0.0)	**1 (1.3)**

Likewise, in DPM-CF-302, the safety data were analysed by age subgroups and the relevant results for the adult only population, the focus of this submission, are reported here. The focus will be on differences between the adult only population and the overall safety population for this study.

Table 49 Most common adverse events in the adult only population: DPM-CF-302

	Bronchitol (N=93)	**Control (N=58)**
Patients with at least one (n (%)):		
Adverse event	81 (87.1%)	46 (79.3%)
Serious adverse event	15 (16.1%)	12 (20.7%)
Treatment-related adverse event[a]	22 (23.7%)	10 (17.2%)
Adverse event leading to withdrawal	9 (9.7%)	2 (3.4%)
Adverse event resulting in death	0	0
Number of events		
All adverse events	281	207
Serious Adverse events	16	14
Treatment related adverse event[a]	44	18
Adverse event resulting in death	0	0

a possibly, probably or definitely causally related to treatment

In the adult only population of DPM-CF-302, the overall pattern of adverse events (Table 49) is very similar to that of the overall population (Table 40). Additionally, the most common events seen in the adult only population (Table 50) show a similar pattern to those in the overall population (Table 42), the main differences being:

- The rate of condition aggravated events is slightly lower in the adult only population that in the overall population but the treatment groups have similar rates in both cases
- In the adult only population, bacteria sputum identified is one of the most common events reported by 5.4% patients for Bronchitol – this was not a common event in the overall population
- The rate of pyrexia appears lower in the adult only population – on the Bronchitol group, the rate in adults only is around half that of the overall rate in the overall population and no adult patients reported pyrexia (whereas 10.7% patients reported this event in the overall population)
- The rate of upper respiratory tract infection in the adult only population was lower than in the overall population for the Bronchitol group but higher for the control group

- Several events were reported by >5% patients in the control group of the adult only population which were not >5% in the overall population: influenza, epistaxis, muscoskeletal pain, diarrhoea, fatigue.

Table 50 Most common adverse events in the adult only population: DPM-CF-302

rhDNase users	Bronchitol (N=93)	Control (N=67)
Condition aggravated	34 (36.6%)	23 (39.7%)
Cough	16 (17.2%)	6 (10.3%)
Pharyngolaryngeal pain	11 (11.8%)	5 (8.6%)
Headache	10 (10.8%)	12 (20.7%)
Haemoptysis	6 (6.5%)	2 (3.4%)
Bacteria sputum identified	5 (5.4%)	2 (3.4%)
Abdominal pain	5 (5.4%)	1 (1.7%)
Pyrexia	5 (5.4%)	0
Nasopharyngitis	4 (4.3%)	3 (5.2%)
Sinusitis	4 (4.3%)	3 (5.2%)
Upper respiratory tract infection	3 (3.2%)	7 (12.1%)
Abdominal pain upper	3 (3.2%)	4 (6.9%)
Influenza	2 (2.2%)	3 (5.2%)
Epistaxis	2 (2.2%)	3 (5.2%)
Musculoskeletal pain	2 (2.2%)	3 (5.2%)
Diarrhoea	1 (1.1%)	3 (5.2%)
Fatigue	1 (1.1%)	3 (5.2%)

All adverse events reported with a frequency of ≥5% overall in the adult only population are summarised

The most common treatment related adverse events in the adult only population (cough, condition aggravated and pharyngolaryngeal pain) were the same as in the overall population and reported with similar frequency. Bacterial disease carrier was reported by 2.2% patients in the Bronchitol group of the adult only population but <2% in the Bronchitol group overall.

Eleven adults experienced adverse events leading to study withdrawal. As expected, and as seen in the overall population, cough was most frequently reported in the Bronchitol group (5.4%) than the control group) and the majority of the events were treatment related in the Bronchitol group.

In the adult only population, the most serious AE was condition aggravated (Bronchitol 14.0% vs. control 12.1%). No other events were reported in more than one patient in either treatment group in the adult only population.

The results reported here for the adult only population are very similar to those seen in the overall population. Therefore, the general safety profile of Bronchitol in the overall CF population can be expected to apply to the adult only population.

Summary of safety from OLP and OLEP of DPM-CF-301

The primary purpose of the OLP and OLEP phases of study DPM-CF-301 were to collect safety data on Bronchitol use over the longer term. These study phases have been described above along with the efficacy results.

A high proportion of patients experienced AEs during the open label phases of the study, with AEs more frequently reported in the patients who received control during the DBP of the study (ex control group 94.5%) than those who received Bronchitol during the DBP (85.6%).

The most common AEs in the open label phases were condition aggravated (Bronchitol 44.3% vs. control 42.5%l), bacteria sputum identified (Bronchitol 24.7% vs. control 16.4%) and cough (Bronchitol 19.6% vs. control 24.7%). Most of the remaining AEs, with the exception of nasopharyngitis and haemoptysis, were reported in similar proportions of patients in the DBP treatment groups.

In the majority of patients (>80%), AEs reported during the open label study phases were either mild or moderate in severity. The most frequently reported severe AE was condition aggravated (8.8%).

The incidence of treatment-related AEs during the open label study phases was higher in patients treated with control (28.8%) than those who received inhaled Bronchitol in the DBP (21.6%). The most common treatment-related AEs were cough, haemoptysis, condition aggravated, bacteria sputum identified and headache. Treatment-related AEs of cough and haemoptysis were more frequent in patients randomised to control treatment than in patients randomised to Bronchitol in the DBP (8.2% versus 3.1%).

For both rhDNase users and non-users, AEs were more frequently reported in patients who were treated with control treatment than those who received inhaled Bronchitol during the DBP. For rhDNase users and non-users, the most common AEs were condition aggravated, cough and bacteria sputum identified (reported for 45.7%, 25.0% and 22.8% rhDNase users, and for 41.0%, 17.9% and 19.2% rhDNase non-users, respectively). The most frequently reported severe AE in rhDNase users and non-users was condition aggravated (8.7% rhDNase users and 9.0% non-users).

For patients exposed to Bronchitol for ≥48 weeks, AEs during the open label phases were also more frequently reported in patients who received control treatment during the DBP (100.0% patients) than those who received inhaled Bronchitol (89.2% patients). The most common AEs in both DBP treatment groups for patients exposed to Bronchitol for ≥48 weeks were condition aggravated, bacteria sputum identified and cough.

The incidence of SAEs during the open label phases was higher in patients treated with control than those who received inhaled Bronchitol during the DBP. The most common SAE in both treatment groups was condition aggravated. No deaths were reported during the open label study phases.

More patients in the DBP control group than in the Bronchitol group discontinued study treatment due to AEs during the open label phases (Bronchitol 5.2% vs. control 16.4%). Condition aggravated was the most common AE that led to discontinuation.

Quarterly incidence data did not show any evidence of an increased incidence of respiratory AEs during the open label phases. With the exception of haemoptysis and pharyngolaryngeal pain, which appeared to decrease in incidence in both DBP treatment groups during the open label phases, there were no notable changes in the incidence of respiratory AEs during the open label extension phases.

The incidence and nature of AEs reported for adults (≥18 years) was comparable to that of the overall safety population.

There were no safety concerns raised due to changes in laboratory parameters, chest examination results or vital signs during the study. No obvious trends in changes in growth of microorganisms were observed.

Table 51 Most common AEs in the adult population: OLP and OLEP of DPM-CF-301

	Number (%) of patients			
	CF301 OLP1		**CF301 OLEP**	
	Mannitol 400 mg BD (n=60)	Control (n=44)	Mannitol 400 mg BD (n=29)	Control (n=14)
At least one SAE	**13 (21.7)**	**11 (25.0)**	**4 (13.8)**	**6 (42.9)**
General disorders and administration site conditions	**12 (20.0)**	**9 (20.5)**	**3 (10.3)**	**4 (28.6)**
Condition aggravated	**12 (20.0)**	**9 (20.5)**	**3 (10.3)**	**4 (28.6)**
Respiratory, thoracic and mediastinal disorders	**1 (1.7)**	**2 (4.5)**	0 (0.0)	**1 (7.1)**
Haemoptysis	**1 (1.7)**	**2 (4.5)**	0 (0.0)	**1 (7.1)**
Infections and infestations	0 (0.0)	0 (0.0)	**1 (3.4)**	**1 (7.1)**
Lower respiratory tract infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastroenteritis	0 (0.0)	0 (0.0)	**1 (3.4)**	0(0.0)
Gastroenteritis viral	0 (0.0)	0 (0.0)	0 (0.0)	**1 (7.1)**
Gastrointestinal disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatobiliary disorders	0 (0.0)	0 (0.0)	**1 (3.4)**	0 (0.0)
Cholecystitis	0 (0.0)	0 (0.0)	**1(3.4)**	0 (0.0)
Surgical and medical procedures	0 (0.0)	**1 (2.3)**	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Immune system disorders	0 (0.0)	0 (0.0)	0 (00)	**1 (7.1)**
Investigations	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Adverse events of special interest

In the treatment of CF, there are certain adverse events which are worthy of special mention: haemoptysis, cough and bronchospasm. Data specific to each of these events is given in Appendix 8 and a short summary is included below.

Haemoptysis

Haemoptysis is a relatively common symptom in CF which originates from enlarged and tortuous bronchial arteries. In DPM-CF-301, the overall incidence of haemoptysis, including that associated with exacerbations of CF, was 15.8% in the Bronchitol group compared to 15.3% in the control group which was an almost identical incidence. Similar results were seen from a corresponding analysis in DPM-CF-302. The overall rates of severe, serious or treatment related haemoptysis events were low in both studies.

Cough

Cough is one of the characteristic symptoms of CF; however it is not possible to differentiate between the negative and positive implications that probably coexist.

In both studies, cough was reported by a higher proportion of patients in the Bronchitol group compared to the control group although the overall rates were much lower in DPM-CF-302. Cough was the most common adverse event leading to withdrawal from the study more frequently in the Bronchitol group compared to control.

Bronchospasm

Bronchitol is known to cause bronchoconstriction in susceptible patients. During the blinded treatment phase of Study DPM-CF-301, 2 patients in the Bronchitol group experiences AEs of bronchospasm, both considered treatment-related. One of the AEs was severe. One patient (rhDNase non-user on Bronchitol treatment) experienced a SAE of bronchospasm. The outcome of this SAE was recovered/resolved. In DPM-CF-302, there were no reports of bronchospasm as severe or serious AEs or as an AE leading to study discontinuation.

5.9.3 Give a brief overview of the safety of the technology in relation to the decision problem

Data from the four Phase II and III studies in CF (DPM-CF-201, DPM-CF-202, DPM-CF-203 and DPM-CF-301), as well as from three non-CF Phase II and III studies in bronchiectasis (DPM-B-201, DPM-B-202 and DPM-B-301) and two pharmacokinetic studies in healthy subjects (DPM-PK-101) and patients with CF (DPM-PK-102), have demonstrated that dry powder Bronchitol administered via inhalation, is safe and well tolerated. Across all studies, the safety data show both predictability and general consistency.

In the safety evaluations of the pivotal trials, the most common treatment emergent adverse events were condition aggravated (CF exacerbation), cough, headache and pharyngolaryngeal pain. Haemoptysis occurred more frequently in the Bronchitol group than in the control group.

There were no apparent differences in mean haematology, liver function or urea and electrolyte parameters between treatment groups or over time. Results suggest that in concurrent rhDNase users the frequency of some adverse events in both the Bronchitol and control groups is slightly higher reflecting more severe disease in the rhDNase sub-group. The results seen in the adult only population are very similar to those seen in the overall population. Therefore, the general safety profile of Bronchitol in the overall CF population can be expected to apply to the adult only population.

The daily dose of inhaled Bronchitol administered in the CF studies ranged from 40mg to 420mg. Across the four CF phase II/III studies overall, just under half the patients were female. In line with the prevalence of CF, the mean age of patients ranged from 13 to 23 years, and the youngest and oldest patients in the studies were aged 6 and 68 years, respectively. The majority of patients were Caucasian. At baseline, mean % predicted FEV_1 ranged across the studies from 62.0% in DPM-CF-301 to 64.6% in DPM-CF-201.

Overall, the MTT appeared to be a safe and effective screening procedure since subsequent airway reactivity during the treatment period was not a notable event since all AEs reported in connection with MTT resolved. The MTT effectively reduced the level of bronchospasm reported in studies; therefore, the initiation dose assessment is expected to provide an effective safety measure in the post authorisation setting. The proportion of patients experiencing AEs pertaining to bronchospasm was low and comparable between the two treatment groups.

In conclusion, the safety data presented demonstrate that inhaled Bronchitol is well tolerated for the treatment of CF in the overall and adult only populations as either an add-on therapy to rhDNase or in patients intolerant to, or inadequately responsive to rhDNase.

5.10 Interpretation of clinical evidence

5.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

In the Bronchitol clinical program, a positive effect was seen in terms of clinically relevant outcomes such as FEV_1 changes and pulmonary exacerbations, overall and in the adult-only target patient population. The evidence that the efficacy of Bronchitol on top of optimised care is clinically relevant is considered compelling, especially due to the strength of the consistent spirometry data across the Bronchitol clinical programme. Treatment with Bronchitol resulted in early and sustained benefit and a meaningful proportion of patients who were considered to have a treatment response.

Patients treated with Bronchitol were shown to have clinically meaningful improvement in lung function over the study period. Importantly, longer term data show that this treatment effect can be sustained over periods of up to 1 year. An FEV_1 decline is associated with worsening morbidity and mortality and in the pivotal RCTs an absolute difference in FEV_1 % predicted was 2.64% in the adult only population. If it is assumed that the estimated rate of decline of % predicted FEV_1 is 0.65% per year then a sustained improvement of % predicted FEV_1 such as

that seen in the pivotal RCTs may translate into a potential 4-year mortality benefit. Sustained improvement with Bronchitol can potentially slow long term disease progression and the FEV_1 improvement is also associated with exacerbation reductions.

The effects of Bronchitol on the key outcomes of interest can be considered clinically meaningful. In order to assess relative response rates, thresholds were defined a priori with CF experts. A significantly higher proportion of responders was seen in the Bronchitol group than in the control group for all three thresholds (100mL, 5% change, absolute change of 5% in FEV_1 % predicted) and the rate ratio of responders was twice that of control. A correlation between FEV_1 change over the treatment period and exacerbation rate in DPM-CF-301 has also been demonstrated which supports the importance of these outcomes measures.

In the management of CF, physicians recognise the high variability in response to therapies. The unmet need may be greatest when rhDNase is not an available option (i.e. patients no longer taking rhDNase due to lack of tolerability or efficacy or patients who have not been prescribed rhDNase due to ineligibility). Based on mechanism of action alone, there is no reason to expect that a lack of response to rhDNase will predict a lack of Bronchitol response. The average treatment effect for Bronchitol includes responders and non-responders - approximately 30% of rhDNase patients improved by ≥ 10% compared with ≥ 35% of Bronchitol patients in both of the pivotal RCTs (DPM-CF-301 and DPM-CF-302). This efficacy of Bronchitol is over and above optimised therapy including rhDNase and appears to be consistently seen in patients who are currently being treated with rhDNase and those who are not.

Overall, the relative efficacy of Bronchitol compares favourably to approved CF therapies and the trials showed a consistent robust benefit across all four Bronchitol studies which included adult patients. The majority of patients receiving Bronchitol experience meaningful responses and these results compare favourably to approved CF therapies. FEV_1 improvements were seen with Bronchitol and were associated with exacerbation reductions. The benefits seen over the 26 week RCT study periods were also shown to be sustained - patients most likely to continue long term therapy saw large benefits in lung function and exacerbations. These results could potentially slow long term disease progression

The safety profile of Bronchitol is good and the initiation dose successfully minimises risk. The most commonly observed adverse reaction associated with the use of Bronchitol is cough, although productive cough is a beneficial component of mucus clearance. Other adverse events which were noted to occur commonly (i.e. frequency at least 1/100) were decreased appetite, headache, haemoptysis, bronchospasm, condition aggravated, pharyngolaryngeal pain, productive cough and chest discomfort). The clinically most important adverse reaction associated with the use of Bronchitol is haemoptysis based on the potential severity.

Overall, in the adult-only target patient population of CF patients, a population of high unmet need, Bronchitol has positive benefit:risk profile irrespective of concomitant rhDNase use and is an effective treatment for CF in that group of patients.

5.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

The two pivotal phase III studies which form the basis of this submission were very similar in terms of study designs, patient populations and outcomes measures and analyses. Results from these studies are consistent with those seen in phase II study populations which include adult patients. In addition to the key outcomes showing consistent results across studies, the results seen were consistent across rhDNase subgroups. The adult only population appear to show similar results to overall population on key measures. These results were analysed in a number of ways and the data were robust to analyses methods including additional consideration of study withdrawals. It is of importance that the positive effects seen in the double blind phases of the pivotal RCTs appear to be sustained over the longer term and these data show positive long term effects.

Although the results from the two studies were relatively robust, analyses across studies did not always lead to the same results. This may be driven by a number of factors including that fact that the rhDNase proportion not the same in each study. However, exploratory analyses addressed many of these possible issues and the overall conclusions are consistent. In order to address the impact of patients withdrawing from the study before the end of the 26 week period (and the resulting missing data) on the primary endpoint, several single imputation methods were carried out and showed that the results were consistent with those seen in the primary analyses. Additional analyses were also carried out to investigate the impact of various modelling assumptions (ANCOVA vs MMRM models) on the primary endpoint and again the results were consistent showing the robust nature of the clinical effectiveness of Bronchitol.

Another consideration is that the target patient population for this submission was not a pre-specified subgroup in both studies. The adult only population was pre-specified in DPM-CF-302 but only for descriptive analyses. The initial clinical trial program was aimed at a general CF population which included children, adolescents and adults; however, the regulatory review has resulted in a focus on the adult only population and this necessitated some post-hoc analyses, particularly for DPM-CF-301. However, the adult population was a major component of the two pivotal RCTs and results seen in the adult only population were very consistent with those seen in the overall ITT population.

5.10.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

The decision problem is defined as the use of Bronchitol as a therapy for the management of CF in adult patients in addition to best supportive care (which includes a variety of interventions). Outcomes which were considered relevant included mortality, lung function, respiratory symptom, rate of pulmonary exacerbations requiring hospitalisation, improvement in exercise tolerance, adverse effects of treatment and health-related quality of life. The two pivotal RCTs which form the basis of this submission include a wide population of patients with CF of which a substantial proportion were adults.

The outcomes of interest were measured using robust well established measures and were generally reported consistently across the two pivotal RCTs. Since CF cannot be cured; the goal of Bronchitol therapy is to clear the airways of mucus, improves respiratory function, reduce respiratory infections and slow long-term decline. FEV_1 change is a recommended primary endpoint because of the obstructive nature of CF lung disease. Data from the pivotal RCTs showed that a positive clinical response in terms of FEV_1 was also associated with a reduction in pulmonary exacerbations. Exacerbations are of real concern to patients since they are associated not only with distress but also with the use of additional medications and the possibility of hospitalisation. In addition, since there are no guidelines on a clinically meaningful threshold for FEV_1 change in CF, threshold definitions were defined in consultation with CF experts in order to better understand the magnitude of effect which would be considered relevant to clinicians and patients.

The use of formal exercise capacity or exercise tolerance as a clinical outcome in clinical trials is still in its infancy and there remain no clear guidelines on which methods should be utilised in clinical studies for CF patients. While exercise tolerance was not directly assessed in the Bronchitol phase III program, patients did report on their physical fitness through the Cystic Fibrosis Questionnaire-Revised (CFQ-R).

The 26-week duration of double-blind treatment phase in the pivotal RCTs was chosen as this was considered sufficient to prove the efficacy. However, in order to confirm the safety of the treatment, the open-label phase of additional 26 to 52 weeks of treatment was added to the double-blind phase. This was an important addition since it generated data on the continued use of Bronchitol and the longer term impact on important clinical outcomes (efficacy and safety).

Therefore the two studies which form the basis of this submission provide robust data which are directly relevant to the decision problem.

5.9.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

For these pivotal RCTs, a population with clinician diagnosed cystic fibrosis who had a FEV_1 of >30% but less than 90% predicted were sought for screening. These criteria would likely be used in clinical practice to manage an adult patient with CF. In the clinical trials the patients were given a mannitol tolerance test before Bronchitol was administered in order to ensure that no patient to with bronchial hyperresponsiveness were included in the study. This may be used in clinical practice for the same purpose and would not restrict the use of Bronchitol beyond what is appropriate.

The pivotal RCTs which form the basis of this submission assessed the use of Bronchitol in addition to usual care in clinical practice. This allowed the studies to be targeted at patients who would be eligible for Bronchitol in routine clinical practice to be enrolled. The inclusion and exclusion criteria were aimed at identifying those patients. The anticipated licence is for patients who are currently taking rhDNase (rhDNase users) and for patients who are ineligible, intolerant in inadequately responsive to rhDNase (rhDNase non users). Therefore the clinical program has included the assessment of Bronchitol benefit in relation to two relevant comparators:

- rhDNase users: for those patients currently on rhDNase, the comparison will be: rhDNase + BSC vs. rhDNase + Bronchitol + BSC.
- rhDNase non-users: for patients who are ineligible, intolerant or inadequately responsive to rhDNase, the appropriate comparison will be Bronchitol + BSC vs. BSC

Usual care could include rhDNase or not and the results seen in the studies demonstrated the positive effect of Bronchitol regardless of rhDNase use at baseline. Additionally, during the study there were some patients who change rhDNase status (i.e. user to non-user of vice versa) – these changes occurred only in a small number of people and did not have a meaningful impact the interpretation of the results. Therefore changes made in clinical practice should not impact the effectiveness of Bronchitol.

In the pivotal RTCs the initial treatment dose for Bronchitol was administered in the clinic setting under medical supervision to ensure subject safety and good administration technique – this may be a useful consideration when using Bronchitol in usual care. The study protocols included only limited restrictions on co-medications or treatment provided as part of BSC thus the study treatments should reflect usual care. Hypertonic saline was excluded during the double blind treatment phase since it has a mode of action similar to that of Bronchitol which could confound the results. In addition, it is not standardised in either its formulation or administration. This may be a limitation it the generalizability of the data if hypertonic saline was routinely used in clinical practice.

The Bronchitol dose of 400 mg was chosen based on the results from the dose finding Phase II trial, where it showed the greatest improvement in spirometry measures. With consideration that utilizing more than 10 capsules may overly compromise subject's compliance with treatment, the 400mg dose appeared to be the most appropriate balance between acceptability/tolerability and efficacy. All of the Bronchitol data generated from the pivotal RCTs in this submission were at this dose.

The primary objective of both studies was to determine the impact of Bronchitol treatment on FEV_1. Frequency of post treatment FEV_1 measures was set to establish the onset time and duration of treatment effect. Other key endpoints were included additional evidence of a clinically relevant improvement and clinical benefit – these included other spirometry measures, pulmonary exacerbations and patient reported quality of life. These outcomes are very relevant in clinical practice and are routinely used in the management of adult patients with CF. The frequency of assessment may not be exactly the same in clinical practice but an assessment at

6 weeks should indicate whether there is benefit with Bronchitol treatment – the data from these studies have shown that patients who have an initial response to Bronchitol are likely to sustain that response over a longer time frame.

Assessment of all the pulmonary function tests (PFTs) was standardised by using a standard calibrated spirometer, site staff trained according to a standard procedure and recommendations on the timing of pulmonary function testing. These measures ensure that the results seen are robust but would not impact the Bronchitol effects which may be seen in clinical practice.

Overall, the pivotal RCTs demonstrated consistent robust outcomes from Bronchitol treatment which lead to an effective treatment for CF in adult patients who are currently taking rhDNase (rhDNase users) and for patients who are ineligible, intolerant in inadequately responsive to rhDNase (rhDNase non users).

6 Cost effectiveness

6.1 Published cost-effectiveness evaluations

Identification of studies

6.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 9.10, appendix 10.

A comprehensive review of the literature was undertaken to identify any existing cost-effectiveness studies in the field of CF. Studies were identified from the published literature by searching PubMed and CRD databases.

The search identified 10 relevant items. The search output is presented in Appendix 10. No items carry out cost effectiveness studies on Bronchitol.

The Cochrane Collaboration was also searched. Two Cochrane reviews were located; the first on hypertonic saline and the second on rhDNase.

- Wark P, McDonald VM. Nebulised hypertonic saline for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2009, Issue 2. Art. No.: CD001506. DOI: 10.1002/14651858.CD001506.[15]
- Jones AP, Wallis C. RhDNase alfa for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2010, Issue 3.Art.No.:CD001127. DOI: 10.1002/14651858.CD001127.[17]

The only comparison to Bronchitol is in Wark et al. 2009 and compares delivery time. There are no economic analyses in the Cochrane reviews.

Description of identified studies

6.1.2 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.

Table 52 Summary list of other cost-effectiveness evaluations

Study	Year	Country(ies) where study was performed	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention,comparator)	ICER (per QALY gained)
Robert[30]	1995	UK	Cost-effectiveness analysis of once-daily rhDNase vs standard care.	Patients ≥ 5 years; excluding patients with severe disease.	No apparent survival benefit. 26% fewer days of treatment with IV antibiotics, 18% reduction in inpatient stay. QALYs not stated.	£ 5,900 per patient per year	£ 25,000 per QALY
Oster[31]	1995	US	Prospective analysis of effect rhDNase versus placebo on health care use and costs over a 24-week timeframe	Patients with a confirmed diagnosis of CF and a FVC of greater than 40% predicted Age: 18.4±9.0 for Placebo (n=325), 18.7±9.0 for rhDNase once daily (n=322), and 19.9±9.0, for twice daily (n=321). FEV_1: 61.0±2.52; 61.1±26.9; 60.0±2.69	FEV was 5.8% (o.d. dose) and 5.6% (b.d. dose) higher than placebo ($p<0.001$). Fewer patients receiving rhDNase once daily (35%; $p<0.05$) or twice daily (33%; $p<0.01$) experienced a RTI compared with placebo (43%).	Estimated mean costs of RTI related care were $6,443; $4,781, and $5,629 among patients in the placebo, rhDNase OD and rhDNase BD groups, respectively. This excluded the costs of rhDNase therapy.	N/A
Menzin[32]	1996	France, UK, Germany, Italy	See Oster 1995; Trial based evaluation of rhDNase once daily versus placebo	See Oster 1995	See Oster 1995	Difference in mean cost of RTI-related care (excluding the costs of rhDNase): FF 7,011, DM 1,970, ItL 1,285,000; £434.	N/A
McIntyre[33]	1999	UK	Cost-effectiveness analysis of once-daily rhDNase vs placebo. Modelling delayed progression of lung function.	See Oster 1995. Treatment is started at the age of 8 and FEV_1 70% of predicted.	LYG with rhDNase = 3. Age at death: 38 for placebo, 41 (40-45) for rhDNase.	Lifetime costs: £ 151,264 for placebo, £ 233,070 (£ 223,440-241,731) for rhDNAse.	£ 27,269 (£ 10,311-45,234) per LYG
Suri[34]	2002	UK	Trial based evaluation comparing 2.5 mg rhDNase o.d., alternate day 2.5 mg	47 CF patients. Age: 12.6 (7-17), FEV_1: 48±15. 2.5 mg rhDNase o.d., alternate day 2.5 mg	Following 12 weeks of treatment there was a mean±SD increase in FEV_1 from baseline of	Mean total cost for 12-week treatment period was £ 4,285for HS,	N/A

Study	Year	Country(ies) where study was performed	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention,comparator)	ICER (per QALY gained)
			rhDNase, to 5 ml 7% HS b.d in children.	rhDNase, or 5 ml 7% HS b.d.	16%±25 in patients receiving daily rhDNase, 14%±23 for alternate day rhDNase, and 3%±21 for HS.	£ 5,711 for daily rhDNase, and £ 5,198 for alternate day rhDNase.	
Grieve[35]	2003	UK	Trial based cost-effectiveness analysis of rhCNase versus HS in children	See Suri 2002	Change in FEV_1 over 12-weeks was for HS 0%±27, for daily rhDNase 14%±27, and for alternate day rhDNase 12%±19.	Mean total cost for 12-week treatment period was £ 4,285for HS, £ 5,694 for daily rhDNase, and £ 5,230 for alternate day rhDNase.	£ 110 (daily), £ 89 (alternate) per 1% gain in FEV_1 over 12 weeks
Browne[36]	2009	Canada	HTA assessment of nebulised hypertonic saline compared to rhDNase.	See Suri 2002	See Suri 2002	See Suri 2002	£ 200 per 1% gain in FEV_1 over 12 weeks
Thornton[37]	2005	UK	Cost-effectiveness analysis comparing home-based and hospital based treatment with IV antibiotics for respiratory exacerbations in adults with CF. Clinical outcome and resource use data were obtained from a retrospective one-year study.	116 CF patients receiving 454 courses of intravenous antibiotics Age: 26 (17-43) for Home (n=47), 26 (16-47) for Hospital (n=51), 25 (19-42) for Both (n=18) FEV_1: 54.8 (19.0); 49.3 (18.6); 50.4 (16.0)	Treatment was deemed effective in 58.8% (hospital based) versus 42.6% (home based) versus 50.0% (both). Effective treatment was defined as ≤2% decline in FEV_1.	Total mean costs were £ 13,528 (1,537-51,898) for home based treatment, £ 22,609 (2,873-99,828) for hospital based treatment and £ 19,927 (5,149-45,813) for patients receiving both home and hospital based treatment.	£ 46,098 (hospital), £ 71,710 (both) per effectively treated patient.
Christopher[38]	1999	UK	Simplified economic model examining the impact of rhDNase	Two populations: 1) all CF patients; 2) patients with FEV1 % predicted < 70%	Continued use of rhDNase over the lifetime of a CF patient	rhDNase cost £ 7,442 per year. Saving of £ 1,746 per	£ 52,500 per LYG in the all

Study	Year	Country(ies) where study was performed	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention,comparator)	ICER (per QALY gained)
			treatment compared to placebo on the decline of lung function. Model assumes death occurs when FEV1 drops below 28%. Lifetime model horizon (30 years).	who demonstrate a sustained improvement of ≥10% with rhDNAse.	might extend their life expectancy by 2 years (all patients) and up to 7 years (subgroup).	patient due to reduced hospitalization.	patients analysis; £ 16,000 per LYG in subgroup analysis
Perras[39]	1996	Canada	Details of economic model not reported. Based on Canadian healthcare perspective. Main clinical outcomes were exacerbations/hospitalisations. Time horizon 6, 12,and 15.9 months.	Adults/children with CF.	The % of patients experiencing an exacerbation was 82%/87% in the group not receiving rhDNase versus 71%/80% receiving rhDNase at 12/15.9 months, respectively. The mean number of hospitalizations for exacerbations was 2.86/3.46 versus 2.67/2.67, respectively.	The overall expected cost in the rhDNase group were $7,565/ $36,605/ $44,010 versus $1,904/ $29,543/ $37,920 in the non-rhDNase group over 6/12/15.9 months, respectively.	$37,740/ 6 months, $15,025/ 12 months and $ 7,000 15.9 months per one less hospitalisation.
HS, hypertonic saline; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALY(s), quality-adjusted life year(s); RTI, respiratory tract infection							

6.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)[**] or Philips et al. (2004)[††]. For a suggested format based on Drummond and Jefferson (1996), please see section 9.11, appendix 11.

See section 9.11 Appendix 11.

6.2 De novo analysis

Patients

6.2.1 What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.4 and 5.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.

The pooled data from the pivotal studies DMP-CF- 301 and DMP-CF-302 forms the basis for this economic evaluation. In line with the expected licensed indication only the adult patient (aged 18 or above) from these 2 trials have been included.

Model structure

6.2.2 Please provide a diagrammatical representation of the model you have chosen.

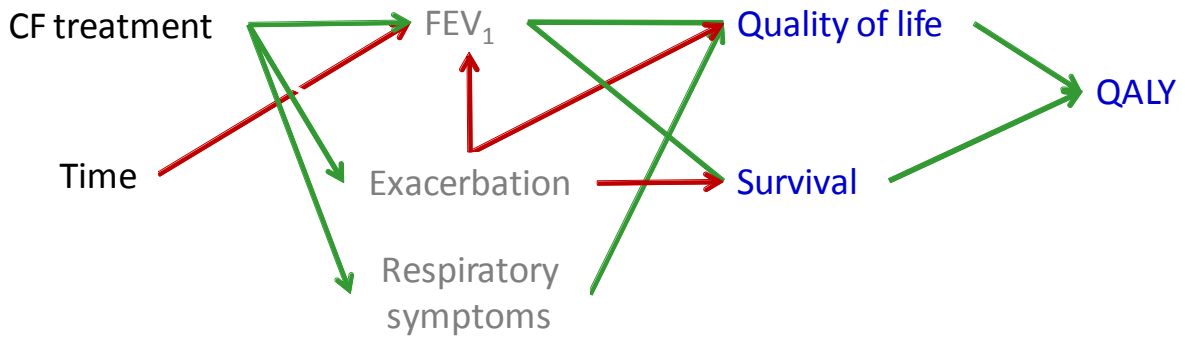
A decision analytical framework was used to develop the economic model of Bronchitol versus standard care in the treatment of cystic fibrosis. The structure of the economic model follows the structure of the clinical algorithm. A simplified version of the economic model is outlined below.

The model is a patient-level simulation Markov model which means that the progression of each individual patient is modelled, rather than the progression of a whole patient cohort at once. As patients move through the model one at a time the model memorises specific patient characteristics like lung function, age, and body mass index (BMI). These characteristics are taken into account when determining the transition probabilities and thus the path through the tree. A schematic presentation of the relationship between treatment, time, clinical endpoints and economic endpoints is shown in Figure 15.

[**] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.

[††] Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

Figure 15 Schematic presentation of the relationship between treatment (black), time (black), clinical endpoints (grey), and model endpoints (blue).



A green arrow indicates a positive relationship and a red arrow indicates a negative relationship between factors.

A graphic presentation of the model structure is presented in Figure 16. The Control treatment arm from study DPM-CF-301 and DPM-CF-302 represents standard care in the real-life setting.

The following strategies are considered:

- Bronchitol
- Control
- Bronchitol + rhDNase
- Control + rhDNase

The model allows patients to move through the model from left to right and they can move from each health state to another except for the health state death. Death is a 'collector health state', which means that once a patient died he cannot return to any of the other health states.

Patients move through the model as follows: all patients start in 'Cystic Fibrosis' and based on their lung function measured by FEV1 they either continue treatment (FEV1 ≥30%), or they are eligible for a lung transplant (FEV1 <30%). This cut-off is based on the treatment guidelines for a lung transplant in CF patients. Patients not responding to Bronchitol treatment will stop Bronchitol treatment and switch to standard therapy (the control arm).

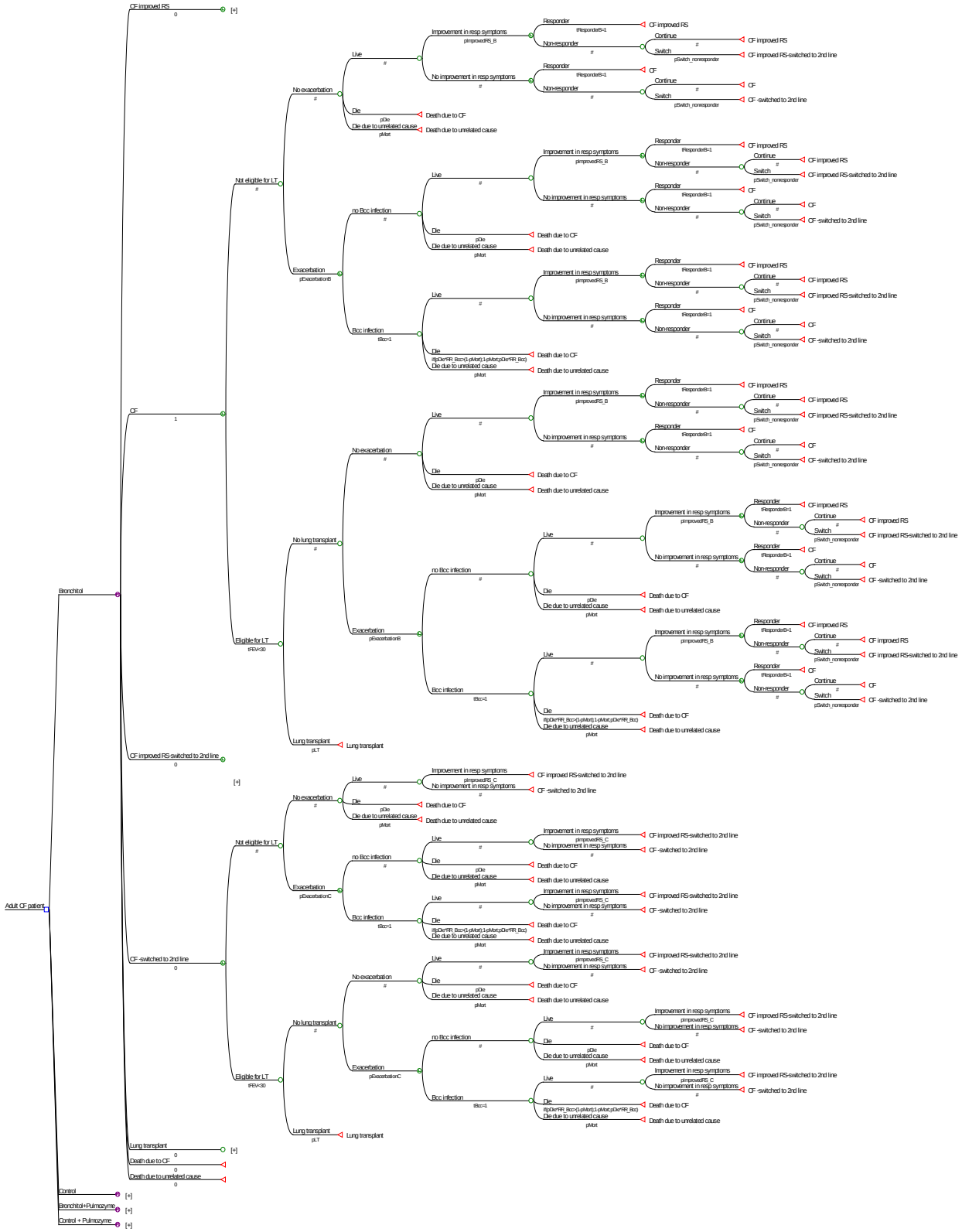
CF patients may experience pulmonary exacerbations. The rate of pulmonary exacerbations depends upon the patient's age, the history of exacerbations in the previous year and whether the patient is receiving Bronchitol or standard therapy. In addition the patient may experience improvement in respiratory symptoms, which corresponds to a slightly improved quality of life.

Each cycle the patient has the chance to die due to CF or to unrelated cause. By default the probability of dying is based on the lung function and age. However this probability is elevated when the patient has an exacerbation in combination with a Bcc infection. In addition, when a

patient received a lung transplant the probability of dying is equal to the annual death rate among transplanted patients with cystic fibrosis, irrespective of lung function and age.

For the first 26 weeks of the economic model for adults an analysis of individual patient level data is undertaken for all adult patients treated with Bronchitol. From here the model extrapolates to a lifetime horizon based on observational data from an Australian database (BioGrid), supplemented with literature data.

Figure 16 Core Model Structure



6.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.4.

The structure of the economic model is consistent with the pivotal clinical trials for Bronchitol; for example, inclusion of 6-week, 14-week and 26-week timepoints. The pivotal trials are in line with the care pathway for patients with cystic fibrosis.

6.2.4 Please define what the health states in the model are meant to capture.

The model includes the following health states:

- Cystic fibrosis
- Improved respiratory symptoms
- Lung transplant
- Death due to CF
- Death due to unrelated cause

The Cystic fibrosis health state captures all CF patients until they die or receive a lung transplant. The health state “improved respiratory symptoms” includes those CF patients with an improvement in respiratory symptoms of ≥4 compared to baseline as measured by the CFQ-R (see section 6.2.4 for further details). Patients who do not have this improvement in respiratory symptoms move to the CF health state.

While exacerbations itself do not form a separate health state and can occur in both the CF and Improved Respiratory Symptoms health state, it does influence the transition to the Lung Transplant health state as well as Death due to CF.

In the Bronchitol arm an additional health states is included that captures patients who do not respond to Bronchitol treatment and are switched to best supportive care. This health state is identical to the “Cystic fibrosis” health state in the Control arm.

The Lung Transplant health state captures all CF patients who have received a lung transplant. Transplanted patients remain in this health state until their death.

The death due to CF is an absorbing health states that gathers patients who have died because of CF. Patients dying from another cause accumulate in the “death due to unrelated cause” health state.

6.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

The health economic model aims to capture the main complications of CF disease that have a large impact on the treatment costs and QALYs and that can be influenced by Bronchitol treatment or its comparator. Bronchitol and its comparator aim at improving mucus clearance in the lung; therefore the model focuses on the symptoms of lung disease.

Cystic fibrosis is a progressive disease. Disease progression was captured by tracking each patient's decline in lung function. As FEV_1 is the most commonly used test for lung function in CF patients and it is an important predictor for the quality of life and mortality, the model is based on FEV_1 status to determine a patient's lung function. In addition, acute worsening of lung function is captured in the model as a pulmonary exacerbation which results in a diminished quality of life and an increase in treatment costs.

Registry data obtained from a virtual data repository provider BioGrid Australia Limited[40] was used to explore long-term survival and lung functioning. The data was extracted from three hospital data bases (Royal Children's Hospital, Monash Medical Centre and The Alfred Hospital, all located in Melbourne, Victoria, Australia) and four databases of registry data related to cystic fibrosis treatment in Victoria, Australia. Together these databases contain information on 2,322 individuals treated as CF patients in Victoria, Australia since the late 1940s. Since 1974, a range of clinical characteristics including lung function data, height and weight and vital status have been maintained on the databases. The following inclusion criteria were imposed to the data: CF patients aged ≥6 years and had maximum FEV_1 % predicted of 90% who were alive on January 1, 1993 and for whom follow-up data were available through July 30, 2010. In addition, there must have been at least two measurements per patient in order to be included into the analysis. These inclusion criteria resulted in 15,832 longitudinal records on 855 patients (324 females, 382 males). For the cost-effectiveness analysis, only those longitudinal records of patients aged 18 to 47 were included. The lower limit (18) excludes children and adolescents to be in line with the expected licensed indication. The upper limit (47) excludes ages where not sufficient data was available (see BioGrid report in Appendix 16).

Several factors have been identified that impact CF mortality and that can be improved by CF treatment, including FEV_1 % predicted, FVC, pulmonary exacerbations, BMI, Bcc infection and Pa infection. Data from BioGrid captured lung functioning, pulmonary exacerbations and BMI but did not capture Bcc or Pa infection. Literature gave mixed results for Pa infection (e.g. not significant in Liou[41]; significant in Courtney[27]). The combination of an exacerbation and a Bcc infection increases mortality.[41,42] The combination of Pa infection and a pulmonary exacerbation was not found to increase mortality. As CF treatment will not impact the chronic infection itself, but does have an impact on the number of pulmonary exacerbations, Bcc infection was also incorporated into the model.

Univariate analyses were used to explore the association between utility measures (i.e. change from screening in HUI2 global utility score at 26 weeks) and health status by means of respiratory symptoms, vitality and exercise tolerance as defined in section 6.3.1 by using the CFQ-R.

The CFQ-R is a validated patient-reported outcomes (PRO) instrument that measures health-related quality of life (HRQoL) in CF patients. The CFQ-R contains both generic and CF-specific scales, including a respiratory symptom domain and a physical domain. Quittner et al determined the minimal clinically important difference (MCID) score for the respiratory domain of the CFQ-R based on two open-label tobramycin inhalation solution (TIS) studies[24]. The MCID score for stable CF (4.0) was used to determine if patients in the 301/302 study had an improvement in respiratory symptoms over the 6-month period, or not.

The use of formal exercise capacity or exercise tolerance as a clinical outcome in clinical trials is still in its infancy.[43] There remains no clear guidelines on which methods should be utilised in clinical studies for CF patients, and while a number of alternatives exist and have been validated (such as step tests, incremental and timed walk tests), the use of these either in studies or even in current clinical practice remains low.[44] Nevertheless, improving exercise capacity is seen as an increasingly important factor in clinical practice for patients with CF as a number of studies have demonstrated a relationship between exercise capacity and pulmonary dysfunction.[45,46] While exercise tolerance was not assessed in the Bronchitol phase III program through any of the methods described, patients did report on their physical fitness through the Cystic Fibrosis Questionnaire-Revised (CFQ-R).

To our knowledge the MCID for the physical and vitality domain have not been determined yet. In a similar manner to the approach described in Quittner et al[24], the MCIDs were determined based on the pooled data from the two pivotal studies DMP-CF-301 and DMP-CF-302.

The univariate analyses showed that only improvement in respiratory symptoms at week 26 (improved/not improved) indicate a statistically significant (p-value<0.05) difference in mean HUI2 global utility scores at 26 weeks, hence exercise tolerance and vitality as defined by means of the CFQ-R were not captured into the model. Further details of Treatment outcome is captured these analyses are presented in Appendix 15.

Aspects of CF that were not taken into consideration were those that Bronchitol or standard care will not improve and which have less impact on overall survival than lung function. These aspects include gastrointestinal, liver, pancreatic, endocrine and bone symptoms, CFRD, growth and pubertal development, bone health, liver disease, urinary incontinence, sinonasal disease, infertility, pain, sleeping problems, and depression.

Most patients taking Bronchitol can be expected to experience adverse reactions. The most commonly observed adverse reaction associated with the use of Bronchitol is cough. Although reported as a common AE, productive cough is a beneficial component of mucus clearance. The clinically most important adverse reaction associated with the use of Bronchitol is haemoptysis. The proportion of patients who experienced haemoptysis as an AE or during exacerbation was comparable between the Bronchitol arm and the Control arm (15.8% vs. 14.6% respectively). These rates of haemoptyis are also consistent with expected rates in the CF community and also published studies of populations of comparable severity, e.g. in Fuchs 1994,haempotysis incidence was 17-21% and in the recently published inhaled tobramycin study (TIP/TOBI) the

incidence was 12-13%[28,47]. Other commonly reported (≥ 1/100) treatment-related AEs were: respiratory, thoracic and mediastinal disorders which included cough, haemoptysis, bronchospasm, condition aggravated, pharyngolaryngeal pain, productive cough, and chest discomfort; plus post-tussive vomiting. None of these AEs led to a substantial increase in costs or prolonged diminished quality of life and were therefore not included in the model.

6.2.6 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

Table 53 Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	Life time (Theoretic maximum of 100 years)	Chronic progressive disease	Guide to the methods of technology appraisal
Cycle length	First cycle 6 weeks, second cycle 8 weeks, subsequent cycles 12 weeks	Availability and best fit to data and clinical practice	Guide to the methods of technology appraisal
Half-cycle correction	0	Cycle length too short to require correction	Guide to the methods of technology appraisal
Were health effects measured in QALYs; if not, what was used?	QALYs		Guide to the methods of technology appraisal
Discount of 3.5% for utilities and costs	3.5% for utilities and costs		Guide to the methods of technology appraisal
Perspective (NHS/PSS)	NHS and PSS		Guide to the methods of technology appraisal
NHS, National Health Service; PSS, Personal Social Services; QALYs, quality-adjusted life years			

Technology

6.2.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

Bronchitol is modelled in line with its indication for the treatment of CF in adults aged 18 years and above as an add-on therapy to rhDNase, and in patients ineligible, intolerant, or inadequately responsive to rhDNase[‡‡].

Patients receive 400 mg twice daily. The duration of Bronchitol use varies for each patient depending on the time spent responding to treatment. In order to optimise the clinical and cost effectiveness of treatment with Bronchitol a treatment continuation rule has been identified to ensure that treatment is focussed entirely on patients who are responding to treatment (at least 5% relative improvement in FEV_1 or an absolute improvement of >=100 ml in FEV_1 after 6 of treatment). Details of this continuation rule are provided in the section below.

The Control treatment arm from study DPM-CF-301 and DPM-CF-302 represents standard care in the real-life setting.

6.2.8 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the 'response' criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

Upon initiation with Bronchitol, patients are placed on a trial for a period of 6 weeks. At the end of the trial period FEV1 improvement is used to assess whether the patient has responded. Patients achieving at least 5% relative improvement in FEV1 or an absolute improvement of >=100 ml in FEV1 after 6 weeks of treatment continue Bronchitol treatment, all other patients discontinue Bronchitol treatment after the 6-week period. This cut-off was chosen as a recognised clinically relevant improvement in FEV_1. The overall efficacy data supports a plateau effect after 6 weeks, hence the 6-week visit was deemed appropriate to make the decision to continue or stop treatment. In addition the 6 weeks fits the time whereby a patient would come back for a clinical review.

[‡‡] The indication granted to Bronchitol is: "Bronchitol is indicated for the treatment of cystic fibrosis in adults aged 18 years and above as an add-on therapy to best standard of care".

We explored the impact of imposing such continuation rule on the Bronchitol treatment effect using raw data from the Bronchitol groups of the combined DPM-CF-301/ DPM-CF-302 database (adult population). The overall absolute mean change from baseline in FEV1 (δ FEV1) was 126 mL at week 6 and the overall relative mean change from baseline in FEV1 (δ FEV1) was 6.0% at week 6. Based on the continuation rule 100/207 (42%) of Bronchitol patients would be defined as responders and continue treatment.

No costs are associated with the implementation of the continuation rule as the FEV1 measurements are standard practice during CF clinic visits.

6.3 Clinical parameters and variables

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical-evidence section of the submission (section 5). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

6.3.1 Please demonstrate how the clinical data were implemented into the model.

The primary source of information used to develop the structure of the model was a detailed analysis of the individual patient data derived from the two pivotal clinical trials for Bronchitol DMP-CF-301 and DMP-CF-302. In line with the expected licensed indication only the adult patients (aged 18 or above) from these two trials have been included. This informed the starting patient population, disease state and the disease progression pathway adopted in the first 26 weeks of the economic analysis.

Both CF-301 and CF-302 showed Bronchitol to be effective as add-on therapy. CF-301 showed significant treatment effect in rhDNase users and non-users. In CF-302, although there were greater improvements in FEV1 changes in the Bronchitol groups versus the control group of both rhDNase users and non-users, however these did not reach statistical significance in the rhDNase use sub-groups. See section 5.5.1 Table 56. Combined analysis (Section 5.6) shows significant treatment effect in both users and non-users. Interaction terms for rhDNase user versus non user for the primary efficacy outcome showed no difference in treatment effect (p=0.310) indicating that Bronchitol works similarly in users and non-users of rhDNase. On the basis of this analysis, the overall treatment effect including rhDNase users and non-users has been used in the economic model.

Baseline patient characteristics

The baseline patient characteristics from the pooled adult population were used in the model.

Table 54 Baseline patient characteristics

Parameter	Bronchitol	Control	Total
N	207	134	341
Gender (% male)	61%	53%	58%
Age (years)	28.3	28.8	28.5
BMI (kg/m^2)	22.6	22.1	22.4
FEV1 % predicted	59.9	58.4	59.3

Effect on lung function

Improved lung function is incorporated in the cost-effectiveness analysis as a one-time increase in FEV_1 % predicted during the first 6 months. A linear regression analysis was performed to obtain a prediction of the FEV_1 % predicted at the end of the trial follow-up period, i.e. week 26. The final model is presented in Table 55 below and details are given in Appendix 17. The covariance structure resulting from the regression model was used in the Cholesky decomposition technique to provide correlated draws from a multivariate normal distribution for the probabilistic sensitivity analysis.

Table 55 Linear regression model for FEV_1 % predicted at week 26 (Adults only)

Variable	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	-7.76767	3.19289	-2.43	0.0156
Treatment group	1.52254	0.84022	1.81	0.0710
BMI at baseline	0.36902	0.12207	3.02	0.0027
FEV_1 % predicted at baseline	0.93357	0.02715	34.38	<.0001
PDPE during DBP	-2.15803	1.00012	-2.16	0.0318
Responder	6.63425	0.83526	7.94	<.0001

The clinical trials both provided treatment periods of only 26 weeks. Bronchitol is intended for lifetime use hence the results of the trials need to be extrapolated over the life time of a patient. We assume that the benefit in lung function achieved in the first six months will be maintained over the patient's lifetime, assuming that he/she will receive therapy for the remainder of his life.

Pulmonary exacerbations

Protocol defined pulmonary exacerbations (PDPE) from the combined DMP-CF-301 and DMP-CF-302 studies were used in the cost-effectiveness analysis to capture acute worsening of lung function. For the definition of PDPE we refer to Section 5.6. The PDPE rate for the adult

population in the combined data observed over the 26 weeks is turned into an annual rate by treatment group based upon years of patient exposure.

The DMP-CF-302 study showed differences in historical rates of pulmonary exacerbations between the Bronchitol and Control group, leading to less pulmonary exacerbations in the Control group. As no information on historical pulmonary exacerbations was collected in the DMP-CF-301 study, the pooled data was not adjusted for this difference. Exacerbations in a CF population vary considerably and are generally a difficult endpoint to measure. In both the DMP-CF-301 and DMP-CF-302 studies a low underlying rate of exacerbations was observed. Thus a small number of exacerbations can cause a relative large change in the exacerbation rates. The effect of this assumption was tested in a scenario analysis using only the DMP-CF-301 data.

The relative risk of having a PDPE for patients who respond to Bronchitol was calculated by the observed difference in PDPE rate in patients who responded to Bronchitol compared to the overall PDPE rate in the Control group. The values used in the economic evaluation are presented in Table 56 below.

Table 56 PDPE rates from combined DMP-CF-301 and DMP-CF-302 (Adults only)

	Control			Bronchitol	
	Non-responder	**Responder**	**Total**	**Non-responder**	**Responder**
Number of PDPEs	30	15	45.00	31	22
Years of exposure	38.18	22.07	60.25	39.42	44.99
Annual Rate	0.79	0.68	0.75	0.79	0.49
Relative Risk*					0.65

* The relative risk was calculated based on the annual exacerbation rate observed in Bronchitol responders compared to the overall Control arm.

In each treatment arm, the risk of having a pulmonary exacerbation was adjusted for patients with a history of exacerbations based on the observed elevated risk of exacerbation for patients with exacerbations in the year preceding the participation in the DPM-CF-302 study (RR=1.59, $p<0.001$). The annual exacerbation rate was based on BioGrid data (see section 6.3.7).

6.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

The transition probabilities for improved respiratory symptoms are calculated from the pooled -CF-301 and DMP-CF-302 data. At baseline all patients start in the CF health state and are assumed to remain there till the end of cycle 2 (corresponding to the 14-week visit). The probability of moving to the “improved respiratory symptoms” at this point was based on the number of patient with ≥4 points improvement in their CFQ-R respiratory domain score. The probability of remaining in the “improved respiratory symptoms” health at each next cycle of 12 weeks was based on the number of patients who maintained a ≥4 points improvement in the CFQ-R respiratory domain score at the 26-week visit compared to baseline. Similarly the

probability of moving to the “improved respiratory symptoms” at each next cycle was based on the percentage of patients who had <4 points improvement in the CFQ-R respiratory domain score at the 14-week visit and a ≥4 points improvement in the CFQ-R respiratory domain score at the 26-week compared to baseline (see Table 57). Patients with missing CFQ-R data were excluded from the analysis.

Table 57 Transition probabilities improvement in respiratory symptoms

Treatment	Respiratory Symptoms	Percentage of patients	n	N
Bronchitol	Improved after 3 months	39%	67	170
	Remain improved after 6 months	69%	46	67
	Improved after 6 months but not at 3 months	17%	17	103
Control	Improved after 3 months	46%	55	120
	Remain improved after 6 months	75%	41	55
	Improved after 6 months but not at 3 months	15%	10	65

In the model a patient is eligible for a lung transplant if the FEV1 percent predicted <30%, which was based on the treatment guidelines for a lung transplant in CF patients. If the patient is eligible for a lung transplant and does receive one, the patient transitions to the ‘Lung transplant’ health state which simulates the life expectancy for patients post-lung transplantation irrespective of their characteristics or treatment. The transition probability to the “Lung Transplant” state is based on the UK CF Registry Annual Data Report 2008. Of those with complete data in 2008, 126 patients had been evaluated and 55 accepted onto the transplant list. 24 received transplants (i.e. a probability of 0.19).

It is not realistic to assume that the patients will continue treatment with Bronchitol for the rest of their life irrespective if there is a benefit or not. And it is unlikely that clinicians would prescribe treatment to those patients that get no benefit. Therefore a continuation rule was implemented in the Bronchitol arm in the cost-effectiveness analysis. As described in section 6.2.8, a responder to treatment is defined as a relative increase of at least 5% or an absolute increase of at least 100ml in the FEV_1 at week 6 from baseline. Patients on Bronchitol who are responders according to the above definition, will continue treatment for the rest of their life. Patients on Bronchitol who are non-responders, will discontinue the treatment with Bronchitol and be switched to a best supportive care which is identical to the Control arm. Table 58 below provides the transition probability of remaining on Bronchitol treatment after 6 weeks.

Table 58 Probability of being a responder to Bronchitol from DMP-CF-301 and DMP-CF-302 (Adults only)

	Bronchitol			Control		
	N	n	%	N	n	%
Responder	207	100	48%	134	46	34%

As the length of both trials was too short to evaluate mortality, these transition probabilities have been derived from BioGrid and UK statistics, see section 6.3.7.

6.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

For the cost-effectiveness analysis, the rate of the lung function decline varies over time. BioGrid data was used for this purpose and details are provided in section 6.3.7.

Historic exacerbation rates predict higher future pulmonary exacerbations. In fact, Liou et al[41] reported that pulmonary exacerbation rates within the year have a large negative impact on 5 year survival, equal to subtracting 12% from the measured FEV_1 % predicted value[41]. This was supported by the observed elevated risk of exacerbation for patients with exacerbations in the year preceding the participation in the DPM-CF-302 study (RR=1.59, p<0.001). Thus the economic evaluation assumes that patients having exacerbations in the previous year are more likely to have an additional exacerbation than those without exacerbations in the previous year.

The annual exacerbation rates used in the model are based on BioGrid data. No change is made to the exacerbation rates over time due to changes in adherence.

6.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

Intermediate outcome measures were not used.

6.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[§§]:

- the criteria for selecting the experts

[§§] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Clinical experts were consulted only in order to understand patient pathways and standards of care.

Summary of selected values

6.3.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

The list of all variables included in the cost-effectiveness analysis is presented in the Table 59 below.

Table 59 Summary of variables applied in the economic model: patient population

Variable name	Variable description	Value	Distribution	Reference to section in submission
Gender	Gender CF patient (% male)	0.58	Beta n = 341, r = 198	Patient characteristics section 5.3.4
Age_start	Age CF patient at baseline	28.52	Sample from table "AgeCFpt"	Patient characteristics section 5.3.4
BMI_start	BMI CF patient at baseline	22.44	Sample from table "bmiCFpt"	Patient characteristics section 5.3.4
FEV_start	FEV1 % predicted CF patient at baseline	59.28	Sample from table "FEV1_CFpt"	Pooled trial results section 5.3.4
Bcc_infection	Prevalence of Bcc infection (age 16+)	0.05	Beta n = 3081, r = 160	Section 6.3.6

With the exception of the Bcc infection prevalence, all the variables that characterise the patient population in the cost-effectiveness analysis are determined from the pooled data from the two pivotal studies DMP-CF-301 and DMP-CF-302. The prevalence of Bcc infection in CF patients aged 16 and above is based on the Annual UK CF registry report (2008) where it is stated that Bcc infection was identified in 160 from the 3,081 cultures taken[48].

Table 60 Calculation of treatment effect

Variable name	Variable description	Formula
FEV_V4_B_improvRS	FEV1 % predicted after 26 weeks of treatment with Bronchitol in patients having improvement in respiratory symptoms	fParameter_intercept+BMI_start*fParameter_BMI+FEV_start*fParameter_FEV1+1*fParameter_Bronchitol+1*fParameter_improvRS+tResponderB*fParameter_responder
FEV_V4_B_no_improvRS	FEV1 % predicted after 26 weeks of treatment with Bronchitol in patients not having improvement in respiratory symptoms	fParameter_intercept+BMI_start*fParameter_BMI+FEV_start*fParameter_FEV1+1*fParameter_Bronchitol+0*fParameter_improvRS+tResponderB*fParameter_responder
FEV_V4_C_improvRS	FEV1 % predicted after 26 weeks of treatment with Control in pts having improvement in respiratory symptoms	fParameter_intercept+BMI_start*fParameter_BMI+FEV_start*fParameter_FEV1+0*fParameter_Bronchitol+1*fParameter_improvRS+tResponderC*fParameter_responder
FEV_V4_C_no_improvRS	FEV1 % predicted after 26 weeks of treatment with Control in patients not having improvement in respiratory symptoms	fParameter_intercept+BMI_start*fParameter_BMI+FEV_start*fParameter_FEV1+0*fParameter_Bronchitol+0*fParameter_improvRS+tResponderC*fParameter_responder

Table 61 Summary of variables applied in the economic model: treatment effect

Variable name	Variable description	Value	Distribution	Reference to section in submission
fParameter_intercept	Parameter estimate of intercept*	-7.966	Multivariate Normal	Section 6.3.7
fParameter_BMI	Parameter estimate of BMI*	0.379	Multivariate Normal	Section 6.3.7
fParameter_FEV1	Parameter estimate of FEV_1 % predicted at baseline*	0.934	Multivariate Normal	Section 6.3.7
fParameter_Bronchitol	Parameter estimate for treatment with Bronchitol*	1.811	Multivariate Normal	Section 6.3.7
fParameter_improvRS	Parameter estimate for improvement in respiratory symptoms used to predict the FEV1 % predicted after 26 weeks of treatment*	1.729	Multivariate Normal	Section 6.3.7

fParameter_responder	Parameter estimate for response to treatment*	5.235	Multivariate Normal	Section 6.3.7
Responder B	Probability of being a responder to Bronchitol	0.48	Beta n = 207, r = 100	Section 6.3.2
Responder C	Probability of being a responder to Control	0.34	Beta n = 134, r = 46	Section 6.3.2

* Parameter estimate in multivariate regression model for FEV_1 % predicted after 26 weeks

Table 62 Summary of variables applied in the economic model: pulmonary exacerbations

Variable name	Variable description	Value	Distribution	Reference to section in submission
RR_ExacerbationB_responder	Relative risk exacerbation with Bronchitol (patients who respond to treatment)	0.66	Log-Normal Mean = -0.424 Std Dev = 0.260	Section 6.3.1
RR_Exacerbation_over30	Relative risk for patient experiencing an exacerbation over the age of 30	1.38	Log-Normal Mean = 0.0437 Std Dev = 1.384	Section 6.3.7
RR_previous_exacerbation	Relative risk of experiencing an exacerbation if patient has experienced an exacerbation in the previous year.	1.59	Log-Normal Mean = 0.4637 Std Dev = 0.0688	Section 6.3.1
rExacerbation_base	Annual exacerbation rate control group	0.70	Beta, n = 1,919, r = 1,344	Section 6.3.7

Table 63 Summary of variables applied in the economic model: respiratory symptoms

Variable name	Variable description	Value	Distribution	Reference to section in submission
dImprovedRS_C_v3	Probability of improved respiratory symptoms at week 14 (V3) for pts treated with Control	0.458	Beta n = 120, r = 55	Section 6.3.2
dImprovedRS_C_v4	Probability of improved respiratory symptoms at week 26 (V4) for Control pts	0.154	Beta n = 65, r = 10	Section 6.3.2
dRemainImprovRS_C_v4	Probability of continuing to have improved respiratory symptoms at week 26 (V4) for pts treated with Control	0.745	Beta n = 55, r = 41	Section 6.3.2

dImprovedRS_B_v3	Probability of improved respiratory symptoms at week 14 (V3) for pts treated with Bronchitol	0.394	Beta n = 170, r = 67	Section 6.3.2
dImprovedRS_B_v4	Probability of improved respiratory symptoms at week 26 (V4) for Bronchitol pts	0.165	Beta n = 103, r = 17	Section 6.3.2
dRemainImprovRS_B_v4	Probability of continuing to have improved respiratory symptoms at week 26 (V4) for pts treated with Bronchitol	0.687	Beta n = 67, r = 46	Section 6.3.2

How decline in lung function and mortality is incorporated in the model is described in section 6.3.7. For completeness the key parameters are listed in Table 64 and Table 65 below.

Table 64 Summary of variables applied in the economic model: decline in FEV_1 % predicted

Variable name	Variable description	Value	Distribution/Formula	Reference to section in submission
fParameter_age	Parameter estimate for age*	-1.02	Multivariate Normal, using Cholesky decomposition	Section 6.3.7
fParameter_ageplus30	Parameter estimate for age over 30*	1.65	Multivariate Normal, using Cholesky decomposition	Section 6.3.7
fParameter_exacerbation	Parameter estimate for exacerbation*	-2.08	Multivariate Normal, using Cholesky decomposition	Section 6.3.7
rFEVdecline	Annual change in FEV_1 % predicted in patients aged 30 or below without an exacerbation	-1.02	fParameter_age+0*fParameter_ageplus30+0*fParameter_exacerbation	Section 6.3.7
rFEVdecline_exacerbation	Annual change in FEV_1 % predicted in patients aged 30 or below who had an exacerbation	-3.10	fParameter_age+0*fParameter_ageplus30+1*fParameter_exacerbation	Section 6.3.7
rFEVdecline_exacerbation_plus30	Annual change in FEV_1 % predicted in patients aged over 30 who did not have an exacerbation	-1.44	fParameter_age+1*fParameter_ageplus30+1*fParameter_exacerbation	Section 6.3.7
rFEVdecline_	Annual change in	0.64	fParameter_age+1*fPara	Section 6.3.7

plus30	FEV_1 % predicted in patients aged over 30 who had an exacerbation		meter_ageplus30+0*fParameter_exacerbation	

***** Parameter estimates mixed model for FEV_1 % predicted

Table 65 Summary of variables applied in the economic model: mortality

Variable name	Variable description	Value	Distribution	Reference to section in submission
RR_Bcc	Relative risk of death due to a Bcc infection in combination with an exacerbation	3.41	LogNormal Mean = 1.2267 Std Dev = 0.5862	Section 6.3.7
HR_FEV	Hazard rate ppFEV1	0.957	LogNormal Mean = -0.0440 Std Dev = 0.00736	Section 6.3.7

Of those with complete data in 2008 (N=6,082), 126 patients had been evaluated and 55 accepted onto the transplant list. 24 CF patients received transplants: 16 bilateral lung, 1 heart and lung, 6 liver and 1 renal. For the model we included all 24 transplanted patients (as it was not clear what number of patients was specifically evaluated for a lung transplant)[4]. Mortality for patients who received a lung transplant were based 10-year survival data from UK patients receiving a lung transplant between 1995-1997.[50]

Table 66 Transplant mortality

Time since LT (years)	Mortality rate (rLT)	Percentage	n	N
1	0.357	30%	90	300
2	0.121	11%	24	210
5	0.122	31%	57	186
10	0.108	42%	54	129

6.3.7 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan-Meier plots.

The pivotal clinical trials both provided treatment periods of only 26 weeks. Bronchitol is intended for lifetime use hence the results of the trials need to be extrapolated over the life time of a patient. Lung function was the primary outcome of the pivotal Bronchitol trials. It is assumed that the benefit in lung function achieved in the first six months will be maintained over the patient's lifetime, assuming that the patient will receive therapy for the remainder of his/her life,

but no further improvement in the FEV1 percent predicted. This is supported by the observed sustained clinically meaningful improvements in lung function in the Bronchitol group during the OLP and OLEP phases of the DPM-CF-301 study (see Figure 13, section 5.8).

Decline in lung function over time

For the cost-effectiveness analysis, the rate of the lung function decline over time was calculated. BioGrid data was used for this purpose.

A repeated measures mixed model analysis was undertaken to estimate the mean rate of decline of FEV_1 % predicted over time as a function of covariates such as age, gender, BMI and of inpatient hospital admission days per quarter. The covariance structure resulting from the repeated measures mixed model was used in the Cholesky decomposition technique to provide correlated draws from a multivariate normal distribution for the probabilistic sensitivity analysis.

The final model results are presented in Table 67 below and details can be found in the BioGrid report (see Appendix 14).

Table 67 Mixed model estimate of effect from BioGrid Data (Adults only)

	Solution for Fixed Effects				
Effect	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept	85.5864	4.4401	391	19.28	<.0001
age	-1.0174	0.1975	368	-5.15	<.0001
age_plus30	1.6536	0.4575	247	3.61	0.0004
hosp_days/qtr > 0 (baseline=0)	-2.0787	0.5581	270	-3.72	0.0002

The model shows that lung function decreases on average by 1.02% per year to the age of 30 after which it tends to increase slightly by 0.64% per year. However hospitalisation during the previous 3 months is associated with a 2.08% decrease in lung function. Possible reasons for the observed increase beyond the age of 30 years include:

1) there were fewer data beyond the age 30 years;
2) potential survival bias;
3) as older patients are more likely to be hospitalised, some of the apparent improvement will be offset by decreases in lung function associated with hospitalisation.

A literature search was also carried out simply to provide a context for the BioGrid data analysis. The search was done in PubMed on the 25th October 2010 using the search term:

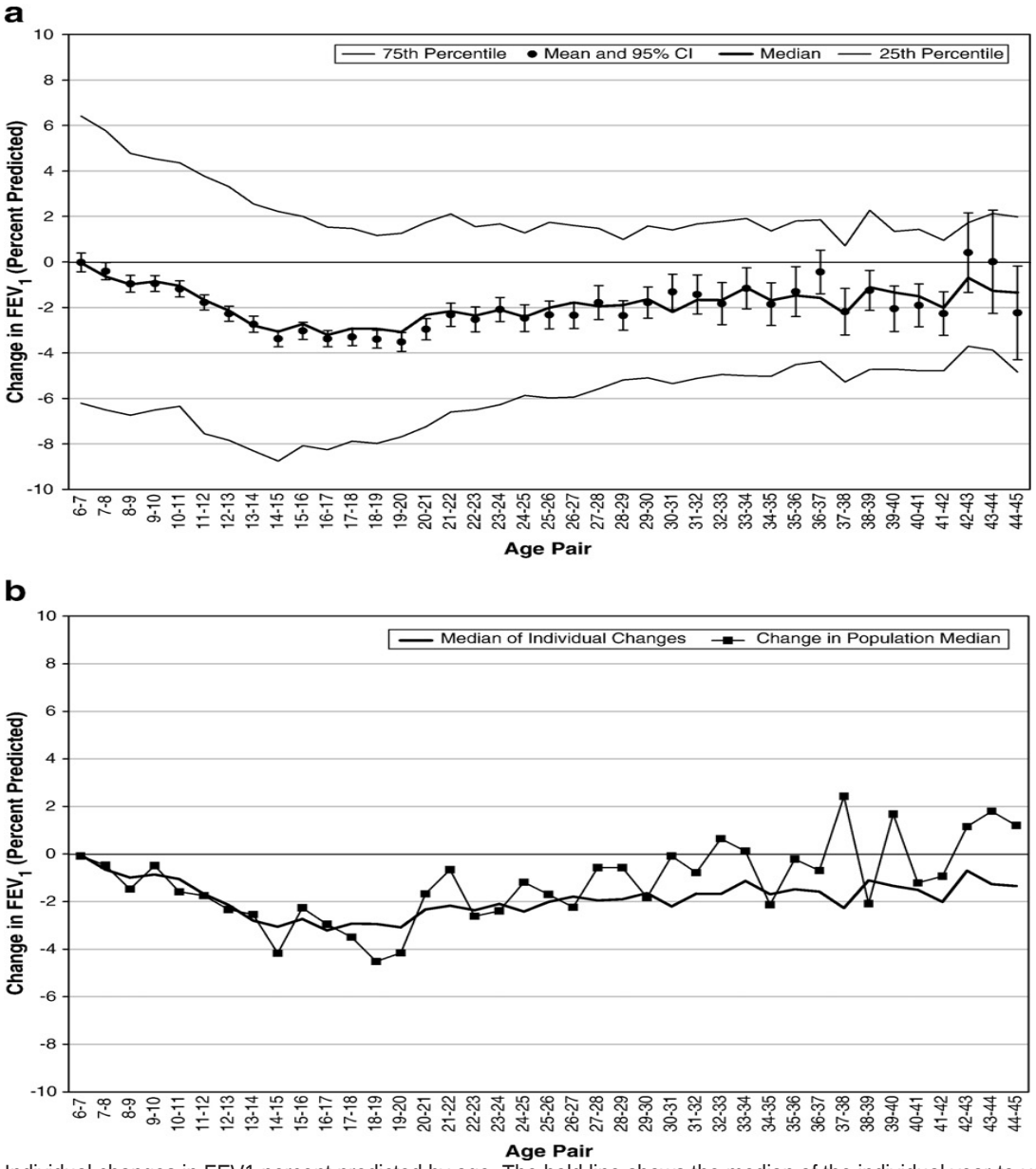
<(cystic fibrosis[MeSH Major Topic]) AND ((lung OR pulmonary) AND function)>

The search was limited to items published in the last 10 years in humans and English language identified 2,305 items. This was considered too expansive to carry out a formal review so a title search was carried out for pertinent items. Further, because of dramatic changes in treatment, survival and diagnostics in the last decade more recent papers were prioritised for relevance and a manual reference search of key recent papers was also done.

Liou et al.[51] was remarked as the most relevant and recent data source on longitudinal change in FEV1. Liou et al.[51] reports the difference in individual versus population based FEV1 outcomes in a cohort of 20,644 (6-45 year olds) in the Epidemiologic Study of Cystic Fibrosis between 1994 and 2005. Differences between individuals and overall population highlight the importance of individual treatment plans and adherence to treatment to maintain FEV1 at optimum levels. The increased risk of adolescents' decreases in lung function, compared to children and older adults especially highlights the importance of maintenance of FEV1 to improve survival outcomes.

Examination of FEV1% predicted values for consecutive years of age reveals that for most ages the individual year-to-year change is a drop of 1 to 3 FEV1% points (Figure 17a). The mean and median of individual year-to-year changes are always negative, with progressively worse declines until about age 15 and smaller declines through adulthood to age 45. Through age 15, the change in median FEV1% based on aggregated population data agrees well with individual data for year-to-year change (Figure 17b). In contrast, the change in median FEV1% based on the population data shows higher variability after age 15, but it appears to stabilise in patients over age 30 although individuals may continue to decline in lung function at approximately 1-2 points per year.

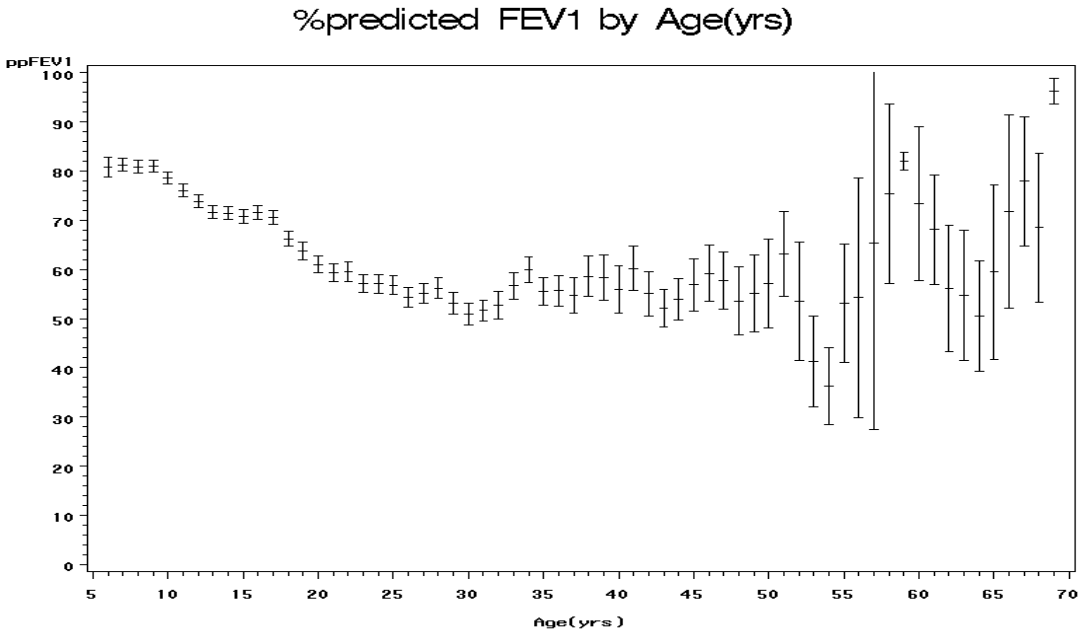
Figure 17 Median individual and population change in FEV1 by age



Individual changes in FEV1 percent predicted by age. The bold line shows the median of the individual year-to-year changes for each age group, while solid circles with bars represent the mean and 95% confidence interval at each age. The lighter curves represent the 25th and 75th percentiles and provide a sense of the variance for each age group. b. Median of individual changes in FEV_1% and change in population median of FEV1% by age. A curve with squares and a light line showing the change in the population median FEV_1% from year-to-year is superimposed on the median of individual year-to-year changes at each age (bold curve). The population aggregate year-to-year changes parallel individual changes through early adulthood
Source: Liou *et al.* 2010[51], p.253

The BioGrid data produced estimates of lung function decline consistent with that reported by Liou et al.[51] (See Figure 18)

Figure 18 Percent Predicted FEV_1 changes by age from BioGrid data



Pulmonary exacerbation rates

Due to the lack of information on exacerbations in the BioGrid database, the number of inpatient hospital admissions per quarter was used as a proxy for the rate of exacerbations.

Table 68Hospitalisation rate in BioGrid data

Patient population	Hospital Days/Quarter				#PTS with hospital days:			
	0		>0		0	>0	All	
	#quarters	%	#quarters	%	N	N	N	Rate
Adults	5,669	72%	2,202	28%	1,634	1,170	2,804	0.785
Adults<=30 years	3,979	75%	1,344	25%	1,190	729	1,919	0.700
Adults>30 years	1,690	66%	858	34%	444	441	885	0.969

Source: BioGrid Australia 2010

The pulmonary exacerbation rate used in the model was the rate observed in adults under the age of 30 years (0.700 per year). For patients aged 30 or above this was corrected by applying a relative risk of 1.38 (0.969/0.700) the baseline risk.

The exacerbation rate in patients on Bronchitol treatment was reduced by the RR observed in the pooled DMP-CF-301 and DMP-CF-302 adult population (RR = 0.66; see section 6.3.1). Finally the exacerbation rate was increased for patients who experienced a pulmonary exacerbation in the previous 48 weeks by applying a relative risk of 1.59 (see section 6.3.1).

Mortality rates

The all cause mortality rate was estimated from UK life tables from the UK Actuaries Department, based upon the gender distribution from the trial and age specific (data not shown to conserve space, but available in the model).

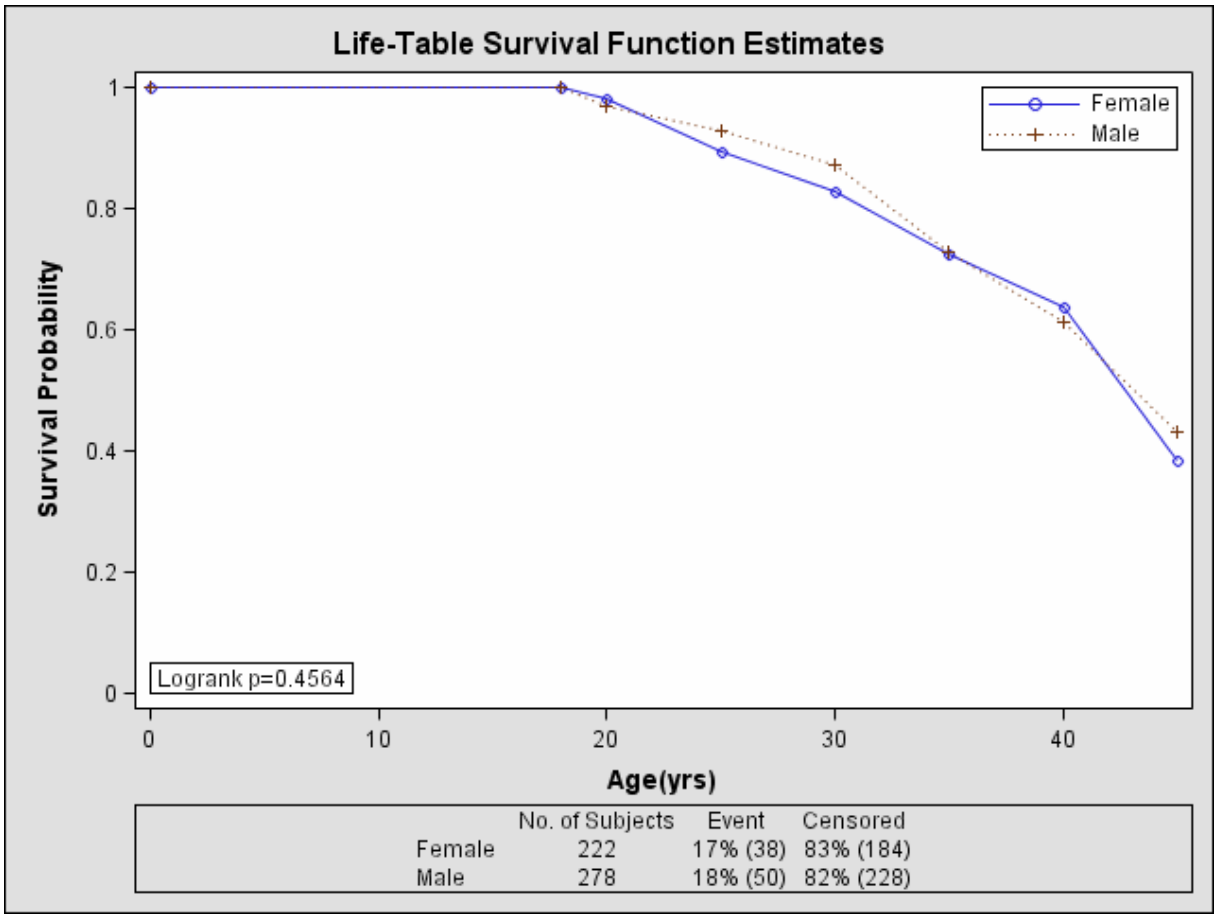
Cystic fibrosis patients have lower life expectancy than the general community. Survival has been linked to lung function and a number of factors including BMI and specific respiratory infections. BioGrid data was used to explore predictors of mortality. A Cox's proportional hazard survival model for CF survival from birth to CF-related death was developed for this purpose. Since FEV_1 was the primary outcome of the Bronchitol pivotal trials particular focus was on the relationship between FEV_1 and survival. Other potential risk factors, like gender and BMI were also investigated. Table 69and Figure 19 present the results of the BioGrid survival analyses. Note that FEV_1 % predicted and BMI were included as time varying covariates in the model.

Table 69 BioGrid analysis of survival (Adults only)

Analysis of Maximum Likelihood Estimates						
Variable	**DF**	**Parameter Estimate**	**Standard Error**	**Chi-Square**	**Pr > ChiSq**	**Hazard Ratio**
ppFEV1	1	-0.04376	0.00736	35.3898	<.0001	0.957
Bmi	1	-0.06900	0.04486	2.3651	0.1241	0.933

Source: BioGrid Australia 2010

Figure 19 Kaplan Meier survival curve BioGrid analysis (18≤ age <48)



A literature search was also done to compare the BioGrid analysis results with previously published studies. This also allowed us to estimate the impact of factors such as Bcc infection and Pa infection which were not available in the BioGrid database.

A literature search was carried out via PubMed on the 18th October 2010 using the search term:

< (cystic fibrosis[MeSH Terms]) AND ((survival[Title]) OR (mortality[Title])) >

The search was limited to items published in the last 10 years and 'human' and 'English' delimiters. The search identified 92 items.

The search was carried out to identify factors impacting on survival in cystic fibrosis patients. Specific focus was on those papers reporting the relationship between FEV_1 and mortality as FEV_1 outcomes were primary outcomes of the Bronchitol clinical trials. We identified six studies which provided an estimate of the relationship between FEV_1 and survival. In each study FEV_1 was expressed as % predicted. Estimates were remarkably consistent across time and for both multivariate and univariate analyses. Only Ellaffi et al. did not show a link between FEV_1 and

survival, however, this study was of older hospitalised patients with very low FEV_1 (28% predicted)[24]. The literature review provides strong evidence that a 1% improvement in FEV_1 is related to a 5% reduction in mortality.

The BioGrid analysis of age at death shows results consistent with those identified in the published literature. A one percent improvement in FEV_1 % predicted is related to a 6% reduction in mortality. Further, a one unit increase in BMI (kg/m^2) results in a 7% reduction in mortality.

Table 70 Items identified in literature search which show the relationship of FEV_1 to survival

Source	Study characteristics	Key results
Courtney et al. 2007[27]	Multi-centre, observational study conducted in Ireland between 1995 and 2005. Study enrolled adolescents/young adults with CF (N=183). Mean age 19 years (14-24)	45 patients died during study period (median age at death was 25 years). Baseline FEV_1 % predicted was higher in survivors (mean 69.8±23.2%) compared to those who died (mean 41.5±15.2%). Baseline FEV_1 % predicted was a significant predictor of mortality (HR 0.95, p<0.0001). Infections with Pa and Bcc were also associated with increased mortality.
Ellaffi et al. (2005)[42]	Single-centre, observational study conducted in France between 1997 and 2001. Study enrolled adult CF patients (N=245). Mean age 28.1 years (17-62).	15 patients died during study period (age at death not reported). Baseline FEV_1 % predicted was not a predictor of survival (HR 1.00, p = 0.231). Infections with Bcc were associated with increased mortality (HR 3.41, p = 0.036)
Sharma et al. 2001[52]	Single-centre, observational study conducted in the UK between 1985 and 1996. Study enrolled CF patients (N=584). Mean age 21±7 years.	137 patients died during study period (age at death not reported). Baseline FEV_1 % predicted was higher in survivors (mean 58%) compared to those who died (mean 32%). Baseline FEV_1 % predicted was a significant predictor of mortality (RR 0.95, p<0.001). $PaCO_2$ and % ideal weight were also independent predictors of mortality.
Kerem et al. 1992[53]	Single-centre, observational study conducted in Canada between 1977 and 1989. Study enrolled children with CF (N=673).	190 patients died during the study period (majority died between 12-23 years of age). A decrease in FEV_1 % predicted ≥ 10% was associated with a significant increase in mortality (RR 1.80, p<0.001). Age and gender were also independent predictors of mortality.
Liou et al. 2001[41]	Multi-centre, longitudinal, observational study conducted in the US between 1993 and 1997. Study enrolled children and adults with CF (N=11,630). Mean age 17.6±9.3 years	1,419 patients died during the study period (age at death not reported). FEV_1 decline was a significant predictor of patient mortality (OR 0.96, p<0.001). Best model of survival included: FEV1 % predicted, weight-for-age (z scores), pancreatic status, diabetic status, Sa infection, Bcc infection, age, gender and number of acute exacerbations.
Augarten et al. 2001[54]	Multi-centre, observational study conducted in Israel between 1985 and 1997. Study enrolled CF patients with FEV_1 % predicted <30% (N=40).	Median survival of patients with FEV_1 slope below the median was 5.33 years. Median survival of patient with an FEV1 Slope above the median was 11.50 years. Age was also an independent predictor of mortality.
Hayllar et al. 1997[26]	Single-centre comparative historical cohort study conducted in the UK between 1969-1987 (Cohort A,	188 patients died during the study period. An increase in FEV_1 % predicted was associated with an improvement in mortality (RR 0.94, p<0.001). Height,

	N=403) and 1988-1993 (Cohort B, N=100). Study enrolled children and adults with CF	hepatomegaly, FVC % predicted, and white blood cell count were also independent predictors of mortality.

A number of other potential risk factors were also identified from the literature search (e.g., BMI, malnutrition, liver complications, Pa infection, Bcc infection[55]) however, based on the clinical trials, none of these were expected to be changed by Bronchitol treatment. The only factor that is changed by Bronchitol is the combination of a pulmonary exacerbation and a Bcc infection. A review of the literature for evidence of the effect of exacerbation rates on mortality found that the combination of having a Burkholderia cepacia complex (Bcc) infection when having an exacerbation was found to be a strong predictor of mortality. The chance of dying increased by a factor 3.41 (Range 1.08 – 10.75) compared to those without a Bcc infection.[42]

Mortality due to CF is modelled using a multiplying hazard function (the risk of dying at any particular point in time) which is constant for all patients at that time point. The mortality rates due to CF are determined by using life table survival estimates obtained on the Biogrid data by age and gender (data not shown to conserve space, but available in the model). The hazard ratio obtained from the Cox regression survival model (HR=0.957) is then applied to the probability of death.

6.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

Response to treatment

- Bronchitol responders are identified at 6 weeks and only they will continue with therapy. Non-responders are switched to best supportive care.
- Drop-outs after the date of assessment at 6 weeks are included in the responder group providing that they meet the responder criteria at the week 6 assessment.
- The effect of Bronchitol is assumed to be same in rhDNase users and non-users.

FEV_1 % predicted and Mortality

- FEV_1 % predicted, BMI and Bcc infection in combination with a pulmonary exacerbation are the only significant predictors for mortality.
- Decline in BMI is deterministic because there are no data around the uncertainty of this decline. (i.e. there is no distribution incorporated into the model to determine uncertainty around the decline in BMI)
- The FEV_1 % predicted is not updated in the model until 26 weeks. In the following cycles FEV_1 % predicted declines according to rate of decline resulting from the repeated measures mixed model provided by BioGrid.
- All-cause mortality (age and gender adjusted) is not decreased to account for CF-related deaths.

Pulmonary Exacerbations

- Pulmonary exacerbations are defined according to the definition in study protocol DPM-CF-301 (Protocol defined pulmonary exacerbations, PDPE).
- A hospitalisation in a quarter is assumed equal to a pulmonary exacerbation
- The chance of having an exacerbation is based on the number of patients that have at least one hospitalisation in a quarter.
- After the initial 6 weeks (at which point the Bronchitol responders are identified) the responders have the exacerbation rates based upon Bronchitol responders, the non-responders to Bronchitol switch back to best supportive care and have the exacerbation rates for the Control group.
- Resource utilisation is determined for patients without exacerbations and for patients with at least one exacerbation, irrespective of the treatment arm the patient was in. Results for both treatment arms were similar and the number of patients that had an exacerbation was only small (n=65) therefore splitting that group over two arms would overestimate uncertainty in resource utilisation.
- The increased risk of mortality during an exacerbation in combination with a Bcc infection is equal to the one reported by Ellaffi[42].
- Patients are assumed to have a chronic Bcc infection or not at the start of the simulation. It is assumed that patients do not develop chronic Bcc infection during the model simulation.
- Patients entering the model are assumed to have had no pulmonary exacerbations in the previous year.

Respiratory Symptoms

- The MCID for determining improvement in respiratory symptoms is equal to 4 as reported by Quittner et al[24].
- It is assumed that transitions between Week 14 and Week 26 remain constant for remainder of model horizon.

Utility

- Duration of utility decrement for a pulmonary exacerbation is assumed to last for 14 days.

Resource utilisation

- Patients are assumed to be 100% compliant to their Bronchitol and rhDNase therapy over the complete time horizon.
- Resource utilisation is not increasing with the patient's age, but is sampled from the same distributions over the model's time horizon.

6.4 Measurement and valuation of health effects

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.4.

The HRQL impact of adverse events should still be explored regardless of whether they are included in cost-effectiveness analysis.

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

Patient experience

6.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

HRQoL in patients with CF has not been studied extensively. Most studies are of cross sectional nature and attempt to explain variance in HRQoL between patients. Information about utility outcomes is limited. In general, CF patients rate their HRQoL higher than one might expect from the impact the disease has on life. For instance, a study matching CF patients to patients from a GP practice showed that global quality of life score was 84.88 for the CF group and 83.33 for the GP group[82]. This difference was significant after controlling for age, sex, educational level, and marital status, indicating that people with CF have better global quality of life. In another study children with CF were matched with their healthy peers who only gave a slightly better HRQoL rating. Domains where CF patients do rate themselves below norm values are in the dimensions of pain, emotion, sleep and functional status. The HRQoL rating given by patients is significantly higher than ratings given by their parents.[56,57] Another anomaly in CF is lower HRQoL rating of female versus male patients[58]. Living with CF appears to have a greater emotional impact on adolescent girls compared to boys[59].

6.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

Quality of life in CF patients appears to be most affected by pulmonary exacerbations[60,61,62]. Recent pulmonary exacerbations have a profound negative impact on HRQOL that is not explained by differences in lung function, nutritional status, or demographic factors.[60] Pulmonary exacerbations affect physical HRQOL more than psychosocial HRQOL. On average, the physical score falls by 6 points per exacerbation and the psychosocial score fall by 3 points. Being hospitalized for exacerbations is associated with improvement in psychosocial HRQOL after exacerbations, whereas not being hospitalized is associated with deterioration.[63]

In a study following patients admitted to hospital with an exacerbation of pulmonary disease, measures of QoL were obtained at the beginning and end of an intravenous course of antibiotic therapy.[64] Two predictors (change in exercise capacity and sputum output) contributed significantly to the change in HRQoL and collectively explained 54% of the variance in QoL. Lung function provides a limited index of HRQoL.

HRQL data derived from clinical trials

6.4.3 If HRQL data were collected in the clinical trials identified in section 5 (Clinical evidence), please comment on whether the HRQL data are consistent with the

reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.

Health related quality of life was assessed via the Revised Cystic Fibrosis Questionnaire (CFQ-R) and Health Utility Index (HUI) in the pivotal clinical trials of Bronchitol used as basis for the economic model. Details on CFQ-R are provided in Section 5.5.1.

The HUI is a generic, preference scored, comprehensive system for measuring health status, health related quality of life and producing utility scores. The HUI is self administered for subjects aged >12 years and proxy administered for children <12 years old. To be noted that HUI was administered only in the pivotal study DMP-CF302. The administered questionnaires are the HUI23S1US.15Q for the self-administered and HUI23P1US.15Q for the proxy administered. Both questionnaires have a recall period of one week.

Measurements were undertaken at VISIT 0 (Screening), VISIT 3 (Week 12), VISIT 4 (Week 26) and at termination visit in case of early withdrawal.

In order to facilitate cost-effectiveness analysis, a HUI2 global utility score was determined for each patient according to the HUI Procedures Manual. Since the population of interest for the cost-effectiveness analysis is the adult population, only the self administered questionnaire was analysed. The mean utility scores at each timepoint are presented in Table 71 below.

Table 71 Mean utility scores (HUI2)

	Control	**Bronchitol**	**Total**
Adults ITT population	**N=58**	**N=93**	**N=151**
HUI2 at Visit 0 (Screening)			
N	58	91	149
Mean (SD)	0.903 (0.094)	0.896 (0.107)	0.899 (0.102)
HUI2 at Visit 3 (Week 12)			
N	54	72	126
Mean (SD)	0.897 (0.090)	0.906 (0.110)	0.902 (0.102)
HUI2 at Visit 4 (Week 26)			
N	50	70	120

Mean (SD)	0.887 (0.121)	0.881 (0.133)	0.895 (0.103)

Mapping

6.4.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

No mapping was used.

HRQL studies

6.4.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 9.12, appendix 12.

A scoping search of the literature was carried out to investigate the health utility impact of cystic fibrosis. Key issues needing to be quantified for the economic model were the impact of:

- Cystic Fibrosis on QoL
- Pulmonary exacerbations on QoL
- Lung transplantation on QoL

The search term was carried out via PubMed on the 20th October 2010 using the search term:

<(cystic fibrosis[MeSH Major Topic]) AND ((quality of life[MeSH Major Topic]) OR ((utility[Title/Abstract]) OR (utilities[Title/Abstract])))>

The search was limited to items; published in the last 10 years and with 'human' and 'English' delimiters. The search identified 119 items.

6.4.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.

- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.
- Appropriateness of the study for cost-effectiveness analysis.

Cystic Fibrosis QoL studies consistently report a correlation between lower lung function scores and physical as well as emotional domains of QoL instruments. Decreased lung function is also associated with depressive symptoms. The literature search however identified scant information on utility values. This makes quantification of the disease and associated problems difficult. Relevant items are summarised in Table 72.

Table 72 Summary of literature on HRQoL and CF

Source	Location	Number	population	Instrument	Results
Bradley et al 2010[78]	UK	14 severe exacerbation; 12 mild exacerbation; 49 no exacerbation	Mean age 28.3 (SD 9.3)	EQ-5d CFQ-R	Effect on utility: Severe exacerbation requiring hospitalisation: u = 0.61 (0.45-0.76) Mild exacerbation (no hospitalisation): u = 0.79 (0.64-0.91) No exacerbation: u = 0.84 (0.78-0.89)
Modi et al 2010[65]	United States	N=52 admitted to hospital	6-18 years with IV AB treatment	Peds QL CFQ-R	Effect of IV AB for PE on HRQoL - significant improvements on CFQ-R Respiratory (t (51) = -4.4, p\.0001) and Weight (t (27) = -4.1, p\.0001) scales - significant improvements found for FEV1% predicted (t (50) = -6.3, p\.001), FEF25–75% (t (50) = -4.8, p\.001), and BMI (t (25) = -3.1, p\.001) - Change in FEV1% predicted was significantly correlated with changes on the CFQ-R Physical Functioning scale (r = .35, p\.01). - Change in BMI was significantly correlated with changes on the CFQ-R Weight (r = .60, p\.05) scale and the Peds QLTM Physical Functioning scale (r = .39, p\.05).
Quittner et al 2010[66]	United States	8,590 patients on a well visit with a PFT as part of ESCF	2,102 adults, 930 adolescents 1,719 children 1,826 Parents.	CFQ-R	Low socioeconomic status was associated with significantly lower CFQ-R scores for children, parents, and adults on the majority of domains.
Hegarty et al 2009[57]	Australia	18 OP 15 IP 20 parents	6-18 yo on admission for acute exacerbation	CFQ-R	Inpatients scores lower than outpatients scores for all domains except 'Digestion' 6-13 yo scored significantly higher than 14-18yo in "emotional', 'body image' and' treatment burden' 6-13yolds perceived less treatment burden than did their parents
Havermans et al 2009[67] and Havermans et al 2008[68]	Belgium	57 consecutive patients attending outpatient clinic includes Non-working and working patients	Adults (mean age 26.8) % pred FEV_1 65.09	CFQ-R Dutch translation Teen/adult	Correlation between Lower lung function (FEV_1 %pred scores) and physical functioning and General Health (r=0.27 and 0.38, p<0.05respectively) Higher BMI associated with higher 'Eating Disturbance' (r=0.44 p<0.01) Nonworking patients had greater disease severity and reported lower QoL than working subjects even after control of medical parameters Patients with depressive symptoms reported lower HRQoL for emotional functioning eating disturbance and body image.

Source	Location	Number	population	Instrument	Results
Eidt-Koch et al 2009[69]	Germany	96 patients	8-17 year olds 57% between 8-13 years	CFQ - disease specific EQ-5D - generic outcomes	44.6% of patients had no problems in any EQ-5D dimensions Several low to strong correlations between dimensions of EQ-5D and CFQ scales for children, parents and adolescents Highest correlation r=0.625 between mobility on EQ-5D and CFQ-R 'physical functioning in adolescents
Abbott et al 2009[70]	UK	N=223 consecutive patients attending CF units	Mean age 25.1 years Mean FEV_1 % 55% pred	CFQoL SF-36	Physical functioning domain of CFQoL and the pain domain of SF-36 had strongest statistical association with survival: Physical functioning HR=0.97(95%CI0.96, 0.99; p<0.001) Pain HR=0.98 (95%CI: 0.97, 0.99: p<0.001)
Riekert et al 2007[71]	United States	76 adults responding to mail questionnaire	Mean age 30.6 years Mean % pred FEV_1 62.8% 30% with depressive symptoms	CFQ Beck Depression Inventory	Higher depressive symptoms associated with poorer lung function (r=-0.25) Higher depressive symptoms associated with poorer HRQoL Better lung function is associated with better HRQoL
Goldbeck and Schmitz 2001[72]	Germany	N=103	Mean age 27 years Mean FEV_1 %pred 62.6	Questions of Life Satisfaction FLZ^M	Factors predicting QoL at second assessment: Longer interval between assessment New colonisation with pA Infection exacerbations Partnership vocation
Thomas et al 2006[73]	Australia	CF N=91 CF outreach subjects N=71	Children and adolescents (2-19 years) parents	Ped QoL - generic CFQ - disease specific	HRQoL as good or slightly better in regional outreach patients compared to patients treated in a CF centre (p=0.05) Declining pulmonary function correlated with worse CFQ scores (p<0.05)
Schmitz and Goldbeck 2006[74]	Germany	N=84 in patient rehab program	16-62 years FEV_1 % pred 52.9	Questions of Life Satisfaction Module FLZ^M	Rehabilitation Program improved objective health outcomes and QoL outcomes (comparison of pre program and post program scores) : general life satisfaction (p=0.025); health related life satisfaction (p=0.008); CF related life satisfaction (p=0.002); FEV_1 % pred (p=0.016); BMI (p<0.001)
Palermo et al 2006[87]	United States	N=46 during routine clinic visit	Mean age 12.9 FEV_1 % predicted mean 80.2% parents	CFQ-R	Assess impact of pain on HRQoL Pain frequency predicted children's HRQoL even after controlling disease severity specific correlations with pain frequency were Respiratory symptoms (r=-0.47), digestive symptoms (r=-0.50), health perception (r=-0.65), vitality/ energy (r=-0.66)
Szyndler et al 2005[75]	Australia	N=52 adolescents attending specialist	Mean age 15.06 years Mean FEV_1 %pred 72.4%	CFQ SCL90-R	Optimism about the future was high (HOPES score) and there was no correlation between it and disease severity

Source	Location	Number	population	Instrument	Results
		CF clinic		HOPES	
Wahl et al 2005[82]	Norway	N=86	Adults	_	Mean global QoL score for group was 84.88 compared with 83.33 for GP control group People with FEV_1 %pred values below 30% reported lowest HRQoL
Vasiliadis et al 2005[76]	Canada	N=124 in Quebec Lung tx programme 1997-2001		Utility via SG	Utilities sourced to Anyanwu et al. 2002 which subsequently sources utility values to Anyanwu et al. 2001 - "The mean utility value of patients on the waiting list was 0.31. In comparison, utility values for recipients 3 years after transplantation were 0.61 for single, 0.82 for bilateral, and 0.87 for heart-lung transplants"
Yi et al 2004[63]	United States	N=48 1997-2001 Inpatients and outpatients	IP mean age = 14.6 OP mean age=19.5 IP mean FEV_1 preex 56% OP mean FEV_1 pre ex 70%	PF-50	Exacerbations associated with statistically significant decrease in FEV_1 (-10%)
Yi et al 2003[77]	United States	N=65 buy telephone or by clinic visit	12-18 years (Mean 15.1±2.1 years) FEV_1 mean 72.8% pred	HUI2	TTO utility = 0.96 ±0.07 SG utility-0.92±0.15

OP=outpatient: IP=inpatient; HRQoL = Health Related Quality of Life; CFQ-R= Cystic Fibrosis Questionnaire - Revised: HOPES = The Hunter Opinions and Personal Expectations: EQ-5D = EuroQoL; PF-50 Child health questionnaire - parent form; SF-36= medical outcomes short form 36

Abbott et al. shows a significant association between the CFQ and survival in a study of 223 consecutive adult patients attending an outpatient CF clinic in the UK.[70] Specifically the physical functioning domain showed a HR of 0.97 (95%CI 0.96, 0.99; p<0.001) and the Pain Domain a HR of 0.98 (95%CI: 0.97, 0.99: p<0.001).

Impact of pulmonary exacerbations on HRQL

Yi *et al.*, whilst not providing a utility value, shows that patients experience a 10% reduction in QoL on HUI 2, during exacerbation when comparing 'excellent health' to 'poor health' states.[63] Yi *et al* however, shows pulmonary exacerbations reducing health perception up to 52% on visual analogue scales (VAS) and so an estimate of 10% reduction in QoL may well underestimate the impact of pulmonary exacerbations on QoL.[77]

Hegarty *et al* [57] reports a 15-20% decline in most domains of the CFQ-R in an Australian population and Goldbeck *et al.*[61] similarly report 20% decline in QoL during exacerbations in a longitudinal study.

A recent poster presented by Bradley et al did report preliminary the impact of mild and severe pulmonary exacerbations in a UK population aged 16 years and older.[78] This observational study conducted at 5 UK hospitals recruited 94 patients and classified them whether they had a pulmonary exacerbation at the day of study entry. The patients were asked to complete the EQ-5D and CFQ-R and demographic as well as clinical data was collected. The preliminary EQ-5D results of 75 patients are presented in Table 73. Mean age of this group was 28 (SD 9.3), 50% was male and 91% were Caucasian. The CFQ-R domains most affected by pulmonary exacerbations were respiratory, physical functioning, vitality, and health perceptions with mean CFQ-R scores for patients with a severe pulmonary exacerbation half that seen in patients without a pulmonary exacerbation.

Table 73 Health status and utility scores from Bradley et al[78]. (2010)

Health state	N	EQ-5D	95% CI	
Severe exacerbation requiring hospitalisation	14	0.61	0.45	0.76
Mild exacerbation (no hospitalisation)	12	0.79	0.64	0.91
No exacerbation	49	0.84	0.78	0.89

As indicated in Section 6.4.3, measurements of the HUI questionnaire were undertaken at VISIT 0 (Screening), VISIT 3 (Week 12), VISIT 4 (Week 26) and at termination visit in case of early withdrawal and the questionnaire had a recall period of one week. Therefore, it was not possible to assess the impact of PDPE on HUI2 utility measure as the PDPE could take place long before the questionnaire was administered.

Impact of lung transplant on HRQL

Three key references were identified which gave utility scores before and after lung transplantation. Groen *et al.* analysed the Dutch lung Transplant Registry which used the EuroQoL to collect prospective QoL data between 1991 and 1995.[79] They reported utility of approximately 0.5 while on the waiting list and a steady improvement to 0.9 after 2 years post transplant. Anyanwu *et al.* also used the EuroQoL to assess QoL in UK patients before and after lung transplantation.[80] They found prior to transplant utility on the waiting list was 0.31 whereas utility after transplant depended on the type of transplant, ranging from 0.61 for single lung and 0.82 for bilateral lung and 0.87 for heart lung transplantation. Vasiliadis et al.[76] used standard gamble to derive utilities for CF and bronchiectasis adult patients enlisted on the Quebec lung transplant waiting list. They reported utility of 0.11 while on the waiting list and an improvement to 0.87 after four years post transplant.

Vermeulen *et al.* have reported improved quality of life with lung transplant but did not report utility.[81] They also noted that QoL in CF patients tended to be better than that of other end stage disease patients.

6.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

In general, CF patients rate their HRQoL higher than one might expect from the impact the disease has on life. For instance, a study matching CF patients to patients from a GP practice showed that global quality of life score was 84.88 for the CF group and 83.33 for the GP group.[82] This difference was significant after controlling for age, sex, educational level, and marital status, indicating that people with CF have better global quality of life. In another study children with CF were matched with their healthy peers who only gave a slightly better HRQoL rating.73 Domains where CF patients do rate themselves below norm values are in the dimensions of pain, emotion, sleep and functional status.[83,84]

Three articles have been identified that report utility values for CF patients. These articles reported slightly lower utility values than observed in the DPM-CF-302 study. Yi et al. derived utilities from an adolescent patient population (mean 15.1, range 12-18 years) with a mean (± SD) predicted FEV1 of 72.8 ± 27.0 %[77]. They reported a HUI2 utility score (± SD) of 0.83 (±0.16).

The other publication that used utility scores related to lung function parameters for CF was Simpson et al.[85] who used utilities reported by Orenstein et al[86]. They based these values on quality of well-being (QWB) scale obtained from 44 patients with CF under care in the Pittsburgh Cystic Fibrosis Center. The population on which the utilities were based had a mean (± SD) age of 16.5 ± 6.9 years (range 7-36 years) and a mean FEV_1 (± SD) of 66.5 ± 32.5 % predicted, which is again younger than the population in the CF-302 study but similar in terms of severity of illness. They reported utility values of 0.75 for patients with symptoms (FEV1 – 60%, range

40%–80%) and 0.68 for patients with severe irreversible symptoms (FEV1 – 30%, range 20–40%).

Finally Bradley et al. reported a utility value of 0.84 in patients not experiencing a pulmonary exacerbation (see Table 72).[78]

Adverse events

6.4.8 Please describe how adverse events have an impact on HRQL.

Pulmonary exacerbations and pain were both found to have a negative impact on HRQL (see section 6.4.6). Spearman rank order correlations between pain symptoms and CFQ-R showed that more frequent pain was associated with decreased vitality, more respiratory and digestive symptoms and poorer perceptions of overall health in children.[87] Children who reported experiencing pain at least once per week (n=21) had significantly reduced overall perception of their health compared with children with no pain or less frequent pain (n=25).

Quality-of-life data used in cost-effectiveness analysis

6.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 6.4.3 to 6.4.8. Justify the choice of utility values, giving consideration to the reference case.

In the cost-effectiveness analysis the HUI2 global utility scores are determined for the "Cystic fibrosis" health state for Bronchitol and Control

The values used as inputs for the model are determined as follows:

- The baseline utility is the average overall HUI2 global utility score at screening irrespective of the treatment (see Table 71 in section 6.4.3);
- Next for each patient the change in utility between Visit 3/Week 14 (or the value reported at the termination visit if the HUI2 global utility value is missing at Visit 3/Week 14) and baseline was calculated. The same was done for the change between Visit 4/Week 26 and baseline;
- The average change in utility from baseline was calculated;
- Finally, the HUI2 global utility scores used into the cost-effectiveness analysis is obtained by summing up the average change and the baseline utility for each health state.

The values used in the cost-effectiveness analysis are presented in Table 74.

Table 74 Summary of quality-of-life values for cost-effectiveness analysis

Variable name	Description	Base case value	Distribution	Reference in submission
u_base	Distribution baseline utility	0.899	Normal Mean = 0.899, Std Dev = 0.102	Section 6.4.3

Variable name	Description	Base case value	Distribution	Reference in submission
d_u_improvRS_B	Change in utility from baseline for patients treated with Bronchitol with improvement in respiratory symptoms	0.019	Normal Mean = 0.019, Std Dev = 0.116	Section 6.4.9
d_u_improvRS_C	Change in utility from baseline for patients treated with supportive care (Control) with improvement in respiratory symptoms	0.009	Normal Mean = 0.009, Std Dev = 0.071	Section 6.4.9
d_u_no_improvRS_B	Change in utility from baseline for patients treated with Bronchitol without improvement in respiratory symptoms	-0.022	Normal Mean = -0.022, Std Dev = 0.105	Section 6.4.9
d_u_no_improvRS_C	Change in utility from baseline for patients treated with supportive care (Control) without improvement in respiratory symptoms	-0.046	Normal Mean = -0.046, Std Dev = 0.166	Section 6.4.9
u_improvRS_B	Utility patient with improvement in respiratory symptoms	0.918	u_base+d_u_improvRS_B	Section 6.4.9
u_improvRS_C	Utility improvement in respiratory symptoms Control	0.908	u_base+d_u_improvRS_C	Section 6.4.9
u_no_improvRS_B	Utility no improvement in respiratory symptoms	0.877	u_base+d_u_no_improvRS_B	Section 6.4.9
u_no_improvRS_C	Utility no improvement in respiratory symptoms control arm	0.853	u_base+d_u_no_improvRS_C	Section 6.4.9
d_Exacerbation	Duration of utility decrement for exacerbation (days)	14	Triangular Min = 1, Likeliest = 14, Max = 361	Section 6.4.9
u_Exacerbation	Utility decrement for exacerbation	-0.23	Beta, alpha = 15.42, beta = 51.62	Section 6.4.6 Bradley 2010[78]
u_LT_WL	Utility for patients with FEV<30	0.31	Normal, Mean = 0.31, Std Dev = 0.0332	Anyanwu AC 2001[80]
u_LT	Utility for lung transplant patients	0.80	Normal, Mean = 0.80, Std Dev = 0.0203	Anyanwu AC 2001[80]

The duration of the utility decrement for an exacerbation was not reported in literature. It was assumed that the duration of the detrimental effect on a patient's QoL corresponded to the overall median days (14; range 1-361) on IV antibiotics in hospital as reported in the UK CF registry report.[4]

Patients eligible for lung transplant were assumed to have a utility equal to that measured in patients on the lung transplant waiting list. Patients who received a lung transplant were assumed to have an average utility as measured in post bilateral lung transplantation patients (the average of 0-6; 7-18; 19-36 and >36 months).

6.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[***]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

The health related quality of life data for CF were collected directly from patients in the pivotal clinical trial DMP-CF-302. The utility values for exacerbation and lung transplant (waiting list) were both taken from UK specific literature. These values were discussed with an expert panel but no expert opinion was used in the model.

6.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

[***] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

HRQL is constant within each health state except when a patient experiences a pulmonary exacerbation or when a patient's FEV1 % predicted drops below 30 (see section 6.4.9).

6.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

One would expect to see a relationship between exercise tolerance and the HRQL. Although several methods are developed for exercise tolerance such as step tests, incremental and timed walk tests, their use in clinical studies on CF patients is limited. One study could be identified in the literature describing the relationship between exercise tolerance and HRQL.[88] They used a 6-min walking test to asses exercise tolerance in 165 patients with CF aged 5 to 45. They failed to prove any association between exercise tolerance and HRQL in this patient population. While exercise tolerance was not assessed in the pivotal studies DMP-CF-301 and DMP-CF302 through any of the direct methods, patients did report on their physical fitness through the CFQ-R. We have used the physical domain of this questionnaire as a proxy for the exercise tolerance and we investigated if there is any association between HUI2 utility and this proxy measure for the exercise tolerance. The analyses showed that exercise tolerance as defined by the physical domain of CFQ-R was not associated with significant differences in HUI2 utility (see Appendix 15 for details). Therefore exercise tolerance was not included in the cost-effectiveness analysis.

Most patients taking Bronchitol can be expected to experience adverse reactions. The most commonly observed adverse reaction associated with the use of Bronchitol is cough. Although reported as a common AE, productive cough is a beneficial component of mucus clearance. The clinically most important adverse reaction associated with the use of Bronchitol is haemoptysis. The proportion of patients who experienced haemoptysis as an AE or during exacerbation was comparable between the Bronchitol arm and the Control arm (15.8% vs. 14.6% respectively). Other commonly reported (≥ 1/100) treatment-related AEs were: respiratory, thoracic and mediastinal disorders which included cough, haemoptysis, bronchospasm, condition aggravated, pharyngolaryngeal pain, productive cough, and chest discomfort; plus post-tussive vomiting. None of these AEs led to prolonged diminished quality of life and were therefore not included in the cost-effectiveness analysis.

6.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

The baseline utility is the average overall HUI2 global utility score at screening irrespective of the treatment (see table 15 in section 6.4.3).

6.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

The HRQL is assumed constant over time, except when the patient's FEV1 % predicted drops below 30 (see section 6.4.9)

6.4.15 Have the values in sections 6.4.3 to 6.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

There are no amendments done to the values from the pivotal study DMP-CF-302.

6.5 Resource identification, measurement and valuation

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.5.

All parameters used to estimate cost effectiveness should be presented clearly in a table and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

NHS costs

6.5.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

Care for CF patients is provided at specialist CF centres by a multi-disciplinary team consisting of clinician, nurse, physiotherapist, dietician, pharmacist, clinical psychologist and social worker, all of whom will be specialists in CF care. Other hospital specialties will also be involved; particularly radiology, surgery, obstetrics, gastroenterology, hepatology, diabetology, endocrinology and rheumatology. Drug costs, especially rhDNase and IV antibiotics, form a very large proportion of the total CF service costs.

Treatment of CF is paid through a pay for performance scheme based on a system of five severity bands for categorising different levels of CF treatment that was developed by Manchester Adult CF Centre.[89] Recently changes have been proposed to make the bands more robust to allow a payment by results costing for a year of care; these bands are being analysed and tested.

A summary of the five bands is as follows:

- Band 1: Patients who only receive outpatient care from doctors, nurses, physiotherapist, dieticians, social workers, etc. No intravenous antibiotics required. No in-patient admissions apart from an annual assessment and review as a day case.
- Band 1a: As above BUT require up to 14 days of intravenous antibiotics (at home or in hospital) and spend a maximum of 7 days in hospital over the course of a 12 month period. OR receive short-term (up to 3 months) nebulised antibiotics for eradication treatment.
- Band 2: Patients who require maintenance nebulised antibiotics for pseudomonas infection or maintenance nebulised Alpha rhDNase. Patients receive up to 28 days of intravenous antibiotics in a year OR spend a maximum of 14 days in hospital.
- Band 2a: Patients who receive both nebulised antibiotics and rhDNase and require up to 56 days of antibiotics intravenously at home or in hospital OR a maximum of 14 days in hospital.

- Band 3: Patients who have more frequent in-patient visits, have up to a maximum of 84 days on intravenous antibiotics (at home or in hospital) OR spend up to 57 days in hospital OR patients with gastrostomy feeding or any of listed CF complications namely CF related diabetes, ABPA, massive haemoptysis, pneumothorax
- Band 4: Patients have severe disease and usually spend up to 112 days in hospital per year, although it is recognised that some patients, at this stage of their illness, prefer to be treated/supported at home with the support of the CF multi-disciplinary team. Patients require a minimum of 112 days per year on IV antibiotics (at home or in hospital). Patients have CF-related complications of diabetes, pneumothorax or haemoptysis
- Band 5: Patients are severely ill and stay in hospital for greater than 113 days per year, awaiting transplantation or receiving palliative care. As above, it is recognised that some patients, at this stage of their illness, prefer to be treated/supported at home with the support of the CF multi-disciplinary team. Patients may be receiving nocturnal ventilation and feeding gastrostomies. Patient's life expectancy is usually no more than a year to 18 months.

The 2008-2009 indicative tariffs (outpatient and inpatient) for these bands are shown in Table 75 and Table 76 below.

Table 75 2008/09 Outpatients Indicative Tariff

Code	Description	Adult First	Adult Follow-up
984	Cystic Fibrosis - Band 1	£2,055	£429
985	Cystic Fibrosis - Band 2	£1,334	£428
986	Cystic Fibrosis - All Other Bands	£1,503	£427

Table 76 2008/09 Inpatient Indicative Tariff

Code	Description	Tariff (£)
CSB2A	Cystic Fibrosis - Band 2 : Adults	2,197
CSB3A	Cystic Fibrosis - Band 3 : Adults	4,236
CSB4A	Cystic Fibrosis - Band 4 : Adults	4,497
CSB5A	Cystic Fibrosis - Band 5 : Adults	879

Table 77 National Schedule of Reference Costs Year: '2008-09' - NHS Trusts Elective Inpatient HRG Data

Code	Description	Activity	National Average Unit Cost	Lower Quartile Unit Cost	Upper Quartile Unit Cost	No. of Bed Days	Average Length of Stay - Days	No. Data Submissions
DZ01Z	Lung Transplant	56	£35,458	£11,054	£63,995	678	12.11	7

6.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

These tariffs are not used in the health economic model because they exclude three types of outpatient attendances (codes 984, 985, and 986), two HRG codes (DZ13 and PA13), nationally commissioned services, home-based care, and most importantly high cost drugs. Therefore these tariffs are not representative for the actual CF-related treatment cost borne by the NHS.

Resource identification, measurement and valuation studies

6.5.3 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 9.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

- country of study
- date of study
- applicability to UK clinical practice
- cost valuations used in study
- costs for use in economic analysis
- technology costs.

A search was carried out via PubMed on using the search term:

<(cystic fibrosis[MeSH Major Topic]) AND (cost[MeSH Major Topic])>

The search was limited to items; published in the last 20 years and with 'human' and 'English' delimiters. The search identified 30 items (see Appendix 13 for details) of which 9 were found relevant (Table 78).

Table 78 Relevant Identified Studies

Source / Country	Selection criteria	Patient population	Currency and costs details	Results
Baumann 2003 [90] Germany	CF patients ≤8 yrs with no other diseases. Patients treated at 1 CF clinic.	N=138. Male: 54% (n=74). >6 yrs old: N=97. Mean age: 10.1±5.6 (range 0–18). Mean FEV_1: 84.5±23.8% (range 23–125; n=101). Pa chronic infection: 48.6% (n=67).	Costs for year 1996-1997 in DM (1996-1997 values) converted to Euro (1 € = 1.95583 DM). Annual discount: 5%.	Resource utilization per patient and year: • Outpatient-clinic: 3.3±1.3 (range 0–7) • Hospitalisation: 14.4±18.4 days (range 0–96), • Lung function tests: 4.7 (>6 yrs old: 6.2±3.6). • Other resources: 1.2 radiographs, 1.1 ultrasound scans, 10.5 microbacterial cultures and 111.1 blood tests Total annual expenditures: • Per patient: €23,989±18,026 (Outpatient visits: 59%; hospital care: 41%; Outpatient drugs: 47%) • Per patient chronically colonized with *P aeruginosa*: €36,421±17,449 (N=67) • For all CF patients in Germany (n=2,358): €56.6 million (0.038% of the German health insurance budget) Over lifetime (median survival: 32 yrs): €396,000/pt Costs related to age (r=0.42, P<0.001), FEV_1 (r=-0.71, P<0.001), radiological signs of lung pathology (r=0.633, P<0.001),
Ouyang 2009 [91] US	CF and no CF pts (1:10) with complete 12 month insurance coverage	CF pts: N=1,250 (2,203 person-years) Control (no CF): n=13,248,536 (21,261,327 person-years) CF >19 years: 38.2%	Data from MSCCE* database for 2004–2006 Healthcare system perspective. Expenditures (US $) from 2004 and 2005 inflated to 2006 equivalents.	Mean annual medical care expenditures per patient: • Total: $48,098 (CF) vs $2,172 (no CF; median: $ 0) • Hospitalisation costs: $16,545 (CF) vs. $467 (no CF) • Per hospitalization: $24,318 (CF) vs $10,908 (no CF) • Prescribed medications: $18,461 (CF) vs. $437 (no CF) • Outpatient visits: $13,092 (CF) vs. $1,267 (no CF) Increase in annual expenditures due to complications: • Malnutrition: by $56,000 (children <10 yrs) and by $83,000 (adult >30 yrs) per person. • Transplantation: by $100,000 (10–29 yrs) and by >$60,000 (>30 yrs) per person • Diabetes or *P. aeruginosa* infection: by > $20,000 (>10 yrs) • Gastroesphageal reflux: by $35,000 (0-9 yrs) and $24,000 (10–29 yrs)
Schreyögg 2006 [92] Germany	CF patients admitted to an inpatient CF unit under routine conditions from	N=135 (24 patients admitted ≥2 times) Age: • <18 yrs:	Healthcare system perspective. €, 2004 values. Costs included staff and laboratory	Mean total costs per case: €7,326 (€429 to €29,636): • Drug costs: 28% • Staff costs: 9% • Laboratory costs: 9% Total costs per lung function severity: €2,150 (mild), €7,135 (moderate)

Source / Country	Selection criteria	Patient population	Currency and costs details	Results
	Jan to Jul 2004 and discharged before Jul 2004	19.1% • ≥18 yrs: 80.9% FEV_1 (n=127): 45.5% FEV1 <40% (n=54): 41.2%	costs.	and €9,965 (severe) Meropenum, ceftazidime, tobramycin, amphotericin B liposomal, domase alfa, cefepime, ticarcillin, tobramycin and sulbactam: account for >70% of all drug costs Cost predictors: FEV_1 (negative correlation in single regression; p<0.001) and disease severity (multiple regression; p<0.001)
Horvais 2006 [93] France	CF patients treated during a 12-month period in 2000–2001 in 3 hospitals	N=65 (children: n=47; adults: n=18) Aged: 13.3 yrs FEV_1 <30%: 3.1% FEV_1 30-50% 9.2% FEV_1 >50%: 87.7%	French NHS perspective. €, 2001 values. Costs from medical records and patient-filled questionnaires.	Costs per patient/year (% of patients needing the resource): • Physiotherapists visits (77.0%): €2,606±469 • Nutritional support: €1,551±350 • Pulmonary treatment (including inhaled tobramycin and rhDNase): €6,053±2,119 • IV antibiotics (21%): €3,364±2,071 • Medical devices: €157±68 • Consultations (scheduled/unscheduled): €502 (±102) • Hospitalisations: €1,458±536 • Total costs: € 16,189±4,020 (range: €22–68,080): – 12% for treatment given in the CF centers – 67% for home care – 21% for home i.v. Abs Hospitalisations: • 111 hospitalisations (13% due to exacerbations) • Mean duration: 1.7±0.6 days
Elliot 2005 [94] UK	CF patients (≥16 yrs) with ≥1 infective respiratory exacerbation treated with IV antibiotics during the previous 1-year period.	N=116 41% (n=47): >60% of i.v. courses at home (HOME) 44% (n=51): >60% of i.v. courses at hospital (HOSP) 16% (n=18): 40%-60% of i.v. courses at home or hospital	NHS perspective £, 2002 values.	Resource utilisation per patient and year: • Number of days with IV antibiotics: 59.9 (HOME: 63.0; HOSP: 54.8; BOTH: 66.3) • Number of IV courses: 3.9 (HOME: 4.0; HOSP: 3.6; BOTH: 4.5) • Number of days in hospital: 28.7 (HOME: 10.6; HOSP: 46.3; BOTH: 26.1) Costs per patient and year: • Antiboitics: £8,974 (HOME: 9,325; HOSP: 7,920; BOTH: 11,044) • Home kits: £24.6 (HOME: 38.7; HOSP: 8.4; BOTH: 33.3) • Laboratory tests: £101 (HOME: 88; HOSP: 113; BOTH: 103) • Clinic visits: £546 (HOME: 789; HOSP: 268; BOTH: 702) • Hospital: £8,856 (HOME: 3,263; HOSP: 14,296; BOTH: 8,041) • Home visits: £ 10.4 (HOME: 24.9; HOSP: 0; BOTH: 4.9)

Source / Country	Selection criteria	Patient population	Currency and costs details	Results
		[BOTH] Mean age: 26 (range: 16–47) Baseline FEV_1: 51.7%		• Total: £18,513 (HOME: 13,528; HOSP: 22,609; BOTH: 19,927)
Wildhagen 1996 [95] Netherlands	CF patients treated in any of two CF centres between 1990-1991.	N=81 Median age: 13 (range 0-37 yrs) Age≥25 yrs: n=8	Societal perspective. £ Costs of a hospital day include physiotherapy for 20 minutes a day (30 min for children). Discount rate: 5% Estimates of the costs of home medication/care based on pt questionnaire.	Resource utilisation: • Hospital days: 18.5 (range: 0 [for 35+ yrs] to 68.8 [<1 yrs])([pre]terminal pts: 106 days) • Number of admissions: 0.9 (range: 0 [for 35+ yrs] to 2.5 [<1 yrs])([pre]terminal pts: 2.7) • Number of lab tests: 116.5 (range: 36.0 [for 35+ yrs] to 216.2 [20.24 yrs]) ([pre]terminal pts: 575.5) • Number of consultations: 6.9 (range: 4.0 [for 35+ yrs] to 13.7 [<1 yrs]) ([pre]terminal pts: 7.9) Average costs per patient and year (% patients): • Hospital care: £4,612 (42%) • Medication: £4,067 (37%) • Home care: £2,229 (20%) • Total: £10.908 (100%) • Medical consumption of patients in (pre)terminal stage: £26,599 (=71% of the costs of (pre)terminal stage) Total cost of care of CF in The Netherlands in 1991: £10.9 million (0.07% of the total health care budget). Costs increase after the age of 15 mainly due to frequent Ab treatment and hospital days due to exacerbations or complications. Lifetime costs of a patient with CF: £409,453 (with discount rate of 5%: £164 365).
Robson 1992 [89] UK	Patients treated in the Adult Cystic Fibrosis Unit in the Monsall Hospital (Manchester) April 1989 to March 1990	N=119 Male: 58% (n=69) Mean age: 20-7 (range 16-44) yrs. Outpatients: n=51 Outpatients with i.v. Abs at home (every 3 months): n=28	District Health Authority's, Family Health Service Authority's and Monsall Hospital's perspective. £, 1989-90 values.	Total costs for Monsall hospital: • Per patient: £8,241 (from £2,792 for outpatients to £19,955 for patients with high level of care) • For the 119 patients: £980,646 • Medical investigations and procedures, and staff accounted for 57.2%, 20.1%, and 19.7% of the total cost. • Drug bill: 41% of the hospital cost and 57% of the total cost of caring for patients with CF Expenditure for District Health Authority's:

Source / Country	Selection criteria	Patient population	Currency and costs details	Results
		Inpatients with i.v. Abs every 3 months: n=32 Pts needing high level of care (i.v. Abs: >4 times/year): n=8		• Per patient: £5,172 (from £677 for outpatients to £16,380 for patients with high level of care) • For all 119 patient: £615,564 (from £34,512 for outpatients to £299,370 for inpatients)
Rosenberg 2005 [96] US	CF patients from two centres with CF diagnosed through a newborn screening program with the CFTR multi-mutation technique	N=145	$.	Implementing an IRT/DNA(CFTR) screening program increases the cost per newborn by 50% (IRT/DNA[ΔF508] test: $2.77; IRT/DNA[CFTR]: $4.16). Hospitalisation for all children (for each centre): • 0.24 – 0.66 hospitalisations/patient/year • LOS: 2.7 – 5.4 days Hospitalisation for inpatient children (n=65): • 0.70 – 1.12 hospitalisations/patient/year • LOS: 8.2 – 9.2 days Median annual total costs (n=6; period: 1995-99): $1,900 (1997) - $4,300 (1998). Median annual total costs for hospitalization (n=6; period: 1995-99): $1,900 (1995) - $39,500 (1999) Inpatient costs: 22% (1995) - 89% (1999) of total costs.
Lieu 1999[97] US	CF patients followed in the Kaiser Permanente's regional CF center with continuous commercial health insurance in 1996. CF patients with Medicaid were excluded.	N=136 Male: 52% White: 93% Mean age: 16.6 yrs (median: 13 yrs; range: 9 months to 56 years) Disease severity: mild: 41%; moderate: 31%; severe: 15%.	$, 1996 values. Resource utilisation and costs are given by disease severity	Resource utilization: • Hospitalisations: 0.5±1.1 (mild: 0.2±0.6; moderate: 0.4±0.9; severe: 1.7±1.9) • Hospital days: 4±12 (mild: 0.8±3.4; moderate: 2.5±9.1; severe: 18±23) • Number of day care: 0.4±1.4 (mild: 0.1±0.3; moderate: 0.3±1.1; severe: 1.4±3.0) • Clinic visits: 7±6.2 (mild: 7±6.4; moderate: 7±5.5; severe: 10±7.4) • Days of i.v. Ab at home: 6.5±21.3 (mild: 1.4±8.3; moderate: 7.0±12.4; severe: 24±46) Costs (1996 $ in 1000s) • Hospitalization: 6.2±20.6 (mild: 1.2±4.1; moderate: 3.9±13.3; severe: 28±42.8) • Clinic visits: 1.5±1.7 (mild: 1.2±1.1; moderate: 1.4±1.4; severe: 3.1±2.9)

Source / Country	Selection criteria	Patient population	Currency and costs details	Results
				• DNase: 2.5±3.7 (mild: 1.5±2.6; moderate: 3.2±3.6; severe: 5.0±5.5) • Outpatient antibiotics: 1.3±4.9 (mild: 4±0.8; moderate: 1.3±2.8; severe: 4.7±11.3) • Pancreatic enzymes: 1.2±1.4 (mild: 1.5±1.5; moderate: 1.2±1.4; severe: 1.2±1.3) • Total costs: 13.3±23.5 (mild 6.3±6.7; moderate: 11.4±14.4; severe: 43.3±44.2) When extrapolated to the overall US CF population: • Total estimated cost of medical care for CF in 1996: $314 million • Mean cost per patient: $13,650

MSCCE: MarketScan® Commercial Claims and Encounters
Ab: antibiotics
i.v.: intravenous
CFTR: Cystic Fibrosis Transmembrane Conductance Regulator
Pt: patient

Resource use in the pooled DPM-CF-301 and DPM-CF-302 studies

Resources were recorded in both pivotal studies from medical records, discharge summaries and patient's diaries. Concomitant medication use was tabulated by treatment group including the generic names, start and stop dates, total daily dose, route and indication. For the cost-effectiveness analysis, we have considered all anti-infectives for systemic use medications (ATC level 1 "J"), respiratory system drugs (ATC level 1 "R") and hypertonic saline. In addition, from the remaining collected medications, we examined the reasons for prescribing the medication, and if any of the following terms were found then the medications were also included: "C.F.", "FIBROSIS", "CF RELATED".

All patients had concomitant medication besides their CF medication. The majority of medication costs were for antibiotics (see Table 79).

Table 79 Concomitant medications

	Control			Bronchitol		
Statistic	**Antibiotic**	**Other**	**Total**	**Antibiotic**	**Other**	**Total**
N	127	131	134	193	203	207
% of patients	95%	98%	100%	93%	98%	100%
Mean (£)	2,515	457	2,972	2,458	794	3,253
SD (£)	2,928	868	3,157	3,101	2,680	4,360

*Pooled data; adult population, ITT

A tabular overview of the hospitalisation and community visits is provided in Table 80 and Table 81 respectively. Nearly all patients had a hospital visit, and little over 40% of patients had a community visit during the 26-week trial period. The proportion of patients having a hospital admission or day case was higher in the Control arm than in the Bronchitol arm. The annual hospitalisation rate was similar in both group, but the average duration of hospitalisation was slightly lower in the Bronchitol arm than in the Control arm (9.46 versus 9.91 days, respectively). However the rate of hospital outpatient visits was on higher in the Bronchitol group than in the Control group and similar to the rate of community visits. The majority of the community visits were with the GP (26%), specialist (25%) or nurse (23%) and similar in both treatment groups.

Table 80 Hospital admission, day case, hospital outpatient and community visits

Type of hospitalisation	**Control**		**Bronchitol**	
	% of patients	**Annual rate**	**% of patients**	**Annual rate**
Hospital admission	32.84%	0.91	24.15%	0.90
Day case	7.46%	0.22	6.76%	0.17
Outpatient	44.03%	3.27	41.55%	3.93
Unkown	26.87%	0.60	32.85%	0.81
No visit/hospitalisation	8.96%	NA	8.50%	NA
Community visits	44.78%	3.17	41.55%	3.42

*Pooled data; adult population, ITT

Table 81 Duration hospital admission

Statistic	Control	Mannitol
Mean	9.91	9.46
StdDev	6.39	6.22
Min	1.00	1.00
Max	37.00	29.00

*Pooled data; adult population, ITT

Resources were costed at patient level. Prices were taken from National reference costs 2008/2009, BNF 59, and PSSRU 2009. The total mean cost per patient over the 26-week trial period are presented in Table 82. Cost for patients experiencing a pulmonary exacerbation were much higher than patients without a pulmonary exacerbation during the trial period.

Table 82 Costs associated with a patient without a pulmonary exacerbation

	Cost (£)	Bronchitol		Control	
		Mean	SD	Mean	SD
No PDPE in trial period	Medication	2,871	4,390	2,617	2,713
	Community visits	48	92	53	122
	Hospitalisations	1,471	4,323	1,994	4,474
	TOTAL	4,391	7,136	4,664	5,492
PDPE in trial period	Medication	4,797	3,919	3,976	4,047
	Community visits	62	93	53	99
	Hospitalisations	7,994	6,829	6,325	7,561
	TOTAL	12,852	7,959	10,354	10,445
All patients	Medication	3,253	4,360	2,972	3,157
	Community visits	51	92	53	116
	Hospitalisations	2,763	5,551	3,125	5,745
	TOTAL	6,067	8,032	6,150	7,510

*Pooled data; adult population, ITT

The day to day costs excluding CF medication for CF patients without an exacerbation are approximately £26/day over a 6 month period. For patients with one exacerbation, this cost increases to approximately £58/day. A large proportion of this cost can be attributed to hospitalisations.

Table 83 Costs associated with a patient experiencing 1 pulmonary exacerbation

Cost (£)	Bronchitol (N=30)		Control (N=25)		Total (N=55)	
	Mean	SD	Mean	SD	Mean	SD
Medication	4,303	4,088	3,925	4,452	4,131	4,221
Community visits	58	79	64	112	61	95
Hospitalisations	6,564	6,081	6,238	7,906	6,416	6,904
TOTAL	10,925	7,451	10,227	11,509	10,608	9,424

The costs for a pulmonary exacerbation were estimated based on patients with one exacerbation, irrespective of the treatment arm the patient was in (Table 81). Results for both treatment arms were similar and the number of patients that had a pulmonary exacerbation was only small (n=65) therefore splitting that group over two arms would overestimate uncertainty in resource utilisation. The cost of a pulmonary exacerbation was calculated by taking the mean overall cost for patients experiencing 1 PDPE and subtracting the mean cost for all patients not having a PDPE during the 26-week time period.

Lung transplant

Lung transplants were included in the model, even though these were not performed during the clinical study. This was due to the short duration of the study, but in real life it is likely that a several CF patients will receive a lung transplant. The cost of post lung transplant costs were adapted from the National Schedule of Reference Costs using the elective inpatient HRG code DZ01Z corresponding to lung transplant (see section 6.5.1). The follow-up cost after a lung transplant were taken from a UK study which reported the mean cost up to 15 years after lung transplant in 1999 UK pounds sterling at an annual discount rate of 6%[98]. This mean total costs was adjusted to 2009 price level and corrected to the 3.5% inflation rate. Each patient undergoing a lung transplant received the mean follow-up LT costs regardless of the patient's survival after the lung transplant.

6.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[†††]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked

[†††] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

No clinical experts were utilised to estimate any of the amounts or values of resources incorporated into the economic model.

Intervention and comparators' costs

6.5.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 6.2.2.

Table 84 Unit costs CF medications

Items	Bronchitol	rhDNase	Control	Ref. in submission
Technology cost per day	£16.88	£16.88	£0	1.10
Administration cost	None	None	None	1.11

Health-state costs

6.5.6 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 6.2.4.

No other health state cost other than those presented for patients with CF (with or without improvement in respiratory symptoms) are applicable to the model. Apart from CF treatment, the model includes transition costs for pulmonary exacerbations and lung transplant. All cost parameters in the model are summarised in Table 85 below.

Table 85 List of health states and associated costs in the economic model

Parameter	Description	Value	Distribution	Reference in submission
c_CF_B	Total 6-monthly cost CF patient treated with Bronchitol	4,391	Gamma, alpha = 11,775 lambda = 2.524	6.5.3
c_CF_C	Total 6-monthly cost CF patient treated with Control	4,664	Gamma, alpha = 31,457, lambda =	6.5.3

Parameter	Description	Value	Distribution	Reference in submission
			7.164	
c_Exacerbation	Cost pulmonary exacerbation	6,115	Exponential; lambda = 1/6,115	6.5.3
c_LT	Cost lung transplant	35,458	Exponential; lambda = 1/35,458	6.5.1
c_postLT	Post lung transplant treatment cost	87,431	Exponential; lambda = 1/87,431	6.5.3

Adverse-event costs

6.5.7 Please summarise the costs for each adverse event listed in section 5.9 (Adverse events). These should include the costs of therapies identified in section 2.7. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 6.2.2.

Adverse events have not been incorporated in the model, see section 6.2.3.

Miscellaneous costs

6.5.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

No additional costs have been included in the model.

6.6 Sensitivity analysis

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.1.11, 5.8, and 5.9.4 to 5.9.12.

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis (PSA) is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

6.6.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

The structure of the model was discussed a priori with an expert in health economics. Various sensitivity analyses have explored the main areas of uncertainty contained within the model.

6.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 6.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

The following parameters have been subjected to deterministic sensitivity analysis: The only parameters that have been omitted are the background mortality rates and CF mortality rates.

Table 86 Parameter and ranges used in deterministic sensitivity analysis

Parameter	Description	Min	Max	Comment
Age_start	Age CF patient at baseline	18	56	Min and max from pooled adult data
Bcc_infection	Percentage of patients with chronic Bcc infection	0	0.09	Max based on highest value report in CF registry report
BMI_start	BMI CF patient at baseline	17	30	Min and max from pooled adult data

Parameter	Description	Min	Max	Comment
c_CF_B	6-monthly cost CF patient Bronchitol arm	4,342	4,440	95% CI
c_CF_C	6-monthly cost CF patient Control arm	4,578	4,748	95% CI
c_Exacerbation	Cost of an exacerbation	376	9,012	Upper and lower quartile
c_LT	Cost lung transplant	10,201	49,155	Upper and lower quartile
c_postLT	Post lung transplant treatment cost	25,152	121,205	Upper and lower quartile
FEV_start	FEV1 % predicted CF patient at baseline	40	90	Min and max from pooled adult data
fParameter_age	Parameter estimate for age[#]	-1.31	-0.72	95% CI
fParameter_ageplus30	Parameter estimate for age over 30[#]	1.62	1.69	95% CI
fParameter_exacerbation	Parameter estimate for exacerbation[#]	-1.81	-2.34	95% CI
fParameter_BMI	Parameter estimate of BMI*	0.45	0.29	95% CI
fParameter_Bronchitol	Parameter estimate for treatment with Bronchitol*	-0.09	3.14	95% CI
fParameter_FEV1	Parameter estimate of FEV_1 % predicted at baseline*	0.99	0.88	95% CI
fParameter_intercept	Parameter estimate of intercept*	-14.30	-1.63	95% CI
fParameter_improvRS	Parameter estimate for improvement in respiratory symptoms after 26 weeks of treatment*	1.19	2.27	95% CI
fParameter_responder	Parameter estimate for response to treatment*	6.40	4.06	95% CI
Gender	Percentage of male CF patients	0	1	All male or all female
HR_FEV	Hazard rate ppFEV1	0.943	0.971	95% CI
pImprovedRS_B_v3	Probability of improvement in respiratory symptoms after 14 weeks for pts treated with Bronchitol	0.32	0.47	95% CI
pImprovedRS_B_v4	Probability of improvement in respiratory symptoms after 26 weeks for pts treated with Bronchitol	0.10	0.24	95% CI
pImprovedRS_C_v3	Probability of improvement in respiratory symptoms after 14 weeks for pts treated with Control	0.55	0.37	95% CI
pImprovedRS_C_v4	Probability of improvement in respiratory symptoms after 26 weeks for pts treated with Control	0.25	0.08	95% CI

Parameter	Description	Min	Max	Comment
pRemainImprovRS_B	Probability continuing to have improved respiratory symptoms for pts treated with Bronchitol	0.57	0.79	95% CI
pRemainImprovRS_C	Probability continuing to have improved respiratory symptoms for pts treated with Control	0.85	0.62	95% CI
pDie	CF related mortality	NA	NA	Absolute mortality increased by 20% and 50%
ResponderB	Percentage of CF patients responding to Bronchitol treatment	0.42	0.55	95% CI
ResponderC	Percentage of CF patients responding to Control treatment	0.27	0.43	95% CI
rExacerbation_base	Baseline annual exacerbation rate	0.68	0.72	95% CI
rLT	Annual lung transplant rate	0.13	0.26	95% CI
rFEVdecline	Annual change in ppFEV1 in patients aged 30 or below without an exacerbation	-1.31	-0.72	95% CI
rFEVdecline_exacerbation	Annual change in ppFEV1 in patients aged 30 or below who had an exacerbation	-2.54	-3.65	Min and max based on 95%CI values for the parameters
rFEVdecline_exacerbation_plus30	Annual change in ppFEV1 in patients aged above 30 who had an exacerbation	-0.85	-2.03	Min and max based on 95%CI values for the parameters
rFEVdecline_plus30	Annual change in ppFEV1 in patients aged above 30 without an exacerbation	0.96	0.31	Min and max based on 95%CI values for the parameters
RR_Bcc	Relative risk of death due to a Bcc infection	1.00	10.75	Min assuming no elevated risk; max 95% CI
RR_ExacerbationB_responder	Relative risk exacerbation with Bronchitol treatment for patients who respond to treatment	0.39	1.08	95% CI
RR_previous_exacerbation	Relative risk of experiencing an exacerbation if patient has experienced an exacerbation in the previous year.	1.00	1.82	95% CI
u_base	Baseline utility score CF patient	0.882	0.915	95% CI
u_Exacerbation	Utility decrement for exacerbation	-0.0004	-0.3264	Combination of min/max utility decrement and duration of utility decrement
u_improvRS_B	Utility patient with improvement in respiratory symptoms	0.889	0.947	95% CI

Parameter	Description	Min	Max	Comment
u_improvRS_C	Utility improvement in respiratory symptoms Control	0.889	0.926	95% CI
u_no_improvRS_B	Utility no improvement in respiratory symptoms	0.855	0.898	95% CI
u_no_improvRS_C	Utility no improvement in respiratory symptoms control arm	0.808	0.896	95% CI
u_LT	Utility LT patients	0.763	0.842	Upper and lower quartile
u_LT_wl	Utility CF patients on LT waiting list (ppFEV<30)	0.245	0.90	Lower quartile
_Disc	Discount rate	0	0.06	See guide to methods for technology appraisal
_Horizon	Time horizon	0.5	100	Min based on trial duration.

***** Parameter estimates mixed model for FEV_1 % predicted; [#] Parameter estimates BioGrid mixed model for FEV_1 % predicted.

6.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 6.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

The distributions used in the PSA are the ones described in section 6.3.6.

6.7 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.

- Link between clinical- and cost-effectiveness results.
- Costs, QALYs and incremental cost per QALY.
- Disaggregated results such as LYG, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.
- A statement as to whether the results are based on a PSA.
- Cost-effectiveness acceptability curves, including a representation of the cost-effectiveness acceptability frontier.
- Scatter plots on cost-effectiveness quadrants.
- A tabulation of the mean results (costs, QALYs, ICERs), the probability that the treatment is cost effective at thresholds of £20,000–£30,000 per QALY gained and the error probability.

Clinical outcomes from the model

6.7.1 For the outcomes highlighted in the decision problem (see section 4), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

The reported outcomes of the pooled DMP-301-CF and DMP-302-CF adult population and the result of the microsimulation (100,000 trials) after 26 weeks comparing Bronchitol mono-therapy with best supportive care are presented in Table 87.

Table 87 Summary of model results compared with clinical data

Outcome	Clinical trial result		Model result	
	Control	Bronchitol	Control	Bronchitol
Lung function (ppFEV$_1$ at baseline)	58.38	59.82	59.27	59.27
Change in ppFEV$_1$	-0.02*	2.55*	-0.86	1.59
% of patients with ≥1 exacerbations after 26 weeks	26%	20%	32%	27%
Exacerbation rate	0.75	0.63	0.76	0.64
Responder	34%	48%	34%	48%
Survival	100%	100%	100%	100%
% of patients with lung transplant	0%	0%	0%	0%
QALYs	0.45	0.45	0.43	0.44

*calculated using mixed model repeated measures analysis of DPM-CF-301 and DPM-CF-302 using imputed height.

Overall the observed clinical trial results correspond well to the modeled result. In the model patient characteristics at baseline (e.g., gender, age, BMI and FEV$_1$ % predicted) were identical in each arm, whereas small differences were observed in the clinical trials. The difference between the modeled change in FEV$_1$ % predicted after 26 weeks of treatment and the observed clinical result relates to the fact that the model predicts the FEV$_1$ % predicted based on a patient's characteristics rather than implementing the observed change in the clinical trial. Finally, as expected the improvement in FEV$_1$ % predicted in the Bronchitol arm is lower than in the clinical trial, because in model patients are switched to best supportive care (Control) after 6 weeks in case if they do not respond to Bronchitol treatment.

The model calculations a slightly higher number of exacerbations than observed in the clinical trial. The baseline exacerbation rate in the model is taken from BioGrid instead of the clinical trial. For patients aged 30 years or below the BioGrid analysis reported a lower exacerbation rate (0.70), but for patients over 30 years the observed rate in the BioGrid data was higher (0.97). As the percentage of patients older than 30 years in the pooled DMP-301-CF and DMP-302-CF adult population was 33%, the average exacerbation rate during the first 26 weeks is

higher (0.79). In addition if a patient has a pulmonary exacerbation after 6 weeks, the chance of experiencing an exacerbation after 14 and 26 weeks in increased by a factor 1.59. Similarly patients experiencing a pulmonary exacerbation after 14 weeks have an increased risk of a pulmonary exacerbation after 26 weeks, leading to an overall exacerbation rate of 0.93 for patients treated with control. It should be noted that due to the relative high exacerbation rate and the chosen cycle length the model will underestimate the exacerbation rate. As expected the modeled exacerbation rate for Bronchitol is slightly higher than observed in the clinical trial because of cross-over to the control arm in case the patient does not respond to Bronchitol. The observed difference in QALY relates to the incorporation of the utility decrement for pulmonary exacerbations in model.

Since the only difference in the model between the mono-therapy and the add-on therapy to rhDNase relates to the cost of rhDNase the modeled clinical outcomes for the add-on arms are identical to those for the respective mono-therapy arms (data not shown).

6.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

Not applicable.

6.7.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

Given that the analysis is based on patient level data the quality of life changes experienced by each patient is individually measured and accrued. The accrued QALYs in each health state over time have been calculated by running the model (100,000 trials each time) for different time horizons. The results of these analyses are presented in Figure 20 and Figure 21below.

Figure 20 Accrual QALY over time by health state – Bronchitol

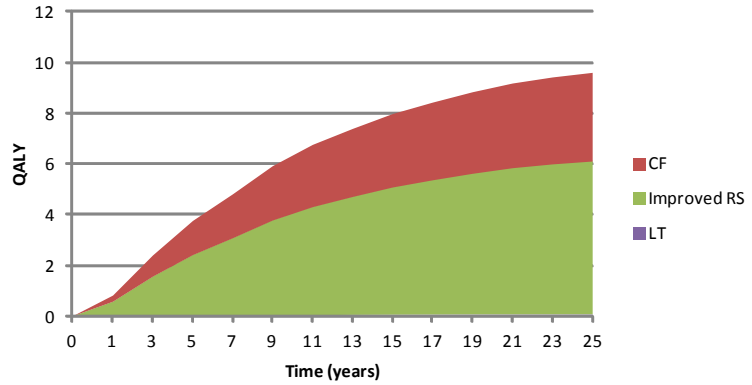
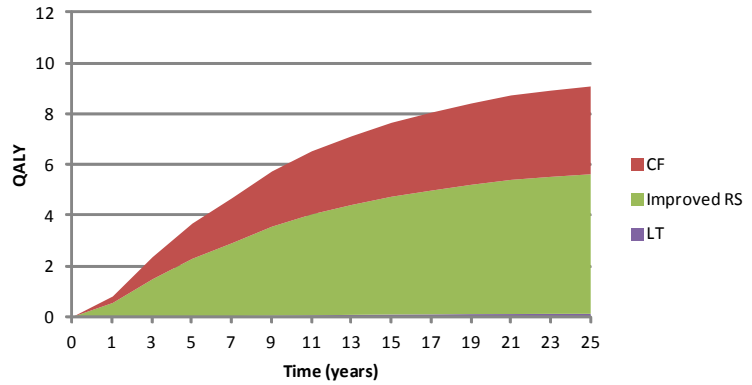


Figure 21 Accrual QALY over time by health state – Control



6.7.4 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

Table 88 lists the life years and QALYs accrued for treatment responder and non-responders, respectively.

Table 88 Model outputs by clinical outcomes

	Bronchitol		Control	
Outcome	Responder	Non-responder	Responder	Non-responder
QALY	11.42	9.83	10.41	9.50
LY	12.93	11.47	12.11	11.13

6.7.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

The disaggregated incremental costs for both the mono-therapy as the add-on therapy are presented in Table 89. The disaggregated costs are presented separately for the mono-therapy (Table 90) and the add-on therapy (Table 91).

Table 89 Summary of QALY gain by health state

Health state	QALY intervention (Bronchitol)	QALY comparator (Control)	Increment	Absolute increment	% absolute increment
CF with improved respiratory symptoms	3.84	3.72	0.12	0.12	14%
CF	6.61	5.91	0.70	0.70	81%
Lung transplant	0.08	0.12	-0.04	0.04	5%
Total	10.52	9.75	0.77	0.86	100%

QALY, quality-adjusted life year

Table 90 Summary of costs by health state– Mono-therapy

Health state	Cost intervention (Bronchitol)	Cost comparator (Control)	Increment	Absolute increment	% absolute increment
CF with improved respiratory symptoms	73,926	65,489	8,436	8,436	24%
CF	135,375	110,566	24,809	24,809	71%
Lung transplant	2,622	4,133	-1,511	1,511	4%
Total	211,923	180,188	31,735	34,757	100%

Table 91 Summary of costs by health state– Add-on therapy

Health state	Cost intervention (Bronchitol + rhDNase)	Cost comparator (Control + rhDNase)	Increment	Absolute increment	% absolute increment
CF with improved respiratory symptoms	100,172	91,223	8,950	8,950	23%
CF	183,064	154,116	28,948	28,948	73%
Lung transplant	2,622	4,133	-1,511	1,511	4%
Total	285,858	249,472	36,386	39,408	100%

Table 92 Summary of predicted resource use by category of cost – Mono-therapy

Item	Cost intervention (Bronchitol)	Cost comparator (Control)	Increment	Absolute increment	% absolute increment
Bronchitol	38,498	0	38,498	38,498	73%
rhDNase	0	0	0	0	0%
CF costs	108,526	104,904	3,622	3,622	7%
Exacerbation costs	62,276	71,151	-8,874	8,874	17%
LT costs	2,622	4,133	-1,511	1,511	3%
Total	211,923	180,188	31,735	52,506	100%

Table 93 Summary of predicted resource use by category of cost – Add-on therapy

Item	Cost intervention (Bronchitol + rhDNase)	Cost comparator (Control + rhDNase)	Increment	Absolute increment	% absolute increment
Bronchitol	38,498	0	38,498	38,498	73%
rhDNase	73,935	69,284	4,651	4,651	9%
CF costs	108,526	104,904	3,622	3,622	7%
Exacerbation costs	62,276	71,151	-8,874	8,874	17%
LT costs	2,622	4,133	-1,511	1,511	3%
Total	285,858	249,472	36,386	57,157	100%

Base-case analysis

6.7.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

Table 94 Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Control (baseline)	180,188	11.40	9.75					
Bronchitol	211,923	12.10	10.52	31,735	0.70	0.77	41,074	41,074
Control + rhDNase	249,472	11.40	9.75	69,284	0.00	0.00	dominated	dominated
Bronchitol+rhDNase	285,858	12.10	10.52	105,670	0.70	0.77	136,768	47,095
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Results are based on 100,000 simulations.

Sensitivity analyses

6.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

Table 95 and Table 96 present the results of the sensitivity analysis for Bronchitol mono-therapy. The model is run with 100,000 iterations each run. The most sensitive parameters are also displayed in Figure 22.

Table 95 Results deterministic sensitivity analysis – Mono-therapy

Variable	Min	Max	Δ Cost	Δ QALY	ICER	Δ Cost	Δ QALY	ICER
Base case	0.00	0.00	31,735	0.77	41,074	31,735	0.77	41,074
Baseline patient characteristics								
Age CF patient at baseline	18.00	56.00	35,117	0.86	40,618	21,496	0.53	40,342
Percentage of patients with chronic Bcc infection	0.00	0.09	31,413	0.75	41,703	31,739	0.78	40,685
BMI CF patient at baseline	30.00	17.00	33,106	0.78	42,578	30,447	0.76	40,146
FEV1 % predicted CF patient at baseline	90.00	40.00	41,806	0.82	51,133	22,482	0.76	29,600
Percentage of male CF patients	1.00	0.00	30,887	0.74	41,495	32,564	0.80	40,797
Responder								
Percentage of CF patients responding to Bronchitol treatment	0.42	0.55	28,442	0.73	39,045	37,332	0.97	38,641
Percentage of CF patients responding to Control treatment	0.43	0.27	31,363	0.76	41,353	33,831	0.91	37,143
Improvement in respiratory symptoms								
Probability of improvement in respiratory symptoms after 14 weeks for pts treated with Bronchitol	0.32	0.47	31,610	0.77	41,285	31,861	0.78	40,890
Probability of improvement in respiratory symptoms after 26 weeks for pts treated with Bronchitol	0.10	0.24	31,603	0.74	42,605	31,884	0.80	39,809
Probability of improvement in respiratory symptoms after 14 weeks for pts treated with Control	0.55	0.37	31,657	0.76	41,444	31,779	0.78	40,866
Probability of improvement in respiratory symptoms after 26 weeks for pts treated with Control	0.25	0.08	31,720	0.74	43,085	31,800	0.82	38,996
Probability continuing to have improved respiratory symptoms for pts treated with Bronchitol	0.57	0.79	31,598	0.75	42,155	31,864	0.80	39,754
Probability continuing to have improved respiratory symptoms for pts treated with Control	0.85	0.62	32,612	0.81	40,078	32,750	0.87	37,783
Estimated FEV1 at week 26								
Cholesky decomposition method for intercept used to predict the FEV1 % predicted after 26 weeks of treatment	-1.63	-14.30	34,537	0.79	43,981	28,651	0.77	37,219
Cholesky decomposition method for BMI used to predict the FEV1 % predicted after 26 weeks of treatment	0.45	0.29	32,113	0.76	42,368	30,591	0.76	40,165
Cholesky decomposition method for Bronchitol treatment used to predict the FEV1 % predicted after 26 weeks of treatment	-0.09	3.14	25,506	0.42	60,703	36,148	1.01	35,775
Cholesky decomposition method for % predicted FEV1 used to	0.99	0.88	32,791	0.76	42,956	30,177	0.76	39,534

Variable	Min	Max	Δ Cost	Δ QALY	ICER	Δ Cost	Δ QALY	ICER
predict the FEV1 % predicted after 26 weeks of treatment								
Cholesky decomposition method for improvement in respiratory symptoms used to predict the FEV1 % predicted after 26 weeks of treatment	1.19	2.27	31,461	0.77	41,084	31,809	0.77	41,081
Cholesky decomposition method for responder used to predict the FEV1 % predicted after 26 weeks of treatment	4.06	6.40	30,822	0.74	41,678	32,625	0.80	40,590
Decline in lung function								
Annual change in ppFEV1 in patients aged 30 or below without an exacerbation	-0.72	-1.31	32,334	0.78	41,575	31,064	0.76	41,038
Annual change in ppFEV1 in patients aged 30 or below who had an exacerbation	-2.54	-3.65	31,568	0.75	41,956	31,713	0.78	40,774
Annual change in ppFEV1 in patients aged above 30 who had an exacerbation	-0.85	-2.03	31,394	0.74	42,384	31,683	0.78	40,381
Annual change in ppFEV1 in patients aged above 30 without an exacerbation	0.31	0.96	29,710	0.70	42,180	33,533	0.83	40,580
Cholesky decomposition method for age used to calculate decline in FEV1 % predicted	-0.72	-1.31	33,750	0.81	41,515	28,990	0.70	41,139
Cholesky decomposition method for age over 30 used to calculate decline in FEV1 % predicted	1.69	1.62	31,932	0.78	41,127	31,521	0.77	41,127
Cholesky decomposition method for Exacerbation used to calculate decline in FEV1 % predicted	-1.81	-2.34	31,761	0.76	41,665	31,640	0.77	40,881
Exacerabation								
Baseline annual exacerbation rate	0.72	0.68	31,521	0.77	40,742	32,958	0.84	39,318
Relative risk for patient experiencing an exacerbation over the age of 30	1.27	1.51	32,007	0.76	42,276	31,185	0.77	40,736
Relative risk exacerbation with Bronchitol treatment - treatment responders	1.08	0.39	42,971	0.50	85,886	24,062	0.96	25,169
Relative risk of experiencing an exacerbation if patient has experienced an exacerbation in the previous year.	1.00	1.82	34,311	0.71	48,109	30,882	0.79	39,091
Lung transplant & mortality								
Annual LT rate	0.26	0.13	31,738	0.77	41,361	31,916	0.78	40,930
Hazard rate ppFEV1	0.97	0.94	28,178	0.60	46,676	34,248	0.89	38,655
Relative risk of death due to a Bcc infection	1.00	10.75	31,413	0.75	41,703	31,280	0.76	41,268

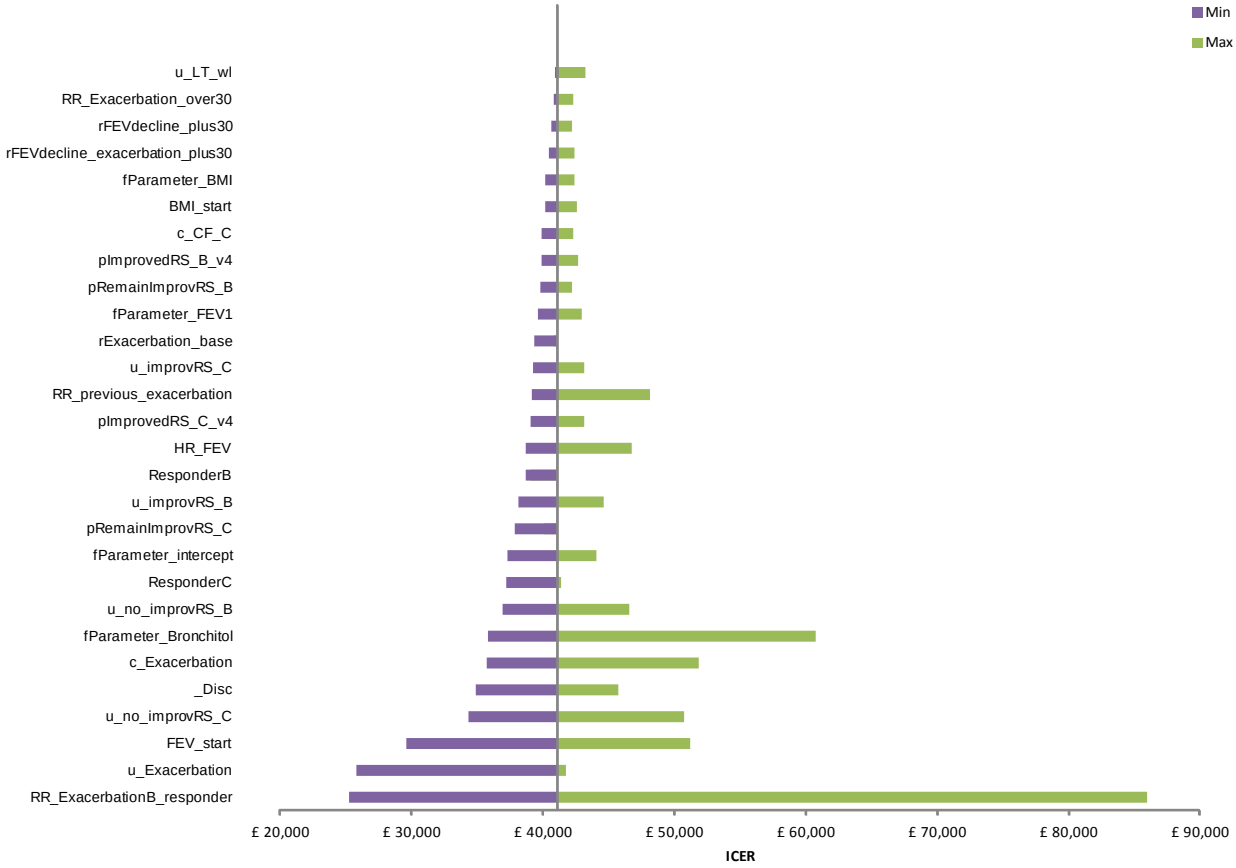
Variable	Min	Max	Δ Cost	Δ QALY	ICER	Δ Cost	Δ QALY	ICER
Utility								
Baseline utility score CF patient	0.88	0.92	31,735	0.76	41,827	31,735	0.79	40,390
Utility decrement for exacerbation	0.00	-0.33	31,735	0.76	41,734	31,735	1.23	25,727
Utility patient with improvement in respiratory symptoms Bronchitol	0.89	0.95	31,735	0.71	44,574	31,735	0.83	38,084
Utility improvement in respiratory symptoms Control	0.93	0.89	31,735	0.74	43,065	31,735	0.81	39,163
Utility LT patients	0.84	0.76	31,735	0.77	41,193	31,735	0.77	40,956
Utility CF patients on LT waiting list (ppFEV<30)	0.90	0.25	31,735	0.74	43,152	31,735	0.78	40,841
Utility no improvement in respiratory symptoms Bronchitol arm	0.85	0.90	31,735	0.68	46,554	31,735	0.86	36,925
Utility no improvement in respiratory symptoms Control arm	0.90	0.81	31,735	0.63	50,743	31,735	0.93	34,245
Costs								
6-monthly cost CF patient Bronchitol arm	4,440	4,342	32,351	0.77	41,872	31,126	0.77	40,287
6-monthly cost CF patient Control arm	4,578	4,748	32,684	0.77	42,303	30,816	0.77	39,886
Cost of an exacerbation	376	9,012	40,063	0.77	51,854	27,529	0.77	35,631
Cost lung transplant	10,201	49,155	32,045	0.77	41,476	31,566	0.77	40,856
Post lung transplant treatment cost	25,152	121,205	32,500	0.77	42,065	31,319	0.77	40,537
Discount rate costs and effects	0.06	0.00	23,225	0.51	45,649	58,758	1.69	34,844

* Parameter estimate in multivariate regression model for FEV_1 % predicted after 26 weeks; # Parameter estimates BioGrid mixed model for FEV_1 % predicted

Table 96 Results varying time horizon and CF mortality – Mono-therapy

Variable	Bronchitol cost (£)	Bronchitol QALYs	Control cost (£)	Control QALYs	Incremental Cost (£)	Incremental QALY	ICER (£)
Time horizon 1 year	19,223	1.00	16,832	0.99	2,391	0.02	149,587
Time horizon 5 years	73,397	3.77	65,612	3.68	7,785	0.09	86,981
Time horizon 10 years	125,408	6.33	111,435	6.11	13,973	0.22	63,539
Time horizon 20 years	181,196	9.03	158,314	8.57	22,883	0.46	49,907
CF mortality increased by 20%	194,616	9.77	165,137	9.12	29,479	0.64	45,806
CF mortality increased by 50%	173,418	8.73	146,664	8.14	26,754	0.59	44,993

Figure 22 Tornado Diagram – Mono-therapy



6.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

The probabilistic sensitivity analysis comparing Bronchitol to Control provided a mean ICER of £43,703 (95% CI 10,030-89,406).

Table 97 Results PSA – Mono-therapy

Statistic	Cost Bronchitol	Cost Control	ΔCost	QALY Bronchitol	QALY Control	Δ QALY	ICER
Mean	211,396	178,865	32,530	9.78	8.92	0.86	46,401
Median	190,265	156,090	34,830	9.84	8.97	0.86	38,864
SD	65,724	71,961	12,344	0.79	0.86	0.31	81,337
Min	131,827	96,341	-54,292	6.59	5.86	-0.04	-955,501
Max	704,583	674,835	96,268	12.08	11.24	1.92	1,286,588
2.5% percentile	147,139	108,467	8	8.09	7.08	0.29	-1,547
97.5%	386,931	384,746	47,653	11.12	10.47	1.50	118,008

percentile							

Table 98 Results PSA – Add-on therapy

Statistic	Cost Bronchitol + rhDNase	Cost Control + rhDNase	Δ Cost	QALY Bronchitol + rhDNase	QALY Control + rhDNase	Δ QALY	ICER
Mean	285,346	248,212	37,134	9.78	8.92	0.86	51,927
Median	264,666	225,394	39,260	9.84	8.97	0.86	44,279
SD	66,162	72,490	12,598	0.79	0.86	0.31	82,669
Min	198,915	157,885	-49,460	6.59	5.86	-0.04	-1,001,108
Max	775,063	740,389	97,082	12.08	11.24	1.92	1,297,467
2.5% percentile	218,318	174,372	6,259	8.09	7.08	0.29	3,333
97.5% percentile	463,944	456,053	53,263	11.12	10.47	1.50	126,873

Figure 23 ICER scatter plot – Mono-therapy

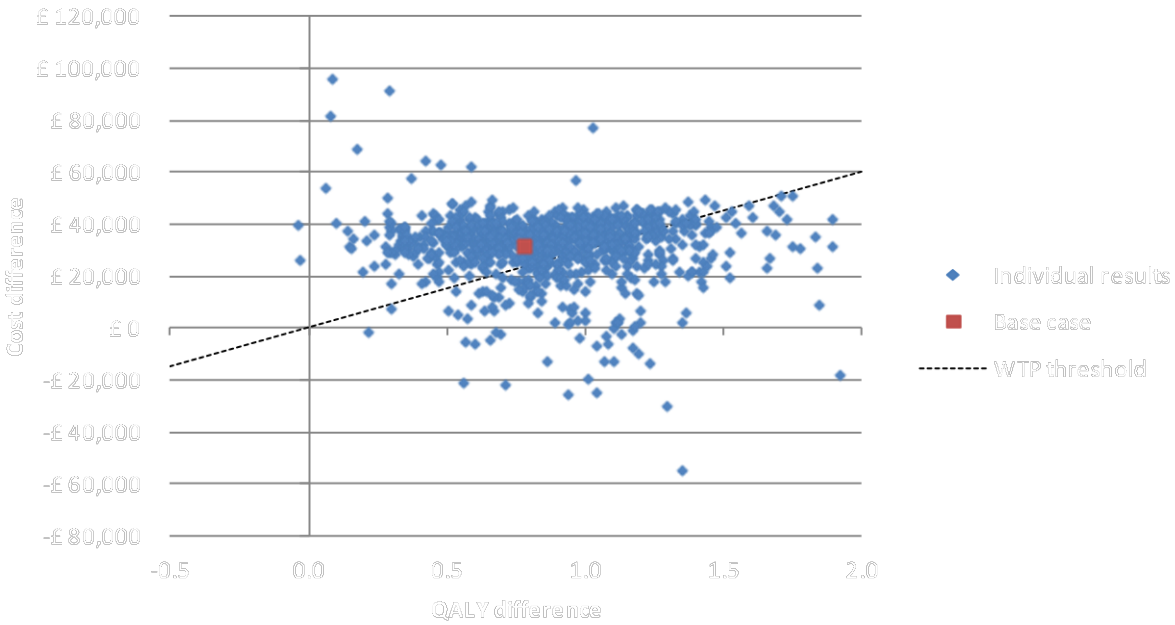


Figure 24 ICER scatter plot – Add-on therapy

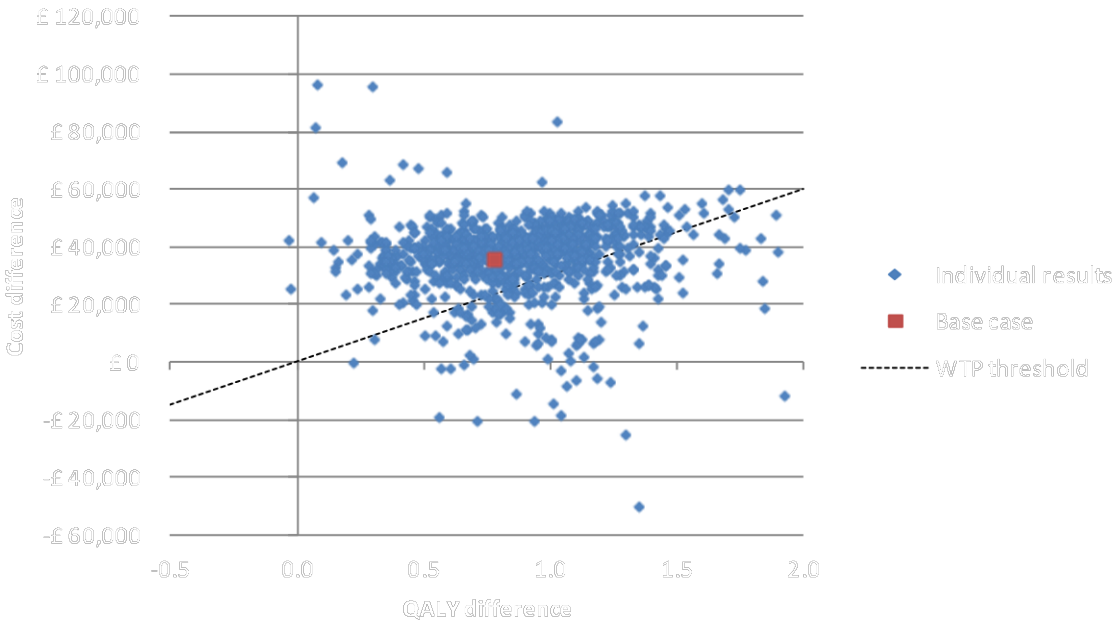
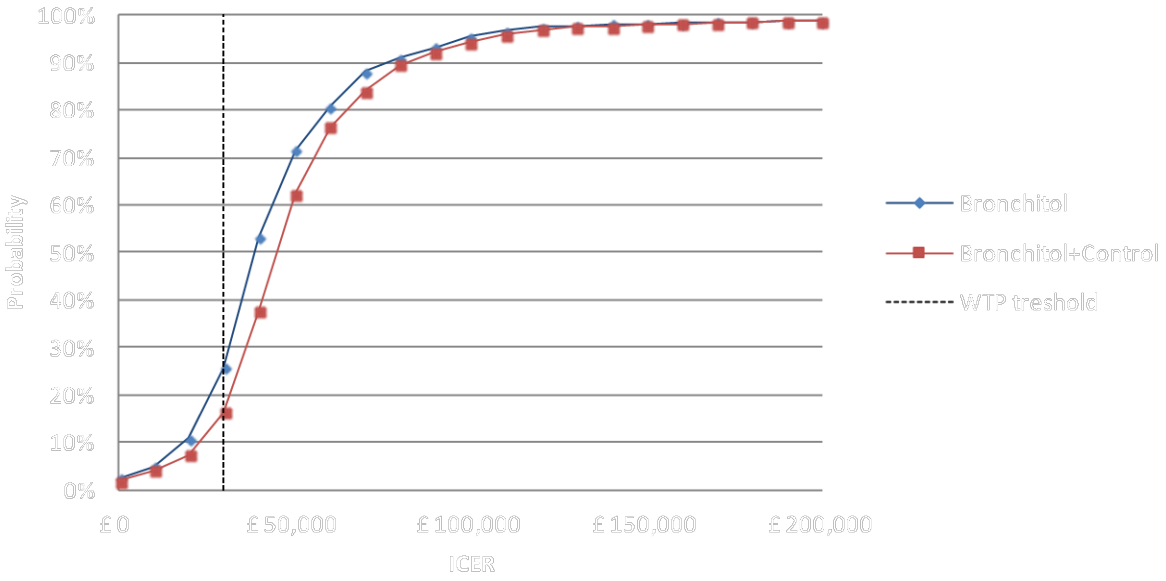


Figure 25 Cost-effectiveness acceptability curve



The results shown in Table 97, Table 98, Figure 23, Figure 24 and Figure 25 are based on 1,000 samples each containing 100,000 trials. The probability of the ICER being below a WTP

threshold of £30,000 was 25.8% for Bronchitol mono-therapy and 16.4% for Bronchitol add-on therapy. At a WTP threshold of £20,000 these probability were 10.9% and 7.4%, respectively.

6.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

Several scenario analyses have been performed. The scenarios with the greatest impact are shown in this section, while scenarios that had less impact are presented in Appendix 18.

Relative risk of pulmonary exacerbation and discontinuation rule
The key parameter in the model is the reduction in pulmonary exacerbations with Bronchitol responders. In addition the continuation rule implies that half of the patient population will discontinue Bronchitol treatment after 6 weeks. The effect of this discontinuation rule as well as the impact on the RR was investigated by running a scenario whereby all patients continue treatment. The following four scenarios were investigated:

In the first scenario the effect of the observed differences in historical rates of pulmonary exacerbations in the DPM-CF-302 was investigated. In this scenario the RR for exacerbations with Bronchitol responders, and also the effect on FEV_1 % predicted was based on the DPM-CF-301 study. Non-responders switch to control after the initial 6 weeks.

In the second scenario, we looked at the impact if all patients continue Bronchitol treatment regardless whether they responded to treatment or not. In the third scenario we looked at the reduction in the pulmonary exacerbations in the overall Bronchitol group (responder and non-responders) compared to the control group and in the last scenario we looked at the overall reduction in pulmonary exacerbations in the DPM-CF-301 study.

Table 99 Results scenario analysis RR exacerbation and discontinuation rule

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
1) RR based on DPM-CF-301 (RR=0.48)								
Control	180,665	11.44	9.79					
Bronchitol	207,593	12.23	10.66	26,928	0.79	0.87	31,090	31,090
Control + rhDNase	250,284	11.44	9.79	69,620	0.00	0.00	dominated	dominated
Bronchitol+rhDNase	282,389	12.23	10.66	101,725	0.79	0.87	117,447	37,067
2) No discontinuation rule, RR based on all Bronchitol responders (RR=0.65)								
Control	180,188	11.40	9.75					
Bronchitol	244,223	12.10	10.62	64,034	0.70	0.87	73,473	73,473
Control + rhDNase	249,472	11.40	9.75	69,284	0.00	0.00	dominated	dominated
Bronchitol+rhD	318,192	12.10	10.62	138,004	0.70	0.87	158,346	78,850

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Nase								
3) No discontinuation rule, RR based on all Bronchitol patients (RR=0.84)								
Control	180,188	11.40	9.75					
Bronchitol	245,417	12.08	10.60	65,228	0.68	0.85	76,579	76,579
Control + rhDNase	249,472	11.40	9.75	69,284	0.00	0.00	dominated	dominated
Bronchitol+rhDNase	319,262	12.08	10.60	139,074	0.68	0.85	163,275	81,935
4) No discontinuation rule, RR based on all Bronchitol patients in DPM-CF-301 (RR=0.69)								
Control	180,188	11.40	9.75					
Bronchitol	237,229	12.27	10.80	57,040	0.87	1.05	54,479	54,479
Control + rhDNase	249,472	11.40	9.75	69,284	0.00	0.00	dominated	dominated
Bronchitol+rhDNase	312,312	12.27	10.80	132,124	0.87	1.05	126,191	60,018

Decline in lung function

The observed increase in lung function for patients over 30 years of age in the BioGrid may not be realistic. Therefore a scenario was run whereby we assume that patients over 30 decline at equal rate as patients under 30. In addition a second scenario was run where the decline in lung function (regardless of age) was set at 2% per year, corresponding to the average observed by Liou et al.[51]

Table 100 Results scenario analysis lung function decline

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Assuming equal decline in lung function for patients aged ≥30 as observed in patient aged <30								
Control	155,387	9.74	8.15					
Bronchitol	178,567	10.16	8.69	23,181	0.43	0.54	42,848	42,848
Control + rhDNase	212,952	9.74	8.15	57,566	0.00	0.00	dominated	dominated
Bronchitol+rhDNase	239,399	10.16	8.69	84,013	0.43	0.54	155,290	48,885
Assuming a doubled decline in lung function (both in age≥30 and age <30)								
Control	144,854	8.87	7.17					
Bronchitol	164,620	9.22	7.64	19,766	0.35	0.47	42,418	42,418
Control + rhDNase	194,964	8.87	7.17	50,110	0.00	0.00	dominated	dominated
Bronchitol+rhD	217,498	9.22	7.64	72,644	0.35	0.47	155,895	48,358

Nase								
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Pulmonary exacerbation rate

The following analysis was done based on recent publications that indicate that the pulmonary exacerbation rate in the UK is higher than the pulmonary exacerbation rate observed in the BioGrid data.[99,78] In this analysis the exacerbation rate was set to 1.50. We analysed the model both in- and excluding the increased risk for pulmonary exacerbations in the previous year.

Table 101 Results scenario analysis using higher exacerbation rate

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Including the RR for previous exacerbations								
Control	214,150	10.74	9.06					
Bronchitol	241,276	11.46	9.87	27,127	0.72	0.81	33,489	33,489
Control + rhDNase	278,811	10.74	9.06	64,662	0.00	0.00	dominated	dominated
Bronchitol+rhDNase	310,912	11.46	9.87	96,762	0.72	0.81	119,455	39,629
Excluding the RR for previous exacerbations								
Control	192,375	11.19	9.53					
Bronchitol	223,282	11.87	10.28	30,907	0.67	0.75	41,022	41,022
Control + rhDNase	260,184	11.19	9.53	67,809	0.00	0.00	dominated	dominated
Bronchitol+rhDNase	295,660	11.87	10.28	103,285	0.67	0.75	137,086	47,085

6.7.10 What were the main findings of each of the sensitivity analyses?

The model was most sensitive the relative risk of a pulmonary exacerbation when responding to Bronchitol treatment. This was caused by the high uncertainty around this parameter (mean 0.65; 95% CI 0.39-1.08). The scenario analyses also indicated that the discontinuation rule has a significant impact on the ICER. In addition to the risk on pulmonary exacerbations the detrimental effects of this on a patient's QoL was another important driver.

When looking at the parameters relating to lung functioning, the effect of Bronchitol on the change in FEV_1 % predicted after 26 weeks and the hazard rate for ppFEV1 were the most influential parameters in the model. The scenario analyses indicated that the impact of the decline in lung function after the first 26 weeks had less impact on the ICER.

Of the utilities, the utility scores for patients with no improvement in respiratory symptoms had the most impact. Finally the patient's FEV_1 % predicted at baseline has a significant impact on the model, the ICER being lowest in older patients with lower FEV_1 % predicted.

The impact of lung transplant rate and costs is low. This is because the absolute difference in events in between the groups is low.

The impact of background costs of CF is low as the uncertainty around the mean cost were small. The cost to treat a pulmonary exacerbation had a greater impact on the ICER.

6.7.11 What are the key drivers of the cost-effectiveness results?

The key drivers of the model are:

- The cost of Bronchitol and the RR of pulmonary exacerbations in the Bronchitol arm. This is because an exacerbation has an impact on both costs and QALY's.
- The impact of pulmonary exacerbations on a patient's QoL
- The patient's FEV_1 % predicted when initiating Bronchitol treatment
- The improvement in FEV_1 % predicted caused by Bronchitol
- The hazard rate of FEV_1 % predicted
- Utility for patients without improvement in respiratory symptoms

6.8 Validation

6.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

Internal validation and debugging of the model was performed using the following validation procedures:

The model was validated using the following techniques:

- The model concept and structural assumptions were reviewed by CF specialty physicians and modelling experts from universities in the UK
- Clinical data, utilities and resource use data were double extracted and double checked by at two statisticians/health economists.
- Calculations in the model were checked by two statisticians/health economists.
- Extreme tests were performed to check the plausibility of model outcomes. Extreme testing was applied to the following parameters: treatment efficacy, cost of CF medication, mortality, exacerbation rate, transplant rates, transition probabilities (improvement in respiratory symptoms), discount rates, and utilities.

6.9 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. This should be explored as part of the reference-case analysis by providing separate estimates of clinical and cost effectiveness for each relevant subgroup of patients.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.10.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, when the costs of facilities available for providing the technology vary according to location).

6.9.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness due to known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 5.3.7.

The economic model is based on a detailed analysis of individual patient data and hence can be subdivided to analyse any sub-group of the patient population (gender, age, BMI, lung function).

Lung function was considered a subgroup (see section 4). In addition a subgroup analysis was performed looking at Bronchitol responders only. Subgroup analysis by prior treatment was not feasible as there was not enough data available.

6.9.2 Please clearly define the characteristics of patients in the subgroup.

The key patient characteristics of the subgroups by lung function are presented in Table 102 below.

Table 102 Patient characteristics of the different subgroups by lung function

Demographic		ppFEV1 >=80	ppFEV1 60-79	ppFEV1 40-59	ppFEV1 <40	Total
N	Control	14	42	65	13	134
	Bronchitol	19	89	73	26	207
	Total	33	131	138	39	341
% female	Control	36%	60%	46%	23%	47%
	Bronchitol	21%	43%	37%	42%	39%
	Total	27%	48%	41%	36%	42%
Age	Control	26.79	27.48	29.94	29.92	28.84
	Bronchitol	22.63	28.25	29.05	30.62	28.31
	Total	24.39	28.00	29.47	30.38	28.52
BMI	Control	23.22	22.63	21.63	21.13	22.06
	Bronchitol	22.73	22.82	22.89	21.00	22.61
	Total	22.94	22.76	22.30	21.04	22.39
ppFEV1	Control	85.32	71.13	49.00	35.78	58.45
	Bronchitol	85.65	69.38	50.69	34.34	59.88
	Total	85.51	69.94	49.89	34.82	59.32

The patient characteristics for responders subgroup analysis were identical to the overall patient population modelled in the base case analysis.

6.9.3 Please describe how the statistical analysis was undertaken.

The model was analysed sampling the patients from the subgroups by lung function as specified in section 6.9.2. Only the baseline patient characteristics were varied. The model estimates their change in lung function over the 26-week period based on the patient's BMI, ppFEV1 at baseline and treatment arm. All other variables, including the RR for pulmonary exacerbations, the chance of responding to treatment, improvement in respiratory symptoms, utilities and costs were kept constant.

For the subgroup analysis on treatment responders all patients in the Bronchitol arm were assumed to respond to Bronchitol treatment, i.e. no patients switched to best supportive care.

6.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 6.7.6 (Base-case analysis).

Table 103 Results subgroup analysis by lung function

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
ppFEV1 >=80								
Control (baseline)	266,516	17.02	14.71					
Bronchitol	309,189	17.78	15.56	42,673	0.76	0.84	50,688	50,688
Control + rhDNase	371,397	17.02	14.71	104,882	0.00	0.00	dominated	dominated
Bronchitol+rhDNase	418,734	17.78	15.56	152,219	0.76	0.84	180,808	56,228
ppFEV1 60-79								
Control (baseline)	212,333	13.50	11.67					
Bronchitol	249,399	14.27	12.48	37,067	0.77	0.82	45,247	45,247
Control + rhDNase	295,492	13.50	11.67	83,160	0.00	0.00	dominated	dominated
Bronchitol+rhDNase	337,312	14.27	12.48	124,979	0.77	0.82	152,562	51,049
ppFEV1 40-59								
Control (baseline)	145,450	9.30	8.00					
Bronchitol	173,488	9.97	8.71	28,038	0.67	0.71	39,511	39,511
Control + rhDNase	202,352	9.30	8.00	56,903	0.00	0.00	dominated	dominated
Bronchitol+rhDNase	234,732	9.97	8.71	89,283	0.67	0.71	125,818	45,630
ppFEV1 <40								
Control (baseline)	112,260	6.60	5.07					
Bronchitol	129,252	7.10	5.79	16,991	0.50	0.72	23,704	23,704
Control + rhDNase	147,083	6.60	5.07	34,823	0.00	0.00	dominated	dominated
Bronchitol+rhDNase	169,122	7.10	5.79	56,862	0.50	0.72	79,326	30,746
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Table 104 Results subgroup analysis Bronchitol responders

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Control	180,188	11.40	9.75					
Bronchitol	245,351	12.86	11.35	65,163	1.45	1.59	40,857	40,857
Control + rhDNase	249,472	11.40	9.75	69,284	0.00	0.00	dominated	dominated
Bronchitol+rhDNase	324,283	12.86	11.35	144,095	1.45	1.59	90,347	46,906

6.9.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 4.

Children (aged 6-18) have not been considered in this analysis as they are not included in the proposed indication (see section 1.3). Subgroups by prior treatment were not considered as the sample size was too small to allow for a separate analysis.

6.10 Interpretation of economic evidence

6.10.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

The patient demographics of the trials, the UK CF registry and the BioGrid data presented in Table 105. The trial population was comparable to the BioGrid population. The UK CF registry data includes children

Table 105 Patient demographics from the trials and CF patient registry

Demographics	CF-301 (adults)	CF-302 (adults)	Pooled data CF-301/302 (adults)	CF Registry 2008*	BIOGRID (≤18 age <48)
Age (SD)	29.3 (9.0)	27.6 (8.0)	28.5 (8.6)	18.7	27.6 (7.2)
Gender (female)	44.2%	39.1%	41.9%	47.5%	46.5%
FEV1 % predicted (SD)	57.8 (16.2)	61.1 (14.7)	59.3 (15.6)	77.9 male, 79.0 female	59.9 (22.3)
rhDNase use	53.7%	69.5%	60.7%	(0-18) 28.5% (18+) 37.9%	N/A
BMI	22.4 (3.5)	22.4 (3.7)	22.4 (3.6)	23.1 male 21.7 female*	21.4 (2.9)

Source: CF-301 and CF-302 from Table 10 section 5.3.3, CF registry from CF registry 2008 (includes adults and children), BIOGRID adult population (2010) * BMI for CF registry includes only adults 18+.

The annual exacerbation rate for the control group is taken from BioGrid data which is based on the assumption that a hospitalization in a quarter corresponds to a pulmonary exacerbation, as no detailed information was available on pulmonary exacerbations. This rate corresponded relatively well to the observed rate in the pooled studies, but it nevertheless may be an underestimate, as two recent publications report a mean number of exacerbations per year of 1.5[78,99].

Median survival in the model was 14.1 year for Control versus 15.5 years for Bronchitol, and median life expectancy was 43.2 versus 44.1 years, respectively. The reported median life

expectancy in the UK registry is as expected lower (38.8 years), as the registry includes children.

The 26-week treatment cost excluding CF medication measured in the trial (£4,664 for Control versus £4,390 for Bronchitol). The trial included multiple countries, and when looking at patients from the UK only (N=84) treatment cost were comparable for Bronchitol while cost for Control were higher (£7,878 for Control versus £4,546 for Bronchitol). Hence the model may have underestimated the differences between CF treatment costs other than CF medication.

Life time average treatment costs on Control varied from £180,188 to £285,858 when taking rhDNase, corresponding to £10,691 to £15,442 per year. These costs are comparable to lifetime costs reported by Baumann and the cost per year reported by Hovais.[90,93] The cost reported by Elliot et al were higher (£18,513 per year), but Elliot et al looked at severe patients with more than one pulmonary exacerbation.[94]

6.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 4?

Yes

6.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The economic model developed evaluated the costs and outcomes of using Bronchitol in adults with CF compared to best supportive care with or without rhDNase. All aspects of the model kept as closely as possible to the requirements of evidence-based medicine to ensure that it provided a robust and reliable basis for healthcare decision making. Such an aim inherently represents a very conservative approach particularly with regard to the evaluation of the savings in overall healthcare consumption that would be expected to arise through the use of Bronchitol in comparison to current resource use in standard care.

The clinical trials which support the structure of the initial 26 weeks of the model does not necessarily exhibit a high degree of external validity as the results may be affected by the trial setting. However, the robust clinical trial evidence generated in support of Bronchitol provides a firm evidence base to support the efficacy of Bronchitol both in terms of its beneficial impact on physical outcomes (improving lung function and decreasing the number of exacerbations) and on patient reported outcomes (CFQ-R and HUI2). The evidence base upon which the model is extrapolated to a life-time timeframe is more limited as it is based on the observational data from an Australian database supplemented with data from literature where necessary. As such, the longer term data should be interpreted with caution.

6.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

The robustness of the analysis could be improved with longer term Bronchitol data.

Section C – Implementation

7 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will allow the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

7.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

The number of patients assumed to be eligible for Bronchitol in year 1 was 72 (see Table 106). According to the Annual Data Report of UK CF Registry in 2008[4] the total number of adults diagnosed with CF and receiving treatment in England and Wales was 3651. A total of 8513 patients were included in the UK CF Registry. This registry includes CF patients from centres in Scotland and Northern Ireland who correspond to approximately 17.5% of all patients in the registry. Overall, 56% of UK CF Registry patients were aged over 16 years old and 44% over 20 years old. Using these cut-off numbers we estimated that approximately 52% of all patients were over 18 years old, i.e., 4427 patients in the UK. When adjusting this number for patients from centres in England and Wales only, the total number of CF adults is 3651.

Approximately 43% of adult CF patients receive rhDNase in the UK. [4]

It is assumed that uptake of Bronchitol as add-on therapy will be the same for patients on best supportive care only and patients on best supportive care and rhDNase (referred to as “patients on rhDNase” in this submission). The estimated uptake ranges from 4.10% to 18.50%, based on market research and other recent specialist product launches.

The proportion of patients responding to Bronchitol applied to our estimates is that observed among adults in the DMP-CF-301 and DMP-CF-302 studies, i.e., 48%. Thus, of the 150 patients starting Bronchitol in year 1, 72 will be responders and will remain on this agent until year 5. Bronchitol treatment will be discontinued after three months of treatment in non-responders. At the end of Year 5, approximately 1047 patients will be treated with Bronchitol.

Table 106 Patients eligible for Bronchitol and remaining on this treatment[4]

	Year 1	Year 2	Year 3	Year 4	Year 5
Uptake	4.10%	8.00%	12.50%	15.50%	18.50%
CF adult patients*[1]	3,651	3,828	4,003	4,179	4,353
Deaths	43	45	47	49	51
New CF adult patients*[2]	220	220	220	223	223
Patients starting Bronchitol*[3]	150	294	464	576	699
Responders among patients starting Bronchitol (48%)	72	141	223	276	335
Responders from previous year		72	213	436	712
All Responders*[4]	72	213	436	712	1047

*[1] These figures correspond to the overall CF adult population included in the UK CF Registry in 2008 when adjusting for adults from centres in England and Wales only.

*[2] New CF adults comprise CF patients who become eligible for Bronchitol treatment, mainly adolescents turning 18 years old.

*[3] These figures correspond to CF adult patients who will initiate treatment with Bronchitol.

*[4] Total responders cover responders among patients who initiated treatment at that particular year and responders already on Bronchitol in the previous year.

7.2 What assumption(s) were made about current treatment options and uptake of technologies?

Bronchitol is an add-on therapy and not a replacement therapy; this is taken into consideration in the budget impact analysis. Current management of the disease follows an integrated approach of prevention and symptomatic treatment. The available treatment options include bronchodilators, steroids, physiotherapy, antibiotics, hypertonic saline and rhDNase. In line with anticipated label indication of Bronchitol the main comparators used in the budget impact analysis are:

- Best supportive care
- Best supportive care plus rhDNase

RhDNase reduces the viscoelasticity of airway secretions by catalysing the hydrolytic cleavage of phosphodiester linkages in the DNA backbone. There is a wide individual variation in response; rhDNase may be ineffective if there is no DNA in airway secretions. In 2008, only 37.2% of all CF patients in the UK CF Registry were using rhDNase. Since rhDNase has been the only drug for assisting with lung clearance ever approved in the UK and available since 1994, it is reasonable to assume based upon other registry data that many of the patients not currently taking rhDNase have previously trialled the drug and are now not using rhDNase because of poor efficacy, tolerability, compliance and/or adverse responses[100,101,38,102].

In our budget impact estimates we consider that uptake and responder rates for Bronchitol is the same for patients on rhDNase and patients on best supportive care only. It is assumed that 48%

of patients initiating Bronchitol therapy will respond and continue with the add-on therapy (responders).

Market uptake is considered as 4.10% for the first year and increases up to 18.50% in Year 5. Market update throughout the first 5 years is assumed to be the same for all patients irrespective of their previous CF treatment. The market uptake provides the number of patients started on Bronchitol. The numbers of responders who will continue on this agent in the first 5 years are displayed in Table 106.

7.3 What assumption(s) were made about market share (when relevant)?

Bronchitol is indicated for the treatment of cystic fibrosis in adults aged 18 years and above as an add-on therapy to rhDNase and in patients ineligible, intolerant to, or inadequately responsive to rhDNase[‡‡‡]. As detailed in sections 7.1 and 7.2, we have assumed that Bronchitol will be administered as an add-on therapy to 4.10% of patients in Year 1 and to 18.5% of patients in Year 5.

7.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

The only additional costs expected to be associated with treatment with Bronchitol are those incurred for the assessment of bronchial hyper-responsiveness to inhaled mannitol during administration of the initial dose. The national average cost of a bronchial reactivity assessment (HRG code DZ36Z for outpatients) when applied in an outpatient setting is £104[103]. The initiation dose assessment is to be performed as described in the Bronchitol SPC.

7.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

The unit costs of Bronchitol applied in the budget impact estimates are based on the acquisition cost of the drug to the NHS. These costs include the inhaler which is provided with the Bronchitol capsules. Bronchitol is available as:

- 14 day carton of 280 capsules and 2 inhaler devices (₤236.25)
- Initiation dose carton containing 10 capsules and one inhaler device (free of charge).

The Bronchitol and other resource use associated costs are detailed in Table 107. As Bronchitol is an add-on therapy, costs of best supportive care and of rhDNase were not considered in the budget impact estimates.

[‡‡‡] The indication granted to Bronchitol is: “Bronchitol is indicated for the treatment of cystic fibrosis in adults aged 18 years and above as an add-on therapy to best standard of care”.

Table 107 Unit costs of technology being appraised

	Responder Bronchitol	Non-responder*[1] Bronchitol
Costs of initial Bronchitol dose	£0.00	£0.00
Drug costs per year	£6,161	£709
Other resource use*[2]	£104	£104
Total	**£6.265**	**£813**

*[1] Patients being responders or not is assessed after six weeks of treatment. Thus, in the budget impact analysis, we consider that non-responders receive Bronchitol for six weeks only.

*[2] Other resource utilisation corresponds to the bronchial reactivity assessment all patients undergo when they receive the first dose of Bronchitol.

To simplify the budget impact model, we assume that all new patients start treatment with Bronchitol at the beginning of the year.

7.6 Were there any estimates of resource savings? If so, what were they?

Based on the results of the DMP-CF-301 and DMP-CF-302 studies, we estimate that the use of Bronchitol in real-life clinical practice will lead to a decrease in the exacerbations rate of CF adult patients (see section 6.3.1). In these two studies, the relative risk of protocol defined pulmonary exacerbations (PDPE) in Bronchitol-responders compared with the Control patients was 0.65. The annual incidence of PDPE among patients on Bronchitol was 0.49 and 0.79 for responders and non-responders, respectively and 0.68 and 0.79 respectively for Control patients.

Based on the reduced rate of exacerbation for Bronchitol-responders, it is estimated that the use of Bronchitol would yield exacerbation-related savings of £2,197 per responder and year. No benefits regarding exacerbations rate is expected for non Bronchitol responders.

7.7 What is the estimated annual budget impact for the NHS in England and Wales?

The budget impact estimates by year are shown in detail in Table 108. These estimates are based on the population eligible for treatment with Bronchitol and described in Table 106.

The costs included in our budget impact estimates include the costs for the initial drug dose as well as for the bronchial hyper-responsiveness test (£104), but do not include costs of best supportive care or costs of rhDNase as these costs are incurred by all patients and will not be affected by the addition of Bronchitol.

The total drug costs would range between £585,459 in year 1 and £4,755,472 in year 5 (Table 108). If we take into account the reduced rate of exacerbations observed in patients treated with Bronchitol (RR of 0.65), Bronchitol as an add-on therapy would save approximately £157,828 yearly in terms of the management of exacerbation episodes in Bronchitol-responders compared with responders on DNase or best supportive care only. Thus, the overall annual budget impact

when considering savings due to reduced risk of exacerbation ion Bronchitol-responders would range between £344,853 in year 1 and £1,748,845 in year 5.

Table 108 Budget impact of Bronchitol add-on therapy for CF adults

	Year 1	Year 2	Year 3	Year 4	Year 5
Uptake	4.10%	8.00%	12.50%	15.50%	18.50%
Newly-treated*[1] (£3,928)	£ 585,459	£ 1,150,938	£ 1,813,228	£ 2,252,428	£ 2,732,963
Previous year responders (£ 6,161)		£ 525,697	£ 1,033,455	£ 1,628,141	£ 2,022,509
Total drug costs	£ 585,459	£ 1,676,636	£ 2,846,683	£ 3,880,569	£ 4,755,472
Savings due to reduced exacerbation rate	£ 157,828	£ 468,099	£ 956,909	£ 1,564,120	£ 2,300,873
Total costs	**£ 344,853**	**£ 962,802**	**£ 1,470,226**	**£ 1,740,906**	**£ 1,748,845**

*[1] Drug costs for newly-treated patients take into account that 52% of patients will be non-responders and thus, they will be treated for six weeks only. These costs also include cost of a bronchial hyper-responsiveness test performed in outpatient facilities (£104).

7.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

As discussed in detail in this submission, Bronchitol reduces the exacerbations rate offering an opportunity for resource savings in terms of GP and clinic visits, hospitalisation and use of antibiotics and other pharmaceutical drugs indicated in the management of exacerbations. All these resource savings have been considered in the cost-effectiveness model; no other impact on healthcare resources is anticipated.

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Please use a recognised referencing style, such as Harvard or Vancouver.

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