NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Overview

Colistimethate sodium powder and tobramycin powder for inhalation for treating pseudomonas lung infection in cystic fibrosis

This overview is a summary of:

- the evidence and views submitted by the manufacturers, the consultees and their nominated clinical specialists and patient experts and
- the assessment report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Key issues for consideration

- What is current UK clinical practice for the treatment of chronic pseudomonas lung infection? Where do colistimethate sodium dry powder for inhalation (DPI) and tobramycin powder for inhalation fit into this treatment pathway?
- In view of the Assessment Group critique of the available clinical trials, is the Committee satisfied that colistimethate sodium dry powder for inhalation (DPI) and tobramycin powder for inhalation are clinically effective?
    - What outcomes do Committee see as important in ascertaining clinical effectiveness? Does the Committee accept forced expiratory volume (FEV) values are sufficient as a single marker for establishing clinical effectiveness?
    - What other outcomes (if any) should be taken into account when establishing clinical effectiveness? For example do the Committee give weight to EMA guidelines.
    - Considering that the key trials were up to 24 weeks duration, what is the Committee's view on the likely long-term efficacy of

colistimethate sodium DPI and tobramycin powder for inhalation as potentially life-long therapy?

- Are Committee satisfied that adverse effects of treatment (for example exacerbations) have been adequately captured in terms of clinical effectiveness?
- There were differences in the trial populations of the COLO/DPI/02/06 and EAGER trials in terms of baseline characteristics and rates of exposure to antipseudomonal antibiotics. In view of the relationship between clinical variables and cystic fibrosis prognosis, does the Committee accept that these trial populations are comparable?

- Colistimethate sodium DPI and tobramycin powder for inhalation are both administered by inhaler, whereas the comparators are administered by nebuliser. Does the Committee consider there to be benefits with the different methods of administration?

- Does the Committee consider the manufacturer's model for colistimethate sodium DPI to be robust?
    - What is the Committee's view on the validity of the assumptions in the manufacturer's model for colistimethate sodium DPI? For example, colistimethate sodium DPI is used according to the same treatment schedule as nebulised tobramycin, that is, each 28-day treatment is followed by 28 days without treatment?
    - Does the Committee accept that the method used to estimate survival gain used in the manufacturer's model for colistimethate sodium DPI is valid?
    - Does the Committee accept that the methods used to obtain the estimate of quality-adjusted life year (QALY) gain in the manufacturer's model for colistimethate sodium DPI are valid?
- Does the Committee consider that the aspects of cystic fibrosis treatment have been adequately captured in the Assessment Group model i.e. impact

of amount of drugs on daily life, adverse effects of treatment leading to IV antibiotics?

- Does the Committee accept that the methods used to obtain the estimate of quality-adjusted life year (QALY) gain in the Assessment Group model are valid?
- Is the Committee satisfied that the estimates of the incremental cost-effectiveness derived from the Assessment Group model are robust? What do the Committee consider to be the most plausible ICERs?

1 Background: Clinical need and practice

1.1 Cystic fibrosis is an autosomal recessive disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. It is characterised by abnormal transport of chloride and sodium across transporting epithelia, leading to thick viscous secretions in the lungs, pancreas, liver, intestine and reproductive tract and to an increased salt content in sweat gland secretions. People with cystic fibrosis have problems with digestion, including prolonged diarrhoea which can affect growth and body mass index, and a troublesome cough, and are prone to lung infections by a range of pathogens including *Staphylococcus aureus*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, and *Burkholderia cepacia*. This is thought to be because the thick mucus makes it difficult for the body to clear inhaled bacteria, and because people with cystic fibrosis have an increased airway inflammatory response to pathogens. Chronic inflammation and progressive lung destruction from chronic infection can lead to bronchiectasis, altered pulmonary function, and respiratory failure.

1.2 Cystic fibrosis affects over 8500 children and young adults in the UK and has an incidence of 1 in 2500 live births. About 1 in 25 people in the UK of white European family origin are carriers of an affected CFTR gene. It is much less common in people of African-Caribbean and Asian family origin. Cystic fibrosis is a progressive condition that reduces life expectancy. In 2010, 103 deaths were recorded in UK patients by the cystic fibrosis registry; the median age at death was 29 years. However, prognosis is improving with the treatments now available and around half of the cystic fibrosis population can expect to live over 38 years.

1.3 Management of the pulmonary component of cystic fibrosis includes a range of measures to aid clearance of respiratory secretions and to decrease inflammation and bacterial growth in the respiratory tract, such as chest physiotherapy, inhaled mucolytics (such as rhDNase and hypertonic saline) and antibiotic treatment. The aim of treatment is to delay or slow deterioration in lung function, measured by forced expiratory volume in 1 second (FEV_1). Ultimately, patients may become eligible for lung transplantation. The care of most patients in the UK is coordinated by a tertiary cystic fibrosis centre, with formal shared care with local clinics. Treatment for cystic fibrosis can be time consuming, with administration of nebulised antibiotics taking up to an hour per day during good health and longer during periods of ill health. The disease also impacts upon carers and requires a considerable commitment of healthcare resources.

1.4 *Ps. aeruginosa* is the most frequent cause of lung infection in people with cystic fibrosis, with around 38% of UK patients having chronic infection in 2010. If recurrent

intermittent infections are not controlled, chronic infection can develop, in which bacterial microenvironments known as biofilms are formed that are difficult for immune cells and antibiotics to penetrate. The length and quality of life for people with cystic fibrosis is thought to be strongly influenced by the success or failure to eradicate *Ps. aeruginosa*; however chronic infection is rarely eradicated.

1.5 Management of *Ps. aeruginosa* lung infection in cystic fibrosis involves treatment with antibiotics, which may be given either in hospital, at home or in a combination of these settings. The aims of antibiotic treatment are three-fold: firstly to eradicate intermittent acute *Ps. aeruginosa* infections; secondly to suppress *Ps. aeruginosa* (with long-term therapy) in patients who have become chronically infected; and thirdly for treatment of acute exacerbations in patients chronically infected with *Ps. aeruginosa*. In addition, treatment aims to maintain lung function and quality of life. Current treatment options include the use of inhaled antibiotics (such as nebulised colistimethate sodium or tobramycin) effective against *Ps. aeruginosa*, oral antibiotics (such as ciprofloxacin) to eradicate first or intermittent *Ps. aeruginosa* colonisation, and intermittent administration of intravenous anti-pseudomonal antibiotics for chronic infection. Azithromycin may be given in combination with these antibiotics to act on the biofilms.

1.6 The Committee for Medicinal Products for Human Use (CHMP) has research guidelines for the development of new medicinal products for cystic fibrosis that recommend that FEV_1 is used as the primary endpoint for studies investigating cystic fibrosis treatments; however a microbiological primary endpoint is also considered necessary for confirmatory trials. The presence of microbial

infection is ascertained using sputum colony density. FEV_1 is converted by use of an equation (for example, Knudson) to a percentage of the normal predicted value for a healthy person of the same age, sex and height to give the FEV_1% predicted or FEV_1%. There are a number of such equations that can be used, which will affect the FEV_1% calculated. There does not appear to be consensus about which equation is most appropriate.

2 The technologies

Colistimethate sodium dry powder for inhalation

2.1 Colistimethate sodium DPI (Colobreathe, Forest Laboratories UK) is a formulation of colistimethate sodium supplied as hard capsules. It belongs to the polymixin class of antibacterials and works by disrupting the structure of the bacterial cell membrane, leading to bacterial death. It is active against aerobic Gram-negative organisms including *Ps. aeruginosa, Acinetobacter baumannii*, and *Klebsiella pneumoniae*. Colistimethate sodium DPI is administered using the 'Turbospin' device (PH&T) which is a breath-activated, reusable dry powder inhaler. Colobreathe is indicated for the management of chronic pulmonary infections due to *Ps. aeruginosa* in patients with cystic fibrosis (CF) aged 6 years and older (for further details see Table 1).

2.2 The summary of product characteristics lists the following adverse reactions for colistimethate sodium dry powder for inhalation: ear and labyrinth disorders , respiratory, thoracic and mediastinal disorders(such as dyspnoea, cough and wheezing), gastrointestinal disorders, musculoskeletal, connective tissue and bone disorders, general disorders

and administration site conditions, and renal and urinary disorders. For full details of adverse reactions and contraindications, see the summary of product characteristics.

Tobramycin powder for inhalation

2.3 Tobramycin dry powder for inhalation (TOBI Podhaler, Novartis) is a dry powder formulation of tobramycin. It acts primarily by disrupting protein synthesis leading to altered cell membrane permeability, progressive disruption of the cell envelope and eventual cell death. Tobramycin inhibits protein synthesis of numerous Gram-negative bacteria and it is active against *Ps. aeruginosa*. Tobramycin powder for inhalation is administered using TOBI Podhaler . TOBI Podhaler is indicated for the suppressive therapy of chronic pulmonary infection due to Ps. aeruginosa in adults and children aged 6 years and older with cystic fibrosis.

2.4 The summary of product characteristics lists the following adverse reactions for tobramycin powder for inhalation: ear and labyrinth disorders , vascular disorders , respiratory, thoracic and mediastinal disorders (such as such as dyspnoea, productive cough and wheezing), gastrointestinal disorders , skin and subcutaneous tissue disorders, musculoskeletal, connective tissue and bone disorders general disorders and administration site conditions. For full details of adverse reactions and contraindications, see the summary of product characteristics.

Table 1 Summary description of technologies

Non-proprietary name	Colistimethate sodium powder for inhalation	Tobramycin dry powder for inhalation
Proprietary name	Colobreathe	TOBI Podhaler
Manufacturer	Forest Laboratories UK	Novartis
Dose	1 capsule (approximately equal to 125 mg of colistimethate sodium) to be inhaled twice daily using the Turbospin inhaler device.	112 mg tobramycin (4 x 28 mg capsules), administered twice daily for 28 days in alternating cycles of 28 days on treatment followed by 28 days off treatment using the TOBI Podhaler device.
Acquisition cost (BNF edition 63)	£968 per 28 day pack £17.30 per dose* These prices exclude VAT	224 x 28mg capsules + 5 Podhalers = £1790.00 56 x 28 mg capsules + 1 Podhaler = £447.50 treatment) These prices exclude VAT

* Information provided by manufacturer, not available in BNF

2.5 In May 2012 the manufacturer of TOBI Podhaler agreed a patient access scheme with the Department of Health to provide TOBI Podhaler [redacted]

2.6 In September 2012 the manufacturer of Colobreathe agreed a patient access scheme) to provide Colobreathe [redacted].

2.7 Appendix B details the annual cost of various anti-psuedomonals for the treatment of chronic *Ps. aeruginosa* in cystic fibrosis patients.

3 Remit and decision problem(s)

3.1 The remit from the Department of Health for this appraisal was: To appraise the clinical and cost effectiveness of colistimethate sodium powder and tobramycin powder for

inhalation within their licensed indications for the treatment of pseudomonas lung infection in cystic fibrosis.

	Final scope issued by NICE	Additional comments or specifications in the Assessment Group's protocol
Population	People aged 6 years and over with cystic fibrosis and chronic *Pseudomonas aeruginosa* pulmonary infection.	Subgroups are considered according to the available evidence for example by number of prior eradication therapies.
Intervention	Colistimethate sodium dry powder for inhalation (used in conjunction with the Turbospin device). Tobramycin powder for inhalation (used in conjunction with the TOBI Podhaler device). *Both interventions are to be used for the ongoing treatment of chronic Ps. aeruginosa infection*	N/A
Comparators	Colistimethate sodium dry powder for inhalation and tobramycin powder for inhalation will be compared with each other and with antibiotics for nebulised inhalation, including: colistimethate sodium for nebulised inhalation and tobramycin for nebulised inhalation.	The availability of evidence of the effectiveness of other less commonly used nebulised antibiotics (for example, aztreonam) with anti-pseudomonal activity is also considered within the assessment. No head to head studies of Tobramcyin or Colistimethate sodium dry powders versus each other were identified
Outcomes	Rate and extent of microbial response (for example, sputum density of *Ps.aeruginosa*), lung function, respiratory symptoms, frequency and severity of acute exacerbations, health-related quality of life, adverse events of treatment (including rate of resistance to antibiotic treatment).	Lung function measured in terms of forced expiratory volume in 1 second (FEV_1) (up to 24 weeks duration)
Economic evaluation	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per 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 compared. Costs will be considered from an NHS and personal social services perspective.	The manufacturer of Colistimethate sodium dry powder for inhalation submission presents a model-based cost-utility analysis. The manufacturer of Tobramycin powder for inhalation submission did not present an economic model

4 Clinical-effectiveness evidence

4.1 The Assessment Group identified three studies comparing colistimethate sodium DPI or tobramycin powder for inhalation with nebulised antibiotics. One study compared colistimethate sodium DPI with nebulised tobramycin, one study compared colistimethate sodium DPI with nebulised colistimethate and one study compared tobramycin powder for inhalation with nebulised tobramycin. There were no direct comparisons of the two inhaled powder interventions. The Assessment Group identified a further 13 studies for a network meta-analysis. However because of clinical heterogeneity a network meta-analysis was not possible. The manufacturer of tobramycin powder for inhalation included a literature review and performed a network meta-analysis as part of their submission.

Colistimethate sodium dry powder for inhalation

4.2 The Assessment Group included two randomised controlled trials in their clinical effectiveness review. The COLO/DPI/02/05 trial assessed the safety and tolerability of multiple doses of colistimethate sodium DPI compared with nebulised colistimethate sodium. The COLO/DPI/02/06 trial investigated the effectiveness of colistimethate sodium DPI as a treatment for pseudomonas lung infection in people with cystic fibrosis compared with tobramycin nebuliser solution for inhalation. These two studies also formed part of the manufacturer's (Forest) submission. The manufacturer of colistimethate sodium DPI powder for inhalation included a literature review as part of the submission.

COLO/DPI/02/05 safety trial

4.3 The COLO/DPI/02/05 trial was a randomised, open-label, crossover study to compare the safety of colistimethate sodium DPI and colistimethate sodium nebuliser solution in children and adults with cystic fibrosis and chronic *Ps. aeruginosa* lung infection. The study was conducted at three centres in the UK. The study compared one capsule of colistimethate sodium DPI given twice daily for 4 weeks with 2 million units of colistimethate sodium nebuliser solution given twice daily for 4 weeks. The study population included 16 people of whom 37.5% were younger than 13 years. The primary objective was to assess the safety (clinical tolerability and laboratory safety) of four weeks treatment with dry powder inhaled colistimethate sodium compared to four weeks treatment with nebulised colistimethate sodium. Change in lung function was a secondary outcome of the trial.

4.4 The incidence of solicited symptoms (both reported on the case report form and on diary cards), adverse events and related adverse events was higher in the DPI group than in the nebuliser solution group. Two patients withdrew as a result of adverse events after the first dose of DPI. No deaths or serious adverse events occurred and the adverse events experienced were mostly mild to moderate and did not deter the patients from taking the treatment. All patients in the DPI group (n = 16) reported a total of 106 treatment emergent adverse events and nine patients (60.0%) in the nebuliser solution group (n = 15) reported a total of 55 adverse events. The most common treatment related adverse events were gastrointestinal disorders (87.5% of patients) followed by cough and throat irritation (both in 81.3% of patients) in the DPI group and cough (46.7% of patients) followed by wheezing (33.3% of patients) in the nebuliser solution group.

4.5 For the secondary outcome of change in lung function between baseline and week 4 the Assessment Group indicated that colistimethate sodium DPI [redacted] than colistimethate sodium nebuliser solution. The difference in FEV_1% predicted as unadjusted mean change from baseline was [redacted]

COLO/DPI/02/06 trial

4.6 The COLO/DPI/02/06 trial was designed as a non-inferiority trial in which twice daily doses of 125 mg of colistimethate sodium DPI administered via a Turbospin device were compared with twice daily doses of 300 mg of tobramycin nebuliser solution for nebuliser inhalation for 24 weeks. The study was powered to detect non-inferiority at a margin of no less than 3% at the lower end of the confidence interval

of the difference between the treatment groups. The study was conducted in 66 centres in the European Union, Russia and the Ukraine. The study included 324 evaluable people aged 6 to 56 years (mean age 21 years [SD 9.49]) with cystic fibrosis who had chronic pseudomonas lung infection that would normally be treated with inhaled antibiotics. Of the study population, 55% were male. Other inclusion criteria were: FEV_1 25–70% of predicted and use of tobramycin nebuliser solution for inhalation (having had a minimum of two on/off cycles) before randomisation. The primary endpoint of the study was change in FEV_1% predicted after 24 weeks of treatment. Secondary outcomes included frequency and time to exacerbations, adverse events, quality of life and physical changes.

4.7 Three populations were analysed as part of the efficacy analysis of the primary endpoint in COLO/DPI/02/06:

- The intention-to-treat (ITT) population (all randomised patients who had received at least one dose of a study drug and had laboratory confirmed chronic pseudomonas lung infection).
- The per-protocol population (results from all randomised patients who had received at least one dose of a study drug and had laboratory confirmed chronic pseudomonas lung infection, were classified as 'efficacy evaluable' [that is, the patients did not receive any medication that affected or biased FEV_1 values, had a baseline FEV_1 predicted result, had at least one post-baseline FEV_1 result, had a recorded date of birth, met all inclusion/exclusion criteria that could affect the primary outcome]).
- The safety population (all randomised patients who had received at least one dose of a study drug).

The primary non-inferiority analysis of the trial was conducted on the ITT population data set. Subgroup analyses were conducted by baseline FEV_1% predicted (less than 50% predicted and greater than or equal to 50% predicted), sex, concomitant medication use (azithromycin and dornase alfa), but the study was not powered to detect statistically significant differences between these subgroup analyses.

4.8 For the primary endpoint of change in FEV_1% predicted after 24 weeks of treatment, the results from the ITT population were −1.16% (95% CI −3.15 to 0.84) suggesting that colistimethate sodium DPI was marginally less efficacious than tobramycin nebuliser solution (the protocol-defined lower limit for non-inferiority was −3%), but the non-inferiority criteria was not met. In the per-protocol population the criterion for non-inferiority was also not met. When a non-parametric analysis was performed non-inferiority was shown, further details of these results are shown in table 2 below.

Table 2 Summary of primary efficacy results for COLO/DPI/02/06 (change in FEV_1, between baseline and 24 weeks)

Population	CDPI (mean)	TOBI (mean)	Overall (mean)	Adjusted mean difference ANCOVA (95% CI)	Adjusted mean difference logistic transformation (95% CI)	Median difference non-parametric analysis (95% CI)ditto
ITT (n = 373)	−0.90	0.35	−0.26	−1.16 (−3.15 to 0.84)	0.980 (0.943 to 1.018)	−0.56 (−2.16 to 1)
Per-protocol (n = 298)	−0.30	1.12	0.45	−1.49 (−3.79 to 0.81)	0.977 (0.935 to 1.020)	−0.67 (2.57 to 1.16)
Per-protocol patients who completed (n = 261)	Not reported	Not reported	Not reported	0.998 (0.943 to 1.036)	−1.10 (−3.08 to 0.97)	−0.15 (−2.14 to 1.17)

CDPI, colistimethate sodium dry powder inhaler; TOBI, tobramycin nebuliser solution; CI, confidence interval; FEV_1, forced expiration volume in 1 second; ITT, intention to treat.

4.9 No significant differences were observed between the colistimethate DPI and tobramycin nebuliser solution groups for any of the subgroup analyses (baseline FEV_1% predicted, age, gender, azithromycin use, dornase alfa use) on the primary outcome (change in FEV1 % predicted) in the COLO/DPI/02/06 trial.

4.10 The proportion of people experiencing at least one protocol defined acute exacerbation in the COLO/DPI/02/06 trial was higher in the colistimethate sodium DPI group than in the tobramycin nebuliser solution group [redacted] compared with [redacted] The mean time to exacerbation was [redacted] among the colistimethate sodium DPI group (66.1 days compared with 59.9 days). Colistimethate sodium DPI had a more favourable exacerbation rate than tobramycin nebuliser solution when non-protocol defined exacerbations

were also considered (38% compared with 39%). The number of patients requiring anti-pseudomonal treatments was similar in both groups.

4.11 In the COLO/DPI/02/06 trial, 347/380 patients (91.3%) were reported to have experienced 2426 adverse events; 243/380 patients (63.9%) experienced 853 adverse events that were assessed by the investigator as being related to the study medication. Twenty-seven of the 380 trial participants (7.1%) were withdrawn because of an adverse event (22 in the colistimethate sodium DPI group, 5 in the tobramycin nebuliser solution group). The incidence of study-medication-related adverse events was higher in the colistimethate sodium DPI group (153/187 patients [81.8%]) compared with the tobramycin nebuliser solution group (90/193 patients [46.6%]). The incidence of patients experiencing a severe adverse event was higher in the colistimethate sodium DPI group compared with the tobramycin nebuliser solution group (48/187 patients [25.7%] compared with 13/193 patients [6.7%]). The most frequent adverse event was cough (15.7% [colistimethate sodium DPI] and 10.3% [tobramycin nebuliser solution]), dysgeusia (10.7% compared with 5.2%), and dyspnoea (6.6% compared with 8.2%). The rate of discontinuation of treatment was higher in the colistimethate sodium DPI group compared with the tobramycin nebuliser solution group (22/187 patients [11.8%] compared with 5/193 patients [2.6%]. The assessment report notes that resistance data from the COLO/DPI/02/06 trial indicated that throughout the 24 weeks resistance to colistimethate sodium remained low (less than or equal to 1.1%). Resistance to tobramycin was reported to not change substantially during the study.

4.12 Health-related quality of life was evaluated in the COLO/DPI/02/06 trial by the Cystic Fibrosis Questionnaire (CFQ) (a disease-specific instrument designed to measure impact on overall health, daily life, perceived wellbeing and symptoms) at several time points. No significant differences in quality of life between baseline and week 24 were seen between the colistimethate sodium DPI and tobramycin nebuliser solution groups. At week 24, quality of life assessments were in favour of colistimethate sodium DPI in most CFQ-R domains in the ITT population (see table 3 below). Detectable differences were reported in the manufacturer's submission for both the ITT and per protocol population for the change in treatment burden domain from baseline to week 4**,** with colistimethate sodium DPI being more favourable in both cases. A non-statistically significant improvement in treatment burden domain for colistimethate sodium DPI compared with tobramycin nebuliser solution was seen between baseline and week 24.

Table 3 Adjusted mean changes in quality of life (CFQ-R) from baseline to week 24/exit (ITT population)

CFQ-R domain	Colobreathe (N=183)	TOBI (N=191)	Adjusted difference	P-value
Physical	0.26	–1.56	1.82	0.353
Vitality	0.86	–1.40	2.27	0.293
Emotion	2.23	0.47	1.75	0.244
Eating	0.48	0.66	-0.19	0.925
Treatment Burden	5.62	2.75	2.87	0.091
Health Perceptions	0.25	–2.71	2.96	0.159
Social	3.10	0.92	2.18	0.153
Body Image	7.83	5.98	1.85	0.385
Role	0.65	1.87	-1.22	0.607
Weight	0.88	–1.93	2.81	0.461
Respiratory	2.99	3.51	-0.53	0.756
Digestion	5.06	2.89	3.22	0.077

Notes:
[1] Adjusted difference (LS Mean difference Colobreathe - TOBI), p-value and confidence intervals were determined using ANCOVA with covariates of baseline score and pooled centre

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Tobramycin powder for inhalation

4.13 The Assessment Group included one trial (EAGER) in its review of the clinical effectiveness of tobramycin powder for inhalation compared with nebulised antibiotics. The manufacturer provided details of two randomised controlled trials (EVOLVE and EAGER) in their submission. Both these trials investigated tobramycin powder for inhalation compared with placebo (EVOLVE) or nebulised tobramycin (EAGER) as a treatment for chronic pseudomonas lung infection in people with cystic fibrosis.

EVOLVE trial

4.14 The EVOLVE trial was a double-blind trial in which tobramycin powder for inhalation administered via a Podhaler device was compared with placebo. Participants received tobramycin powder for inhalation (112 mg tobramycin) twice daily (n = 46) or placebo (n = 49) by inhaler for one cycle, followed by two open-label cycles (all patients). Cycles were 28 days on treatment, 28 days off treatment. The study was conducted in Europe, South and North America and included people aged 6 to 21 years with cystic fibrosis who had chronic pseudomonas lung infection. Entry criteria included having a baseline FEV_1% predicted greater than 25% and less than or equal to 80%. The aim of the study was to demonstrate the efficacy of a 28-day dosing regime of tobramycin powder for inhalation compared with placebo, as measured by the relative change in FEV_1% predicted from baseline.

4.15 The study was terminated early based on positive results in the interim analysis. Tobramycin powder for inhalation significantly improved FEV_1% predicted compared with

placebo at day 28 (difference 13.3, 95% CI 5.31 to 21.28; p = 0.0016). The manufacturer also reported that tobramycin powder for inhalation also reduced sputum *Ps. aeruginosa* density, respiratory-related hospitalisation and anti-pseudomonal antibiotic use compared with placebo.

EAGER trial

4.16 The EAGER trial was designed as a non-inferiority trial in which twice daily doses of 112 mg of tobramycin powder for inhalation administered via a Podhaler device were compared with twice daily doses of 300 mg nebulised tobramycin administered by nebuliser for 24 weeks. The study was powered to detect non-inferiority at a margin of no less than 6% at the lower end of the confidence interval of the difference between the treatment groups . The study (n = 513) included people aged 6 years or above (powder group mean age 26 years [SD 11.4], nebulised group mean 25 years [SD 10.2]) with cystic fibrosis who had chronic pseudomonas lung infection. Of the study population, 55% were male. The primary endpoint was the incidence of adverse events; however the trial was powered to detect change in FEV_1% predicted from baseline to week 20. Other outcomes included microbiological measures (e.g. bacterial susceptibility), body mass index changes, laboratory safety endpoints.

4.17 The results indicated that tobramycin powder for inhalation was associated with an improved mean FEV_1% predicted compared with nebulised tobramycin at 20 weeks of 0.59 (SE 0.92) and the manufacturer reported non-inferiority. Only limited data were presented for lung function at 24 weeks and the Assessment Group noted that they would expect FEV_1% levels to be lower at that stage. The

Assessment Group calculated the difference in FEV_1% mean change from baseline between intervention and comparator to be; [redacted] at 4 weeks, [redacted] at 20 weeks and 2.2 (SE 1.69) at 24 weeks.

4.18 In the EAGER trial, resistance (8 mg/L breakpoint) to tobramycin started at around 20% (the baseline value was at the end of 28 days off treatment) and was lower at 24 weeks (also at the end of 28 days off treatment). *Ps. aeruginosa* sputum density data showed a reduction in the tobramycin powder for inhalation group (−1.61 log colony forming units [CFU]) compared with the nebulised group (−0.77 log CFU).

4.19 The number of patients experiencing lung disorders was greater in the tobramycin powder for inhalation group (33.8%) than in the nebulised tobramycin group (30.1%). However no information was provided on the number of events experienced by patients and therefore it is not known whether some patients experienced multiple events. Mean duration of anti-pseudomonal antibiotic treatment was also slightly shorter in the tobramycin powder group than in the nebulised tobramycin group (30.9 days compared with 33.4 days). The number of patients receiving additional anti-pseudomonal treatments was higher in the tobramycin powder arm.

4.20 The treatment satisfaction questionnaire for medication (TSQM) results showed higher values in the tobramycin powder for inhalation group than in the nebulised group. Least squares mean difference average over visits were; 9.36 (SE 1.460) for effectiveness, −0.5 (SE 1.218) for side effects, 24.35 (SE 1.547) for convenience and 5.20 (SE

1.655) for global satisfaction for tobramycin powder compared with nebulised tobramycin.

4.21 Adverse events were more common in the tobramycin powder for inhalation group (90.3% of patients) compared with 84.2% in the nebulised tobramycin group. A total of 57 patients (40 in the powder group and 17 in the nebulised group) were withdrawn from the EAGER trial because of an adverse event. The most common adverse events in the two groups were cough (48.4% in the powder group and 31.1% in the nebulised group). Adverse events that appeared to be worse in the powder group included [redacted], chest discomfort and dysphonia. The proportion of patients who experienced an exacerbation resulting in at least one hospitalisation were similar in the two groups (24.4% in the powder group compared with 22.0% in the nebulised group). Episodes of 'lung disorder' were similar in both groups (33.8% for the powder group compared with 30.1% for the nebulised group). The rate of discontinuation of treatment was higher in the tobramycin powder for inhalation group compared with the nebulised tobramycin group (83/308 patients [26.9%] compared with 38/209 patients [3.8%].

4.22 The Assessment Group only included the EAGER trial in their clinical effectiveness review of tobramycin powder for inhalation compared with nebulised tobramycin. The EVOLVE trial was excluded because the comparator was placebo and therefore not based on the scope provided by NICE.

Assessment Group comments

4.23 The Assessment Group commented that the quality of the included studies was generally poor to moderate. None of

the included trials scored well on all risk of bias items, with blinding and non-adherence to the European Medicines Agency (EMA) research guidelines (see table 9 of the Assessment Group report for further details). The Assessment Group stated that this could lead to selection and reporting bias for subjective outcomes such as adverse events, inaccuracies and imprecision in the results, and may limit the generalisability of the studies. The Assessment Group judged that follow-up may allow for detection of effects in respiratory efficacy, but was not long enough to detect slowing of the rate of decline in respiratory function, according to EMA research guidelines. The Assessment Group report highlighted that because FEV_1% is a surrogate outcome, the EMA recommend that it should be considered alongside microbiological outcomes and 'harder' clinically relevant outcomes such as frequency of exacerbations and antibiotic use.

4.24 The Assessment Group stated it was not possible to determine whether the changes seen in the colistimethate sodium DPI arm were significantly different to the changes seen in the tobramycin powder for inhalation arm because of a lack of data at 24 weeks, different population analyses of results and uncertain comparability of patient characteristics at baseline.

Mixed treatment comparison (tobramycin powder for inhalation)

4.25 The manufacturer of tobramycin powder for inhalation performed a literature review followed by a network meta-analysis using data from seven studies to assess comparative clinical effectiveness of TOBI Podhaler (tobramycin powder for inhalation) with TOBI (tobramycin nebuliser solution), Bramitob (tobramycin nebuliser

solution), Colomycin nebuliser tablets (colistin sulphate, an antibiotic used to treat *Ps. aeruginosa* infections in people with cystic fibrosis), Cayston (aztreonam nebuliser solution) and placebo. Colobreathe (colistimethate sodium DPI) was not included in the analysis because studies of this technology were not in the public domain. The manufacturer explained that in the network meta-analysis there were underlying differences in the included trials in terms of trial populations, outcomes used and study design.

4.26 The manufacturer explained that because of the small number of studies and underlying differences in the study populations, it carried out a series of subgroup analyses stratified by baseline mean FEV_1, study publication date (the oldest study publication was 1987, followed by 1999 and 2002, all other studies were published in 2006), naive or exposed status to active treatment stratified by study arm, and mean age at baseline (less than or equal to 18 years or greater than 18 years).

4.27 The manufacturer concluded that the TOBI Podhaler is expected to be comparable with other alternatives (Bramitob, TOBI, Colomycin and Cayston) in improving FEV_1% predicted at 4 weeks. However, they highlighted that the results should be considered with caution because of large credible ranges around point estimates. The results of the relative efficacy of each technology compared with placebo are detailed in tables 4 and 5 below.

Table 4 Network meta-analysis results for percentage change from baseline in FEV_1 at 4 weeks: Relative efficacy versus placebo

Treatment effect relative to placebo	Difference in % CFB FEV_1	2.5% CI	97.5% CI
TOBI Podhaler (powder for inhalation)	**12.27**	–1.9	26.32
TOBI (nebuliser solution)	**12.53**	–1.71	26.65

Bramitob (nebuliser solution)	**12.27**	–3.91	28.47
Colomycin (tablets)	**6.23**	–11.59	23.81
Cayston (nebuliser solution)	**8.43**	–5.76	22.55
CI, credible interval; CFB, change from baseline; FEV_1, forced expiratory volume in 1 second.			

Table 5 Network meta-analysis results for percentage change from baseline FEV_1 at 4 weeks: Relative efficacy of TOBI Podhaler versus alternatives

Treatment effect of TOBI Podhaler relative to alternatives	**Difference in % CFB FEV_1**	**2.5% CI**	**97.5% CI**
Placebo	12.27	–1.9	26.32
TOBI (nebuliser solution)	–0.26	–8.32	8.23
Bramitob (nebuliser solution)	0	–13.31	13.83
Colomycin (tablets)	6.04	–7.38	19.78
Cayston (nebuliser solution)	3.84	–7.45	15.37
CI, credible interval; CFB, change from baseline; FEV_1, forced expiratory volume in 1 second.			

Assessment Group comments

4.28 The Assessment Group did not carry out an evaluation or provide specific comments on the Novartis network meta-analysis because they judged that given the available evidence, a network meta-analysis was not possible. The Assessment Group concluded that it was not possible to draw any firm conclusions as to the relative efficacy of any intervention compared with any other intervention (except when there was direct evidence comparing the dry powder formulations with nebulised tobramycin) because of missing data, uncertain comparability of patient characteristics and incompatible populations .

Summary of clinical effectiveness

4.29 Table 6 presents a summary of the lung function results for the three trials included in the Assessment Group report. The Assessment Group highlighted that when assessing the clinical effectiveness, FEV_1% predicted is a surrogate

outcome and should be considered alongside other clinically relevant outcomes. Both tobramycin powder for inhalation and colistimethate sodium DPI seemed to result in more exacerbations or more people experiencing exacerbations than nebulised tobramycin, but less time on antibiotics. Adverse events were similar between arms within the trials except for cough**,** which was higher in both powder arms. More patients in the dry powder for inhalation arms withdrew because of adverse events in both key trials. The Assessment Group was unable to draw definite conclusions as to the relative efficacy of any intervention.

Table 6 Summary of comparative analyses for FEV_1% between intervention and comparator

Time	Study	No imputation Difference in % mean change from baseline between intervention and comparator (calculated by reviewer)	No imputation Adjusted difference	LOCF Adjusted difference (ANCOVA)
4 weeks	COLO/DPI/02/05 (CDPI vs NC)	[redacted]	[redacted]	[redacted]
	COLO/DPI/02/06 (CDPI vs NT)	[redacted]	[redacted]	[redacted]
	EAGER (TPI vs NT)	[redacted]	[redacted]	[redacted]
20 weeks	COLO/DPI/02/06 (CDPI vs NT)	[redacted]	NR	–1.40% (95% CI −3.43% to 0.63%) (LOCF analysis)
	EAGER (TPI vs NT)	[redacted]	[redacted]	NR
24 weeks	COLO/DPI/02/06 (CDPI vs NT)	[redacted]	–0.43% [redacted]	–1.16% (95% CI −3.15 to 0.84)
	EAGER (TPI vs NT)	2.2 (SE 1.69)	NR	NR*

* These data were requested from the manufacturer by the Assessment Group, but were not provided.

CDPI, colistimethate sodium dry powder for inhalation; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; LOCF, last observation carried forward; NT, nebulised tobramycin; TPI, tobramycin powder for inhalation; RC, reviewer calculated; NR, not reported; SE, standard error; SD, standard deviation; NC, nebulised colistimethate

5 Comments from other consultees

5.1 Clinical specialists noted that inhaled antibiotics for the treatment of pseudomonas infection in cystic fibrosis are used as a short-term treatment (1 to 3 months) to eradicate new infection or as a long-term treatment to suppress chronic pseudomonas infection. They also noted that once started, treatment usually continues for life but occasionally

if lung function is normal and the patient is free of pseudomonas infection for over 12 months, inhaled antibiotics may be discontinued, at least for a trial period.

5.2 Clinical specialists noted that there are currently three inhaled antibiotics licensed for the treatment of chronic *Ps. aeruginosa* infection in the UK, colistin sulphate, preservative-free tobramycin nebuliser solution and tobramycin nebuliser solution (TOBI). Historically, nebulised colistin sulphate has been used as a first-line therapy for both eradication and prophylactic maintenance treatment for chronic *Ps. aeruginosa* infection. Clinical specialists noted that some patients are unable to tolerate colistin sulphate because they get wheezy or a tight chest on administration. They also noted that nebulised tobramycin is often used as a second-line treatment for chronic *Ps. aeruginosa* infection.

5.3 Clinical specialists noted that lack of adherence to treatment is a problem in the treatment of chronic *Ps. aeruginosa* infection. Therefore colistimethate sodium DPI and tobramycin powder for inhalation may be preferred or better tolerated by some patients, may be easier to use and therefore could result in improved adherence to treatment, quality of life and length of time between chest exacerbations. The clinical specialists noted that clinical staff may need initial training in using the new technologies, but it is anticipated that there would be no additional requirements in terms of staffing or NHS resources.

5.4 Clinical specialists also noted that inhalers may offer advantages over nebulisers in terms of speed of delivery – thereby reducing therapeutic burden. They also note that cleaning of nebulisers is not always done adequately and

inhalers only need wiping down after use. Additionally, clinical specialists commented that inhalers are portable and can be used in a wide range of settings.

6 Cost-effectiveness evidence

6.1 The cost-effectiveness evidence consists of the manufacturer's model for Colobreathe (colistimethate sodium DPI), a re-analysis of the manufacturer's model by the Assessment Group, a de novo model produced by the Assessment Group and the Assessment Group economic analysis in response to the patient access scheme submitted by the manufacturer of tobramycin powder for inhalation.

6.2 The Assessment Group identified three published economic evaluations: a cost–consequence analysis of home intravenous therapy in people with cystic fibrosis (Wolter et al. 1997), a cost-effectiveness analysis comparing hospital and home care in people with cystic fibrosis (Thornton et al. 2005) and a cost–consequence analysis of inhaled tobramycin nebuliser solution in people with cystic fibrosis. None of these three studies relates to either colistimethate sodium or tobramycin powder. The Assessment Group judged that these studies provide some information about the costs and outcomes of the comparator therapies and explain some of the key methodological problems surrounding the economic evaluation of treatments for cystic fibrosis for example, short-term lung function improvements rather than QALY gains.

Manufacturer's model for colistimethate sodium DPI

6.3 A model-based cost–utility analysis was used to compare colistimethate sodium DPI with nebulised tobramycin. The population modelled were people aged 6 years or older with documented cystic fibrosis who had chronic pseudomonas lung infection (the same population as the COLO/DPI/02/06 trial). The model had a 24 week time horizon and took a UK NHS perspective.

6.4 The main assumptions of the model were:

- Colistimethate sodium DPI is used according to the same treatment schedule as nebulised tobramycin, that is each 28-day treatment is followed by 28 days without treatment.
- All patients have a fixed maximum life expectancy of 37.4 years
- There is no difference in adverse events between colistimethate sodium DPI and nebulised tobramycin.

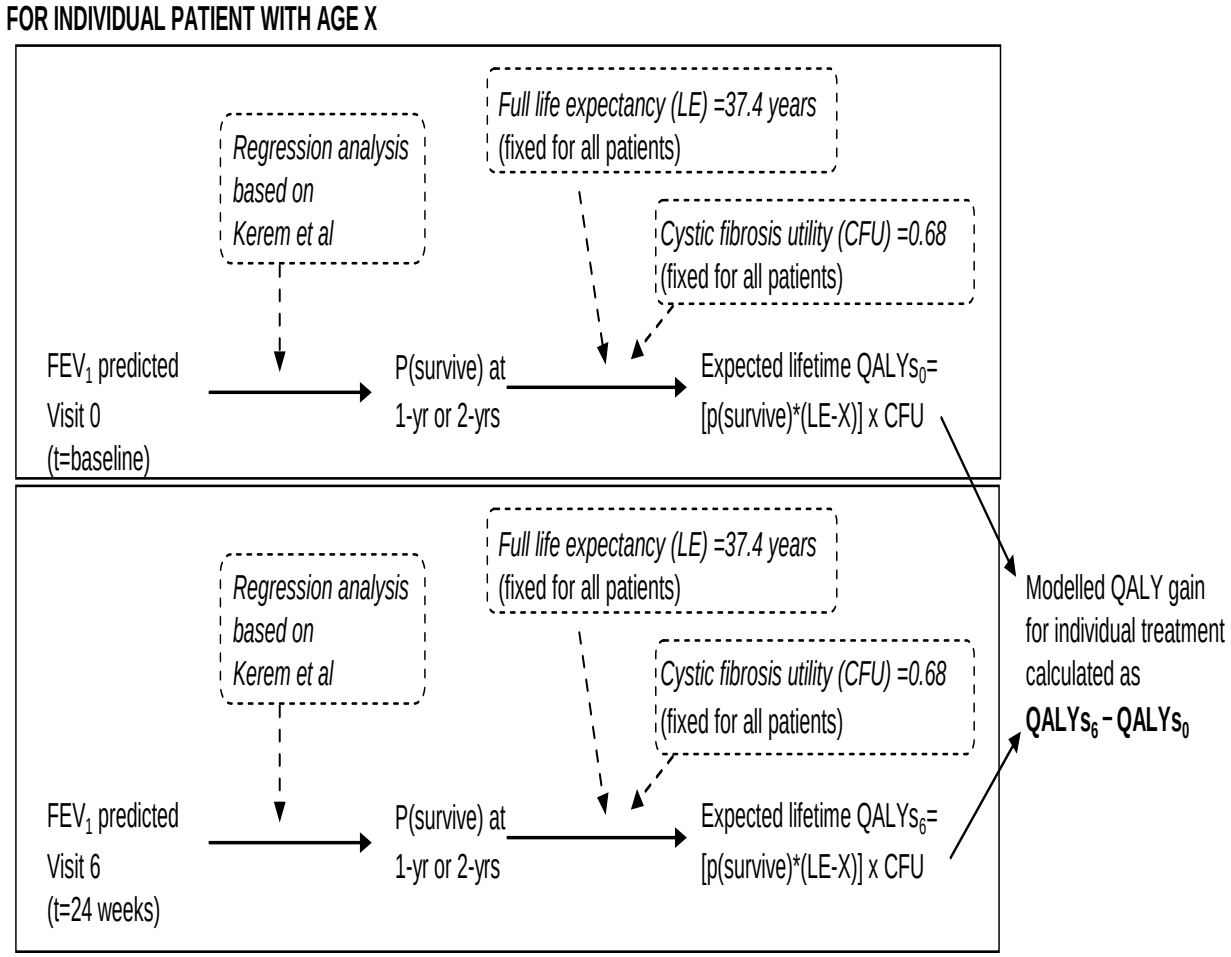
Utilities

6.5 The COLO/DPI/02/06 trial did not collect health-related quality of life data using a preference-based instrument. Utility estimates in the manufacturer's model were obtained from the CFQ used in the COLO/DPI/02/06 study, mapped to EQ-5D using regression equations with coefficients derived from patient-level data from a published study in people with cystic fibrosis (Eidt-Koch et al. 2009). In this study, data were collected in 2006 across four cystic fibrosis centres in Germany. A cohort of 96 patients with cystic fibrosis completed both the German version of the CFQ and the EQ-5D-Y. Patients included in this study were generally young (the mean was approximately 13 years, range 8 to 17 years) and mean FEV_1% predicted was generally high both in the children and adolescent groups (93.6% and 90.7% respectively). This mapping exercise

produced a single utility value of 0.68 for people with cystic fibrosis with chronic *Ps. aeruginosa* lung infection.

6.6 QALY gains from treatment were then estimated by a series of steps (see figure 1 below) and are a function of mortality risk and the single utility value for people with cystic fibrosis. Predicted mortality differences between colistimethate sodium DPI and nebulised tobramycin were estimated by regression equations for mortality at 1 and 2 years using reported data from a retrospective analysis of the risk of mortality by Kerem et al. (1992). This study used FEV_1% predicted, forced vital capacity (FVC), partial pressure of oxygen (PaO_2) and carbon dioxide ($PaCO_2$), sex, weight and height to predict mortality at 1 and 2 years. The manufacturer fitted several polynomial regression equations to the Kerem et al. data for mortality risk at 1 or 2 years by FEV_1 group. The manufacturer then applied the best fit regression equation to patient level data from COLO/DPI/02/06 to calculate the 1 and 2 year mortality risk for the intervention and comparator groups based on FEV_1% predicted only.

Figure 1 Method used to derive QALYs in the Forest model



FEV_1, forced expiratory volume in 1 second; QALY; quality-adjusted life year.

6.7 The resulting QALY gains for the trial population for 1 and 2 year mortality rates are given in table 7 below**,** showing the beneficial QALY gain for colistimethate sodium DPI compared with nebulised tobramycin.

Table 7 Change in expected QALY, by treatment, for patients in COLO/DPI/02/06 using 1 year and 2 year mortality rates

Assumed mortality rate	QALY change per patient		Benefit of Colobreathe
	Colobreathe	TOBI	
1 year mortality rate	0.194	0.163	0.031
2 year mortality rate	0.209	0.168	0.041

Assumed mortality rate	QALY change per patient	Benefit of Colobreathe
QALY; quality-adjusted life year, Colobreathe; colistimethate sodium dry powder for inhalation, TOBI; tobramycin nebuliser solution.		

Costs

6.8 The manufacturer's model included costs for acquisition of medication and costs associated with exacerbations. Acquisition costs for nebulised tobramycin were taken from the 'British national formulary' (BNF) edition 61. The model assumes a cost per dose of tobramycin of £21.20 (annual cost of £7738, excluding VAT), corresponding to a regimen in which two doses of nebulised tobramycin are used each day, and each 28-day treatment period is followed by 28 days without nebulised tobramycin. The manufacturer's economic analysis priced Colobreathe the same as nebulised tobramycin. Exacerbations were costed from NHS reference costs (number of exacerbations for Colobreathe patients was calculated from patient level data in the pivotal trial).

6.9 The manufacturer reported results in terms of incremental net benefit. The incremental net benefit was [redacted] per patient per year. The manufacturer highlights this is an underestimation of the benefit as there are several additional benefits such as cost of devices and consumables for nebulisation, the more favourable performance of colistimethate sodium DPI with respect to antimicrobial sensitivity, and the benefit to patients in terms of ease of use.

6.10 Table 8 presents the Assessment Group's base-case results of the manufacturer's model in which colistimethate sodium DPI dominates nebulised tobramycin (that is,

colistimethate sodium DPI is less expensive and more effective).

Table 8 Assessment Group's base-case results of manufacturer's economic model for colistimethate sodium DPI compared with nebulised tobramycin

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Assuming 1 year mortality risk					
Colistimethate sodium DPI	£22,584	0.194	N/A	N/A	N/A
Nebulised tobramycin	£23,634	0.163	£1050	0.031	Colistimethate sodium DPI dominates
Assuming 2 year mortality risk					
Colistimethate sodium DPI	£22,584	0.209	N/A	N/A	N/A
Nebulised tobramycin	£23,634	0.168	£1050	0.041	Colistimethate sodium DPI dominates
ICER; incremental cost-effectiveness ratio, QALY; quality-adjusted life year. N/A; not applicable.					

6.11 The Assessment Group identified limitations in the manufacturer's model.The model deviated from the NICE reference case in the following ways:

- no discounting was undertaken for costs because of the short time horizon
- results are incremental net benefit rather than incremental cost per QALY gained
- no probabilistic sensitivity analysis was carried out.

6.12 Other limitations of the manufacturer's model included:

- The short study duration of the COLO/DPI/02/06 trials means a high degree of censoring of mortality estimates.
- The model uses changes in FEV_1% predicted measured in the short term to predict long-term mortality benefits.

- The model assumption that each 28-day treatment is followed by 28 days without treatment does not reflect the protocol for the COLO/DPI/02/06 trial or the marketing authorisation for colistimethate sodium DPI. The result is that the modelled treatment benefits reflect those associated with the continuous use of colistimethate sodium DPI at only half the cost of generating these benefits.
- There were shortcomings in the mapping exercise used to produce the model utility estimate for example, in terms of the population used for mapping the CFQ to the EQ-5D, and there was ambiguity in the selection and justification of the mapping function.
- The validity of the model assumption that there is no difference in the rate of adverse events between colistimethate sodium DPI and nebulised tobramycin.
- There was little justification for the modelling approach adopted. The methods used to identify, select or use particular sources of evidence (for example, Kerem et al.) are not discussed in the submission.
- There is an absence of direct comparative evidence of impact on health-related quality of life and limited evidence of survival benefit.

6.13 The Assessment Group carried out a literature search and concluded that FEV_1 alone was not a valid predictor of survival, and judged that the survival estimated in the manufacturer's model derived from the Kerem et al. data lacked validity because of the potential for confounding from other prognostic factors.

6.14 The Assessment Group carried out an exploratory analysis of the Forest model to try and correct for some of the issues identified with the manufacturer's model. It

acknowledged that it could not fully resolve the problems regarding the time horizon, the health impact of adverse events, or the uncertainty surrounding the QALY benefits for colistimethate sodium DPI. The results of this analysis are shown in table 9 and show that if colistimethate sodium DPI is priced lower than nebulised tobramycin it may dominate because of lower costs from avoided exacerbations and incremental QALY gains. If the price is higher than nebulised tobramycin, the incremental cost per QALY gained ranges from £42,872 to £485,550 depending on assumptions regarding time horizons and drug acquisition costs.

Table 9 Results of the exploratory analysis

Revised scenario	**Incremental results for colistimethate sodium DPI versus nebulised tobramycin**		
	Incremental QALYs gained	**Incremental costs**	**Incremental cost per QALY gained**
1-year mortality prediction model results			
Forest base case	0.031	–£1050.49	Dominating
Scenario 1 (£9.11/dose)	0.031	–£987.20	Dominating
Scenario 2 (£10.60/dose)	0.031	–£484.84	Dominating
Scenario 3 (£15.98/dose)	0.031	£1329.05	£42,872.44
Scenario 4 (£19.64/dose)	0.031	£2563.03	£82,678.35
Scenario 5 (£21.20/dose)	0.031	£3088.99	£99,644.80
Scenario 6 (£39.29/dose)	0.031	£9188.10	£296,390.38
2-year mortality prediction model results			
Forest base case	0.041	–£1050.49	Dominating
Scenario 1 (£9.11/dose)	0.041	–£2138.94	Dominating
Scenario 2 (£10.60/dose)	0.041	–£1050.49	Dominating
Scenario 3 (£15.98/dose)	0.041	£2879.60	£70,234.12

Scenario 4 (£19.64/dose)	0.041	£5553.23	£135,444.61
Scenario 5 (£21.20/dose)	0.041	£6692.81	£163,239.24
Scenario 6 (£39.29/dose)	0.041	£19,907.55	£485,550.09
QALY; quality-adjusted life year.			

Assessment Group de novo model

6.15 The Assessment Group developed a de novo probabilistic state transition model to compare colistimethate sodium DPI with nebulised tobramycin in people with cystic fibrosis who had chronic *Ps. aeruginosa* infection. It did not include tobramycin powder for inhalation in the economic analysis because patient level FEV_1 data were not available from the manufacturer at the time the report was produced (this information was provided by the manufacturer when the patient access scheme was considered) and information on the price of tobramycin powder for inhalation was not available until February 2012. Other comparator treatments were not included in the analysis because of lack of data (nebulised colistimethate sodium) or because it is not recommended for use in UK (aztreonam). The model had a lifetime time horizon and a UK NHS perspective. The cycle length was 24 weeks and treatment duration is assumed to be equivalent between the competing treatments. Mean survival for patients in the model was estimated using data from Dodge et al. 2009. This study reported survival data up to the end of 2003 for all people with cystic fibrosis born in the UK between 1968-1992 collated via active enquiry of CF clinics and other hospital consultants. The model had three health states: FEV_1 70–99%, FEV_1 40–69% and FEV_1 less than 40%. The 24-week transition probability

estimates were based on those observed in COL/DPI/02/06. The Assessment Group stated that some people may switch between tobramycin and colistimethate sodium at some point in their lives. However, this feature was not included in the model because clinical-effectiveness data on the effect of treatment switching were not available.

Utilities

6.16 Different levels of health-related quality of life were assumed for each health state. Total QALYs were calculated as the total time in each health state weighted by the respective utility for that health state, less any QALY losses resulting from exacerbations. Utility estimates were obtained from the Bradley (2010) study (see table 9 below for further details).

Table 9 .Health utility estimates reported by Bradley et al (from Novartis submission

FEV_1 stratum / exacerbation severity	**Mean EQ-5D (Standard deviation)**
>70% predicted	**0.864 (0.165)**
40-79% predicted	**0.81 (0.216)**
<40% predicted	**0.641 (0.319)**
Major exacerbation	**0.174 decrement (0.341)**
Minor exacerbation	**0.015 decrement (0.048)**

Costs

6.17 Costs in each treatment group include drug acquisition costs and the costs of managing exacerbations (either in hospital or at home). Potential cost savings associated with reduced maintenance of nebulisers were also included in the economic analysis. Costs associated with follow-up and concomitant medications were assumed to be equivalent between treatment groups.

6.18 Table 10 presents the base-case results for the Assessment Group model for a lifetime time horizon. The results suggest a QALY loss (0.13) over a patient's lifetime associated with colistimethate sodium DPI compared with nebulised tobramycin. If colistimethate sodium DPI is priced at £15.98 or above it is dominated by nebulised tobramycin. If colistimethate sodium DPI is priced at £10.60 per dose, the model suggests an ICER of £23,788 per QALY gained. However it should be noted that this positive ICER lies in the south-west quadrant of the cost-effectiveness plane and represents a QALY loss and cost savings for colistimethate sodium DPI compared with nebulised tobramycin.

Table 10 Base-case results of the Assessment Group probabilistic model (long-term reference case)

CDPI price	QALYs			Costs			ICER
	CDPI	TOBI neb	Inc.	CDPI	TOBI neb	Inc.	
£9.11	9.48	9.61	–0.13	£93,915.58	£110,518.68	–£16,603.10	£126,259
£10.60	9.48	9.61	–0.13	£107,390.59	£110,518.68	–£3128.08	£23,788
£15.98	9.48	9.61	–0.13	£156,045.35	£110,518.68	£45,526.67	Dominated
£19.64	9.48	9.61	–0.13	£189,145.05	£110,518.68	£78,626.38	Dominated
£21.20	9.48	9.61	–0.13	£203,253.12	£110,518.68	£92,734.45	Dominated
£39.29	9.48	9.61	–0.13	£366,852.48	£110,518.68	£256,333.80	Dominated

CDPI; colistimethate dry powder for inhalation, TOBI neb; tobramycin nebuliser solution, Inc; increment, ICER; incremental cost-effectiveness ratio, QALY; quality-adjusted life year.

6.19 The Assessment Group analysis found that if cost per dose is assumed to be £9.11 (the lowest estimate used), at a maximum acceptable ICER of £20,000 per QALY gained colistimethate sodium DPI had a probability of 0.98 of being cost effective, and also a probability of 0.92 of being cost effective at a maximum acceptable ICER of £30,000 per QALY gained.

6.20 The Assessment Group analysis found that if cost per dose is assumed to be £39.29, (the highest estimate used, and used in the Forest economic model) at a maximum acceptable ICER of £30,000 per QALY gained then colistimethate sodium DPI had a 0% probability of being cost effective, and the probability that colistimethate sodium DPI was dominated was approximately 77%.

6.21 The Assessment Group stated that although there is considerable uncertainty surrounding the extrapolation of the COLO/DPI/02/06 trial data, this element of the model has virtually no bearing on the economic conclusions of the model, because colistimethate sodium DPI remains dominated when the price is set higher than that of nebulised tobramycin. The Assessment Group highlighted that the deterministic sensitivity analysis (performed on utilities, transition probabilities, utility decrement from exacerbation, cost of hospitalisation, point estimates for parameters) showed that the choice of utility value had the most significant effect on the cost-effectiveness estimate. The Assessment Group re-ran the analysis using a 24 week time horizon, that is 'within trial'; the results are shown in table 11. The results show an expected small decrease (0.002) in QALYs for colistimethate sodium DPI compared with nebulised tobramycin. If the price of colistimethate sodium DPI is higher than that of nebulised tobramycin the model shows an increased incremental cost and hence it is dominated by nebulised tobramycin. If priced at £9.11 per dose or £10.60 per dose, colistimethate sodium DPI is expected to be less expensive than nebulised tobramycin and results in ICERs of £276,814 and £49,596 per QALY gained respectively. Similar to the long-

term model these positive ICERs are the result of cost savings and QALY reductions.

Table 11 Results of the Assessment Group short-term probabilistic model

CDPI price	QALYs			Costs			ICER
	CDPI	TOBI neb	Inc.	CDPI	TOBI neb	Inc.	
£9.11	0.35	0.35	0.00	£3469.00	£4075.35	–£606.35	£276,814
£10.60	0.35	0.35	0.00	£3966.71	£4075.35	–£108.64	£49,596
£15.98	0.35	0.35	0.00	£5763.82	£4075.35	£1688.48	Dominated
£19.64	0.35	0.35	0.00	£6986.40	£4075.35	£2911.05	Dominated
£21.20	0.35	0.35	0.00	£7507.49	£4075.35	£3432.15	Dominated
£39.29	0.35	0.35	0.00	£13,550.21	£4075.35	£9474.86	Dominated
CDPI; colistimethate dry powder for inhalation, TOBI neb; tobramycin nebuliser solution, Inc; increment, ICER; incremental cost-effectiveness ratio, QALY; quality-adjusted life year.							

6.22 In the Assessment Report, the Assessment Group included a simple threshold analysis on tobramycin powder for inhalation. The results indicated that the incremental lifetime cost was £46,167.90 for tobramycin powder for inhalation compared with nebulised tobramycin and the QALYs required to achieve an ICER of £20,000 and £30,000 per QALY gained would be 2.31 and 1.54 respectively.

7 Additional analyses from the Assessment Group evaluating colistemethate sodium DPI compared with nebulised tobramycin.

7.1 The Assessment Group also undertook an additional analysis in response to the patient access scheme submitted by the manufacturer of colistimethate sodium DPI (see section 2.6). Only the price of colistimethate sodium DPI was amended and all other assumptions and parameters in the model remained unchanged.

7.2 The Assessment Group explained that when the list price is used, colistimethate sodium DPI is dominated by nebulised tobramycin. When the proposed PAS price of [redacted] for colistimethate sodium DPI incorporated into the analysis, the resulting ICER is £52,700 per QALY gained. This ICER lies on the South-West quadrant of the cost-effectiveness plane (less effective and less expensive). The cost-effectiveness results which include the PAS are summarised in table 12 below.

7.3 The analysis based on the short term "within trial" model (excluding the unobserved extrapolation period) found that that when the list price is used, colistimethate sodium DPI is dominated by nebulised tobramycin. When the proposed PAS price of [redacted] for colistimethate sodium DPI incorporated into the analysis, the resulting ICER is £113,664 per QALY gained. This ICER lies on the South-West quadrant of the cost-effectiveness plane (less effective and less expensive). The cost-effectiveness results which include the PAS are summarised in table13 below.

Table 12. Results of the Assessment Group reference case probabilistic model

Colistimethate price per dose	QALYs			Costs			ICER
	Coli DPI	Tobi neb	**Inc.**	Coli DPI	Tobi neb	**Inc.**	
Without PAS							
£17.30 per dose	9.48	9.61	**-0.13**	£167,982.95	£110,518.68	**£57,464.27**	**dominated**
With PAS							
[redacted]	9.48	9.61	**-0.13**	£103,592.27	£110,518.68	**-£6,929.41**	**£52,672**

Table 13. Results of the Assessment Group short term probabilistic model.

Colistimethate price per dose	QALYs			Costs			ICER
	Coli DPI	Tobi neb	**Inc.**	Coli DPI	Tobi neb	**Inc.**	
Without PAS							
£17.30 per dose	0.35	0.35	**-0.00**	£6,204.75	£4,075.35	**£2,129.40**	**dominated**
With PAS							
[redacted]	0.35	0.35	**-0.00**	£3,826.41	£4,075.35	**-£248.93**	**£113,644**

7.4 The Assessment Group also carried out probabilistic sensitivity analysis. The probability of colistimethate sodium DPI producing more net benefit than nebulised tobramycin without the inclusion of the PAS at a threshold of £20,000 and £30,000 per QALY was 0.00. The probability of colistimethate sodium DPI producing more net benefit than nebulised tobramycin with the PAS at a threshold of £20,000 per QALY was 0.79 and at a threshold of £30,000 per QALY was 0.66.

7.5 The Assessment Group also carried out an analysis using the price of nebulised tobramycin based on estimates from the Commercial Medicines Unit (CMU) Electronic Marketing Information Tool (E-MIT) rather than the BNF list price. In September 2012, the estimated average price of tobramycin paid by the NHS was £970.12. The Assessment Group pointed out colistimethate sodium DPI still produces fewer QALYs than nebulised tobramycin and the introduction of the proposed PAS does not change this situation. The results of this additional analysis suggest that based on the list price, colistimethate sodium DPI is dominated by nebulised tobramycin, and when the proposed PAS is incorporated into the analysis, colistimethate sodium DPI remains dominated.

8 Assessment Group comments on the additional analyses evaluating colistimethate sodium DPI compared with nebulised tobramycin.

8.1 The Assessment Group concluded that based on the list price, colistimethate sodium is expected to be dominated by nebulised tobramycin. When the proposed PAS is included in the analysis, the incremental cost-effectiveness of nebulised tobramycin versus colistimethate sodium DPI is expected be around £52,700 per QALY gained (i.e. colistimethate sodium DPI is less effective but also less expensive than nebulised tobramycin). However as this analysis includes a comparison only against nebulised tobramycin, the relative cost-effectiveness of colistimethate sodium DPI versus any other comparator is unclear.

9 Additional analyses from the Assessment Group evaluating tobramycin powder for inhalation compared with nebulised tobramycin

9.1 The Assessment Group produced an economic analysis in response to the patient access scheme submitted by the manufacturer of tobramycin powder for inhalation. This analysis used the Assessment Group de novo model (used for colistimethate DPI), but transition probabilities and exacerbation parameters were based on those observed in the EAGER trial. The Assessment Group explained that the manufacturer had provided individual patient-level FEV_1% data together with aggregated data on exacerbations from the EAGER trial, in conjunction with the PAS, and this data had been previously unavailable to the Assessment Group. All other base-case assumptions in the model remained unchanged (See section 6.15 above) (including that both

the intervention and comparator are used for 28 days at 8 capsules per day followed by 28 days without use of the drug, in line with the marketing authorisations).

9.2 The Assessment Group undertook three analyses: 1) Pre-dose FEV_1% at week 0 to FEV_1% at week 24; 2) Pre-dose FEV_1% at week 0 to pre-dose FEV_1% at week 20; 3) Post-dose FEV_1% at week 0 to post dose FEV_1% at week 20. The Assessment Group explained that it was uncertain which of these analyses should be considered the most reliable due to the effect of tobramycin on FEV_1% immediately after administration. The Assessment Group stated that the analysis 'Pre-dose FEV_1% at week 0 to FEV_1% at week 24 (analysis number 1)' was the most appropriate and should be considered to be the base case analysis. The cost-effectiveness results which include the PAS are summarised in tables 14 and 15 below.

Table 14 Results of the Assessment Group reference case probabilistic model

Scenario	QALYs			Costs			ICER
	Tobi DPI	Tobi neb	Inc.	Tobi DPI	Tobi neb	Inc.	
Without PAS							
Pre-dose wk0-24	8.73	8.38	**0.34**	£136,965.02	£94,511.82	**£42,453.20**	**£123,563**
Pre-dose wk0-20	8.72	8.52	**0.19**	£136,912.19	£94,761.35	**£42,150.84**	**£218,158**
Post-dose wk0-20	8.62	8.58	**0.04**	£136,695.90	£94,852.38	**£41,843.53**	**£1,005,476**
With PAS							
Pre-dose wk0-24	8.73	8.38	**0.34**	£75,237.19	£94,511.82	**-£19,274.63**	**Dominating**
Pre-dose wk0-20	8.72	8.52	**0.19**	£75,208.17	£94,761.35	**-£19,553.18**	**Dominating**
Post-dose wk0-20	8.62	8.58	**0.04**	£75,089.36	£94,852.38	**-£19,763.01**	**Dominating**

Table 15 Results of the Assessment Group short term probabilistic model

Scenario	QALYs			Costs			ICER
	Tobi DPI	Tobi neb	Inc.	Tobi DPI	Tobi neb	Inc.	
Without PAS							
Pre-dose wk0-24	0.36	0.35	**0.00**	£5,696.47	£3,956.13	**£1,740.35**	**£375,998**
Pre-dose wk0-20	0.36	0.35	**0.00**	£5,696.43	£3,956.22	**£1,740.22**	**£481,987**
Post-dose wk0-20	0.36	0.35	**0.00**	£5,696.15	£3,956.28	**£1,739.87**	**£2,800,138**
With PAS							
Pre-dose wk0-24	0.36	0.35	**0.00**	£3,129.22	£3,956.13	**-£826.91**	**Dominating**
Pre-dose wk0-20	0.36	0.35	**0.00**	£3,129.20	£3,956.22	**-£827.02**	**Dominating**
Post-dose wk0-20	0.36	0.35	**0.00**	£3,129.04	£3,956.28	**-£827.24**	**Dominating**

9.3 The Assessment Group also undertook a one way sensitivity analysis on the following parameters: deterministic point estimates of parameters on utility values, transition probabilities, utility decrement for exacerbations and costs of hospitalisation These analyses indicated that tobramycin DPI dominated nebulised tobramycin when the patient access scheme was included except for:

- When the EQ5D values from Stahl et al (BTS criteria) were used the resulting ICER for pre-dose week 0-20 was £2,604,059 per QALY gained. (less cost and fewer QALYs).

- When the EQ5D values from Stahl et al (BTS criteria) were used the resulting ICER for post-dose week 0-20 was £9,171, 576 per QALY gained (less cost and fewer QALYs).

- When the transition probabilities for nebulised tobramycin were set as equal to tobramycin DPI the ICERs for pre-dose week 0-24, pre-dose week 0-20 and post dose week 0-20 were £9,943,642 per QALY gained (less cost and fewer QALYs).

9.4 The assessment group also carried out probabilistic sensitivity analysis. The probability of tobramycin DPI being producing more net benefit than nebulised tobramycin (without the inclusion of the PAS) at a threshold of £20,000 and £30,000 per QALY was 0.00 for all of the three analyses undertaken The probability of tobramycin DPI producing more net benefit than nebulised tobramycin (with the inclusion of the PAS) at a threshold of £20,000 and £30,000 per QALY was 1.00 for all of the three analyses undertaken.

9.5 The Assessment Group also carried out an additional analysis using the price of nebulised tobramycin based on estimates from the Commercial Medicines Unit (CMU) Electronic Marketing Information Tool (E-MIT). In September 2012, the estimated price of tobramycin (nebulised) paid by the NHS was £970.12. These results indicated that with the introduction of the proposed PAS tobramycin DPI consistently dominated nebulised tobramycin irrespective of which FEV_1 data are used.

10 Assessment Group comments on the additional analyses evaluating tobramycin powder for inhalation compared with nebulised tobramycin

10.1 The Assessment Group concluded that the introduction of the PAS could be expected to result in tobramycin DPI consistently dominating nebulised tobramycin irrespective of which FEV_1% data is used. However the Assessment Group pointed out the following uncertainties remained:

- Owing to absence of sufficient evidence relating to any other comparator, the economic analysis of tobramycin DPI is restricted solely to an economic comparison against nebulised tobramycin.

- Data on minor and major exacerbations was not collected in the EAGER trial. The Assessment group explained that lung disorder may represent a reasonable proxy for pulmonary or cystic fibrosis exacerbations and, hence these data were used to estimate the probability of any exacerbation (minor or major) in each treatment group. The mean probability of exacerbation for tobramycin DPI was estimated to be 0.34 and the mean probability of exacerbation with nebulised tobramycin was 0.30. The manufacturer provided trial data estimates of the number of patients receiving any new antibiotic, total days used, and the number of patients who required both additional antibiotic treatment and hospitalisation in each treatment group. The estimates of the number of patients who required both additional antibiotic treatment and hospitalisation, combined with the estimated number of exacerbation events from Konstan et al, were used to produce an estimate of the pooled probability that an exacerbation event was major. The analysis produced an estate of the mean probability that an exacerbation was

major (pooled across both intervention groups) of [redacted]. The Assessment Group explained that this estimate is very similar to that derived from the COLO/DPI/02/06 trial but the validity of this estimate remains questionable.

- Much of the incremental benefit is driven by the small QALY gains observed within the trial period which are inflated considerably by extrapolating over the patient's remaining lifetime. Over the patient's lifetime this incremental QALY gain is expected to range from 0.04 QALYs (post-dose 0-20 weeks) to 0.34 QALYs (pre-dose 0-24 weeks)

11 Equalities issues

11.1 Consultees raised the issue that some people may have difficulties manipulating an inhaler device, putting a nebuliser together and cleaning the equipment. Therefore the scope specifies that consideration will be given to people who may have difficulties using inhaler devices. No additional equalities issues were identified in the evidence submitted.

12 Innovation

12.1 Both colistimethate sodium DPI and tobramycin powder for inhalation have the potential for faster and easier administration compared with current technologies (nebulised antibiotics). Hand-held inhalers need minimal set up and cleaning and may have a lower risk of bacterial contamination compared with nebulisers. Increased portability and ease of administration could reduce treatment times by 30 minutes and may increase adherence to treatment. Clinical specialists noted that inhalers for treatment of chronic *Ps. aeruginosa* infection

may go some way towards normalising one element of cystic fibrosis management.

13 Authors

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Appendix A: Supporting evidence

Related NICE guidance

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

Mannitol dry powder for inhalation for the treatment of cystic fibrosis.

Expected date of publication October 2012.

Appendix B: Estimates of the annual cost of anti-Pseudomonal drugs for cystic fibrosis.

Drug	Dosing regimen	Cost per dose	Annual cost (excluding VAT)	Source price
Colistiumethate sodium nebuliser	Twice daily 1-2 million units	£1.68 million unit vial	£1,226.40 (1 million unit dose) £2, 452.80 (2 million unit dose)	BNF BNF
Colistimethate sodium DPI	Twice daily 1 million unit vial	£17.30	£12, 629.00 [redacted]	List price PAS
TOBI nebuliser	Twice daily 300mg 4 weeks on 4 weeks off	£21.20	£7, 738.00 £6,323.10	BNF CMU
TOBI DPI (includes podhaler device cost)	Twice daily 300mg 4 weeks on 4 weeks off	£31.96	£11,675.00 [redacted]	BNF PAS
Colomycin	Twice daily 1-2 million units	£1.68	£613.20	BNF
Cayston	Three times daily 75mg	£30.55	£16,72808	BNF

	4 weeks on 4 weeks off			
Bramitob	Twice daily 300mg 4 weeks on 4 weeks off	£21.20	£7,736.70	BNF
Promixin	Twice daily 1-2 million units	£4.60	£1,679	BNF