10 October 2011
EMA/913717/2011
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Colobreathe

colistimethate sodium (rinn)

Procedure No.: EMEA/H/C/001225

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ACI	Andersen cascade impactor
ADME	Absorption, distribution, metabolism, elimination
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
API	Active Pharmaceutical Ingredient
AR	Assessment report
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BMI	Body mass index
BSAC	British Society for Antimicrobial Therapy
BUN	Blood urea nitrogen
C	Colistin
cAMP	Cyclic adenosine monophosphate
CEP	Certificate of Suitability
CF	Cystic fibrosis
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
CFQ	CFQ – Cystic Fibrosis Questionnaire
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFTR	Cystic fibrosis transmembrane regulator protein
CI	Confidence interval
CM	Colistimethate sodium
CMIP	Colistimethate sodium inhalation powder
CNS	Central nervous system
CRF	Case Report Form
CS	Colistin sulphate
CVMP	Committee for Veterinary Medicinal Products
DD	Delivered Dose
DDU	Delivered Dose Uniformity
DPI	Dry powder inhaler

EMA	European Medicines Agency
EU	European Union
F	female
FEF25-75	Forced expiratory flow between 25% and 75% of the FVC
FEV1	Forced expiratory volume in one second
FVC	Forced vital capacity
FPD	Fine Particle Dose
FPM	Fine Particle Mass
GC	Gas Chromatography
GCP	Good Clinical Practice
GI	Gastrointestinal
HPLC	High Performance Liquid Chromatography
IgG	Immunoglobulin G
IL	Interleukin
ITT	Intention to treat
IU	International Units
IR	Infrared Spectroscopy
i.v.	Intravenous
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LOD	Limit of Detection
LOQ	Limit of Quantitation
LOCF	Last observation carried forward
LPS	Lipopolysaccharide
LPM	Litres per minute
M	Male
MAA	Marketing Authorisation Application
MIC	Minimum inhibitory concentration
MIC50	Minimum inhibitory concentration which inhibits 50% of isolates
MIC90	Minimum inhibitory concentration which inhibits 90% of isolates
MDI	Metered dose inhaler
MMAD	Mass median aerodynamic diameter
MSLI	Multi stage liquid impinger
NE	Neutrophil elastase

NOAEL	No observable adverse effect level
PA	Pseudomonas aeruginosa
PDCO	Paediatric Committee
PEFR	Peak expiratory flow rate
PP	Per protocol
QoL	Quality of Life
QOS	Quality Overall Summary
QP	Qualified Person
Ph.Eur.	European Pharmacopoeia
PSD	Particle Size Distribution
RH	Relative humidity
RMS	Reference Member State
SAE	Serious adverse event
sGaw	Specific airways conductance measurements
SmPC	Summary of Product Characteristics
TEAE	Treatment emergent adverse event
TNSFI	Tobramycin nebuliser solution for inhalation
TOBI	Trade name for tobramycin nebuliser solution for inhalation
UK	United Kingdom

1 Background information on the procedure

1.1 Submission of the dossier

The applicant Forest Laboratories UK Ltd. submitted on 4 September 2009 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Colobreathe, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 October 2007.

Colobreathe was designated as an orphan medicinal product EU/3/02/088 on 19 February 2002 in the following indication:

> Treatment of *Pseudomonas aeruginosa* lung infection (including colonisation) in cystic fibrosis

The calculated prevalence of this condition at time of designation was 1.26 per 10,000 EU population. A revised estimate of prevalence of CF with associated P. aeruginosa lung infection was stated to be 0.45 per 10,000 persons, supported by more recent literature.

Following the CHMP positive opinion and at the time of the review of the orphan designation by the Committee on Orphan Medicinal Products (COMP), this product was withdrawn from the Community Register of designated orphan medicinal products on 12 October 2011 on request of the sponsor.

The applicant applied for the following indication:

> The treatment of *Pseudomonas aeruginosa* pulmonary infection in patients aged 6 years and over with cystic fibrosis.

The legal basis for this application refers to:

A - Centralised / Article 8(3)

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision (P/32/2010) on the agreement of a paediatric investigation plan (PIP) and the granting of a product-specific waiver.

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

The PDCO issued an opinion on compliance.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application contained a critical report addressing the possible similarity with authorised orphan medicinal products

Derogation from Market Exclusivity

Not applicable.

Protocol Assistance

The applicant received Protocol Assistance from the CHMP on 30 April 2002, 23 June 2003 and 15 March 2005. The Protocol Assistance pertained to clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2 Manufacturers

Manufacturer responsible for batch release

Penn Pharmaceutical Services Ltd.
23-24 Tafarnaubach Industrial Estate
Tredegar, Gwent NP2 3AA
United Kingdom

The inspection of the above manufacturing site was carried out by the relevant Competent Authority. The findings of the inspection are in compliance with the EU Good Manufacturing Practice requirements.

1.3 Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Ian Hudson Co-Rapporteur Piotr Fiedor

- The application was received by the EMA on 4 September 2009.
- The procedure started on 26 May 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 August 2010. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 23 August 2010.
- During the meeting on 20-23 September 2010, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 September 2010.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 March 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 27 April 2011.
- During the CHMP meeting on 16-19 May 2011, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant. The final List of Outstanding Issues was sent to the applicant on 1 June 2011.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 19 August 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP members on 5 September 2011.
- During the meeting on 19-22 September 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Colobreathe on 22 September 2011.
- The CHMP adopted a report on similarity of Colobreathe with Cayston and TOBI Podhaler on 5 October 2011.
- The CHMP issued a revised positive opinion for granting a Marketing Authorisation to Colobreathe on 10 October 2011.

2 Scientific discussion

2.1 Introduction

Patients with Cystic Fibrosis (CF) have viscous mucus in the lungs that, in time, becomes colonised with various bacteria and eventually with *Pseudomonas aeruginosa*. This leads to further lung damage and ultimately contributes to premature death, often in association with other organ damage due to the systemic nature of the disease.

The very first acquisition of *Pseudomonas aeruginosa* occurs during infancy and early childhood but this is usually intermittent and sequential cultures can be negative for variable periods of time. As age increases cultures commonly become persistently positive for this pathogen and chronic infection is established, accompanied by a transition from non-mucoid to mucoid *P. aeruginosa*. In the first instance *Pseudomonas aeruginosa* attaches within the respiratory tract using pili and other adhesins to form microcolonies. Over time there is formation of mature biofilms consisting of a community of bacteria embedded within an extracellular matrix. In these biofilm environments the bacteria communicate with each other by quorum sensing and are physiologically resistant to conventional antibacterial agents.

Antibacterial agents can be used during early infection in efforts to temporarily eradicate pathogens. They are also used to treat pulmonary exacerbations and for chronic suppression of bacterial numbers with the aim of improving lung function in the short term and slowing the decline in lung function in the longer term. In 1981 Hodson et al. showed that a combination of inhaled carbenicillin and gentamicin in selected patients with CF led to improvement in lung function and to a reduction in hospital admissions for intravenous treatment. Similar results were obtained from other studies (e.g. Wall et al., 1983; Mukhopadhyay et al., 1996; Littlewood et al., 1985).

Antibacterial agents that are active *in vitro* against *Pseudomonas aeruginosa* (including anti-pseudomonal beta-lactam agents, aminoglycosides and colistimethate sodium) are administered to CF patients via the parenteral route or by inhalation. Intravenous preparations (i.e. powders made up into small volume solutions and delivered by nebulisation) are often used to provide inhaled antibacterial therapy. For example, Colomycin powder for solution for injection or inhalation is made up in 2-4 mL solution (depending on the dose) to deliver colistimethate sodium by nebulisation. A concentrated solution of tobramycin (300 mg in 5 mL) formulated specifically for use in nebulisers (TOBI) is also available.

The administration of inhaled antibacterial agents by nebuliser may take more than 15-20 minutes depending on the minimum volume of solution that is possible, the viscosity of the preparation and the model of nebuliser and compressor used. In addition, nebuliser systems generally deliver no more than about 10% of the dose to the lungs. CF patients may need to take inhaled antibacterial therapy at least twice daily together with a range of other inhaled therapies such as bronchodilators and DNAse. The periods of time spent taking nebulised medications each day and the lack of portability of nebuliser systems (i.e. including a compressor) may have an adverse impact on quality of life.

In 1990, Goldman et al. showed that it is possible to deliver antibacterial agents by dry powder inhaler (DPI). The authors compared delivery of 160 mg gentamicin solution by nebuliser with 180 mg micronised gentamicin powder (30 mg per gelatine capsule) by Rotahaler DPI. Similar concentrations of gentamicin were found in bronchoalveolar lavage fluid with the different delivery systems. Many dry powder inhalers are of a multi-dose design intended for asthma therapy and are incapable of delivering high powder doses conveniently. Crowther Labiris et al. (1999) showed that effective quantities of

gentamicin could be delivered by a multi-dose DPI (Clickhaler, Innovata biomed) but this required administration of 32 doses (each dose 5 mg gentamicin) over 30 minutes. In the current application a novel unit-dose DPI - Turbospin DPI – has been used to deliver 125 mg (equivalent to 1,662,500 IU) colistimethate sodium per dose from gelatine capsules.

About the product

Polymyxins are a group of lipopeptide antibiotics isolated from the spore-forming soil bacterium *Bacillus polymyxa*. Five major, chemically distinct members of the group have been recognised and designated as polymyxin A, B, C, D and E. Polymyxin B and E have been in clinical use for more than 40-50 years.

Colistin is a naturally occurring multi-component polymyxin antibacterial agent produced by a selected strain of *Bacillus polymyxa var colistinus*. Composed mainly of polymyxin A (E1) and B (E2) it is often denoted simply as polymyxin E. It has the characteristic polymyxin structure that includes a cyclic heptapeptide joined to a tripeptide chain with a single fatty acid substituent. All the amino groups are subject to derivation. All groups are initially sulphomethylated but approximately two are hydrolysed to amino-methylol groups in aqueous solutions.

For parenteral and aerosol therapy colistin is used in the form of the sodium salt of the negatively-charged methane sulphonate derivative known as colistimethate sodium (also called colistin sulphomethate, colistin methanesulphonate or sulphopolymyxin E sulphomethate and abbreviated to CMS). Colistimethate sodium is not microbiologically active. It is hydrolysed to the active, positively charged colistin in solution and also after administration along with a complex mixture of partially sulphonated derivatives that also seem to possess variable antibacterial activity.

Colistimethate sodium is manufactured from colistin base by the action of formaldehyde and sodium bisulphite and has an approximate molecular weight of 1750.

It is very important to note that while colistimethate sodium is used for administration (including in Colobreathe, which includes the mass of 125 mg of active substance per dose) the definition of an international unit is biological and 1 IU of colistin is defined as the amount of colistin that inhibits the growth of *Escherichia coli* 95 I.S.M. in 1 ml broth at pH 7.2. Pure colistin base has been assigned a potency of 30,000 IU per mg, while colistimethate sodium has a potency of 12,500 IU per mg.

Polymyxins are cationic agents that are able to disrupt the hydrophobic outer membrane of susceptible aerobic Gram-negative bacteria. Colistin binds to the lipid A (endotoxin) moiety of lipopolysaccharides and to phospholipids in the outer membrane of Gram-negative bacteria. It inserts between adjacent molecules of lipopolysaccharide and displaces membrane stabilising magnesium ions. This causes the outer membrane to expand and distort so that the bacterium loses control over the influx and efflux of cations (e.g. potassium and sodium).

Disruption of the outer membrane also allows colistin molecules to penetrate through to and incorporate within the inner cytoplasmic membrane to result in increased permeability to small molecules. This increased permeability allows vital cellular constituents such as nucleic acids and proteins to leak out.

Due to its limited spectrum of activity, limited distribution in body compartments and adverse event profile colistin has never been widely used for parenteral therapy of bacterial infections. Parenteral administration is usually reserved for patients who cannot receive other antibacterial agents that might be suitable for the infection to be treated. For example, patients hypersensitive to numerous other agents and those infected with organisms that are resistant to all the preferred alternatives. The use of intravenous colistin has become relatively common in some EU hospitals due to the increasing number

of nosocomial infections caused by organisms that are resistant to all beta-lactam agents (including carbapenems), to aminoglycosides and to fluoroquinolones.

Nebulised colistin has become established since the 1980s as a treatment for patients with CF who are colonised with Pseudomonas aeruginosa. In this mode of use systemic absorption is said to be limited and few adverse events are reported other than airways irritation and hypersensitivity. However, the clinical data that support the safety and efficacy of the doses currently recommended were not collected systematically and clinical use has evolved over many years. The published studies were generally uncontrolled, were performed by a wide variety of investigators and have been reported to a variable standard of detail.

Colobreathe has been developed as a quicker, more convenient alternative to nebulised delivery of colistin. The aim was to increase the acceptability of dosing regimens and hence increase the adherence to therapy by patients. Colobreathe is presented as a hard gelatin capsule containing 125mg of colistimethate sodium for inhalation using the Turbospin device. There are no excipients.

The pharmacy and chemistry information relating to the drug substance has undergone a full assessment by the EDQM and the Certificate of Suitability demonstrates the compliance of colistimethate sodium used in this product with the monograph of the Ph. Eur. and Directive 2001/83/EC. The Turbospin device already carries a CE mark.

2.2 Quality aspects

2.2.1 Introduction

Colobreathe contains 1,662,500 IU colistimethate sodium as the active substance and is presented as an encapsulated powder for inhalation in gelatin hard transparent capsules. The capsules are packed in aluminium/aluminium blisters and supplied with a breath-actuated Turbospin® powder inhaler. The Turbospin® powder inhaler is an inspiratory flow driven dry powder inhaler made of medical grade polypropylene and is CE marked.

Colistin is a naturally occurring multi-component polymyxin antibacterial agent produced by a selected strain of Bacillus polymyxa var colistinus. Composed mainly of polymyxin A (E1) and B (E2) it is often denoted simply as polymyxin E. It has the characteristic polymyxin structure that includes a cyclic heptapeptide joined to a tripeptide chain with a single fatty acid substituent. All the amino groups are subject to derivation. All groups are initially sulphomethylated but approximately two are hydrolysed to amino-methylol groups in aqueous solutions.

For parenteral and aerosol therapy colistin is used in the form of the sodium salt of the negatively-charged methane sulphonate derivative known as colistimethate sodium (also called colistin sulphomethate, colistin methanesulphonate or sulphopolymyxin E sulphomethate and abbreviated to CMS). Colistimethate sodium is not microbiologically active. It is hydrolysed to the active, positively charged colistin in solution and also after administration along with a complex mixture of partially sulphonated derivatives.

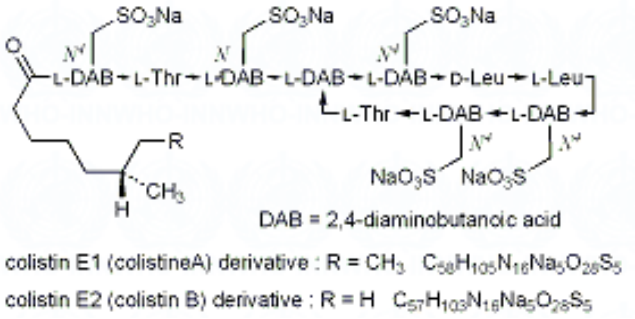
The full list of ingredients is defined in section 6.1 of the SPC.

2.2.2 Active Substance

Colistimethate sodium (INN) is a well known drug substance for which a Ph. Eur. Monograph exists. It is a white or almost white, odorless, hygroscopic powder, very soluble in water, slightly soluble in alcohol and practically insoluble in acetone and ether. The specific optical rotation of a 5% aqueous

solution of colistimethate sodium is -46° to -51° (Ph Eur). Colistimethate sodium is hygroscopic. The active substance exists as an amorphous form and there are no other polymorphic forms. The empirical formula is $C_{58}H_{105}N_{16}Na_5O_{28}S_5$ and the structural formula is represented below.

Figure 1:



colistin E1 (colistineA) derivative : R = CH_3 $C_{58}H_{105}N_{16}Na_5O_{28}S_5$

colistin E2 (colistin B) derivative : R = H $C_{57}H_{103}N_{16}Na_5O_{28}S_5$

Manufacture

Colistimethate sodium is manufactured from colistin base by the action of formaldehyde and sodium bisulphite and has an approximate molecular weight of 1750.

The manufacture of the active substance is covered by a Certificate of Suitability.

The particle size distribution is a physicochemical characteristic of relevance to the applied drug product. Full details of the micronisation process were provided. Micronisation is considered to be part-process manufacture and the GMP compliance of the manufacturer was confirmed.

Specification

The drug substance complies with the requirements of the European Pharmacopoeia monograph 0319 for colistimethate sodium and with the additional specification for particle size distribution. An additional test for heavy metals is added to the European Certificate of Suitability. The specification applied by the active substance manufacturer and the Applicant are satisfactory. Ph.Eur. methods are used, except the additional in-house analytical procedures for moisture content and particle size distribution. Validation data of the in-house test procedures have been provided.

Batch data of five batches were provided confirming the compliance with the specification and consistency of the manufacturing process.

Stability

The retest period of five years is stated on the Certificate of Suitability if the drug substance is stored in a container consisting of aluminium bottle with PE insert and PP or PE lid.

2.2.3 Finished Medicinal Product

Pharmaceutical Development

The product has been developed in accordance with the requirements of the relevant guideline EMEA/CHMP/QWP/49313/2005 Corr. *Guideline on the pharmaceutical quality of inhalation and nasal products*. Formulation development of this dry powder delivery system was conducted to produce a more convenient and effective alternative method of respiratory delivery of colistimethate sodium with the aim of delivering the equivalent respirable mass of antibiotic when compared to that delivered by the nebulised product.

In vitro formulation studies were carried out to determine the respirable mass of colistimethate sodium from a nebuliser. The capsule fill weight was therefore chosen in order to achieve a similar respirable mass based on the particulate size profile of the micronised powder. *In vivo* deposition study was then carried out. Data from an *in vivo* deposition study assessing total and regional deposition of colistimethate sodium delivered using Turbospin® powder inhaler and a nebuliser device in subjects with cystic fibrosis showed that lung deposition of colistimethate sodium was proportionately significantly higher when delivered with the Turbospin® powder inhaler than by a nebuliser. The 1,662,500 IU (125 mg) of colistimethate sodium given as a dry powder is therefore intended to deliver a dose to the lung at least equivalent to 2 million IU nebulised.

Adventitious agents

The gelatin used in the manufacture of the capsule is the subject of European Certificates of Suitability for TSE.

Manufacture of the product

The manufacturing process is a simple process which involves the filling of the hygroscopic micronized drug substance into hard gelatin capsules under controlled manufacturing conditions. The amount of colistimethate sodium used is calculated based on potency and moisture content. The in-process controls are considered to be appropriate and ensure compliance with the finish product specification.

The validation of the manufacturing process has been performed on commercial scale batches of Colobreathe 1,662,500 IU, inhalation powder, hard capsule. The results demonstrate that the manufacturing process is capable of consistently producing product that meets the finished specification.

Product specification

The specification complies with the Ph.Eur. requirements and ICH guidelines. The control of the product includes: identification, appearance of powder, appearance of capsule, moisture content of powder, potency, particle size distribution, fine particle mass, uniformity of delivered dose and microbiological purity. All test methods are satisfactorily described and validated.

Data from five batches show that the batches were consistently manufactured and comply with the proposed specification.

Stability of the product

Satisfactory stability data under ICH conditions have been provided to support the shelf life and storage conditions as defined in the SmPC, There were no changes in uniformity of delivered dose, fine particle mass and uniformity of mass. All samples complied with the stability specification for average content of colistimethate sodium and microbial testing.

Comparability Exercise for Finished Medicinal Drug Product

Not applicable

GMO

Not applicable

2.2.4 Discussion on chemical, pharmaceutical and biological aspects

The information on development, manufacture and control of the drug substance and drug product are acceptable.

2.2.5 Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.3 Non-clinical aspects

2.3.1 Introduction

The non-clinical dossier comprises published literature, much of which predates the establishment of Good Laboratory Practice (GLP). Therefore most of the studies will not be compliant with the principles of GLP, with the exception of some of the more recent genotoxicity studies that were reportedly GLP-compliant.

2.3.2 Pharmacology

Primary pharmacodynamic studies

Polymyxins are a group of lipopeptide antibiotics isolated from *Bacillus polymyxa*. They are selective cationic agents acting on Gram-negative bacteria by targeting the phospholipids in the bacterial cell membrane. Colistin, which is isolated from B polymyxa var. colistinus, consists of a mixture of several closely related decapeptides (polymyxin E) and has the characteristic polymyxin structure of a cyclic heptapeptide joined to a tripeptide chain with a single fatty acid substituent. The two main components are colistin A (polymyxin E1) and colistin B (polymyxin E2), which differ only in their fatty acid side chain.

Colistimethate sodium is hydrolysed to colistin, the positively charged active moiety, which has a two-step mode of action against Pseudomonas aeruginosa, the bacterium targeted in the produced indication. In the first step, colistin binds to the lipopolysaccharide component of the outer membrane of sensitive Gram-negative bacteria by interaction between the peptide ring of colistin and phosphate groups present on the lipid A and core region of lipopolysaccharide. This displaces magnesium ions from phosphate groups and results in distortion of the outer membrane structure and loss of the permeability barrier. Once the permeability barrier is lost, colistin penetrates the cell wall to the underlying cytoplasmic membrane target. The disorganisation of the outer membrane also alters the cell's permeability to various hydrophobic substances including antibiotics. Insertion of colistin molecules between the phospholipid and protein components of cell membranes results in loss of membrane integrity, leakage of cytoplasmic constituents and cell death.

The susceptibility of clinical isolates of Gram-negative bacteria to colistimethate sodium, colistin sulphate, colistin and other polymyxins has been reported in the literature. The Minimum Inhibitory Concentrations (MIC) are dependent upon what compound is tested and this is not always clear in the literature. Additional confusion arises from differences in expression of potency in IU. Some clinical isolates of *P. aeruginosa* have shown resistance to colistin. These issues are discussed further in the part dealing with "Clinical aspects".

Comparison of different forms of colistin in mice in vivo indicated that subcutaneous administration of colistimethate sodium is more effective than colistin sulphate or polymyxin B sulphate against infections with *K. pneumoniae*.

Secondary pharmacodynamic studies

Receptor screening studies have not been reported in the literature. However colistin is known to have an effect on nerve conduction and can cause bronchoconstriction when nebulised.

Safety pharmacology programme

Conventional safety pharmacology studies have not been conducted but relevant endpoints have been reported, and a general pharmacology screen was conducted by Japanese workers in the early 1970s.

In an early series of general pharmacology studies with colistimethate sodium, a neuromuscular blocking effect was seen at lethal doses in mice. Similar effects have been reported in other species. The neuromuscular blocking effect appears to result from inhibition of acetylcholine release from somatic nerve endings in skeletal muscle. Mutual potentiation of the muscular blocking effect between colistin and the muscle relaxant succinylcholine has been reported. The doses of colistimethate sodium causing paralysis of the respiratory muscles and death are much higher than those used clinically.

Colistimethate sodium did not have a local anaesthetic effect or mucous stimulating effect. There was no effect on intestine or uterus.

At high concentrations, solutions of colistimethate sodium depressed cardiac function measured in isolated rat atrial preparations, and induced vasodilatation in the blood vessels of isolated rabbit ear preparations. In vivo, there was no predictable effect on blood pressure or respiration in rabbits; variable changes in blood pressure were attributed to a potential histamine liberating effect.

Intravenous colistimethate sodium (up to 6.5mg/kg) had no effect on blood pressure in dogs, but colistin sulphate at 10-fold lower doses caused a drop in blood pressure. Clinically, effects on the cardiovascular system are not common.

Colistin is mainly excreted in the urine when given parenterally. Nephrotoxicity is a potential toxic effect of colistimethate sodium in humans and is generally associated with the use of higher than recommended doses in patients with normal renal function, failure to reduce dosage in patients with renal impairment, or concomitant use with other nephrotoxic medications. There was no effect on urinary output in rabbits nor on renal function in dogs treated intravenously with colistimethate sodium at doses up to 10 mg/kg or 40mg/kg, respectively. However in another study, renal function was depressed in one of two dogs given colistimethate sodium at 2.2mg base/kg/6h (8.8mg base/kg/day). There was also evidence of drug accumulation at this dosage. Lower doses had no effect. In other studies, repeated doses of polymyxins in rabbits and dogs showed no increase in proteinuria with polymyxin E, whereas other polymyxins produced various degrees of proteinuria in dogs.

The effects on nervous and renal systems have been well documented over the years of clinical use of colistin. Exposures expected from inhalation of colistimethate sodium are likely to be much lower than those achieved in the animal studies and therefore the risk of these known effects is minimised.

Pharmacodynamic drug interactions

The possible interactions resulting from co-administration of drugs acting on the nervous system or those with nephrotoxic effects are covered in the proposed SmPC.

2.3.3 Pharmacokinetics

No animal studies on the inhalation of colistimethate sodium have been identified in the literature. When colistimethate sodium is administered to humans using a dry powder inhaler, the potential systemic exposure is either by absorption directly into the pulmonary circulation or gastrointestinal absorption following ingestion of oropharyngeal deposition and drug particulates removed from the lung by its mucociliary transport system. Therefore pharmacokinetic investigations in laboratory animals following parenteral or oral administration provide data that are relevant to inhalation exposure.

The early studies used bioassays to determine colistin levels in various matrices and were limited to measuring pharmacologically active forms of the compound. Subsequent studies have employed high-performance liquid chromatography (HPLC) methods that are more discriminatory. In many of the studies it is not clear what is being measured.

Absorption

Oral administration of colistimethate sodium or colistin sulphate to rats, rabbits, dogs, pigs and cows has resulted in little or no absorption into the systemic circulation. However, appreciable absorption from the gastrointestinal (GI) tract of colistimethate sodium may occur in humans with disturbed or damaged gut mucosa; limited absorption of colistin from the GI tract has been reported in newborn animals and in children less than six months of age, in which the gut is more permeable.

Parenteral administration of colistin sulphate or colistimethate sodium to rats, rabbits and dogs has produced measurable levels of drug-related material in the plasma, although in the older studies it is not clear what is being measured and pharmacokinetic parameters have usually not been calculated.

In more recent studies in which free colistin and colistimethate moieties could be distinguished using an HPLC method, the plasma half-life of colistin was significantly longer than that of colistimethate following IV administration of colistimethate sodium to rats (55.7 and 23.6 minutes, respectively) and to cystic fibrosis patients (251 minutes and 124 minutes, respectively).

The longer plasma half-life of colistin compared with colistimethate sodium suggests that its disposition after colistimethate sodium administration is rate-limited by its elimination and not by its formation from the hydrolysis of colistimethate sodium.

The plasma drug concentration in rabbits and dogs receiving a single IM dose of colistimethate sodium was higher and disappeared faster than the plasma drug concentration after a single IM dose of colistin sulphate. Higher plasma concentrations are also achieved in humans following IM administration of colistimethate compared with IM administration of colistin sulphate.

Higher serum drug concentrations and faster elimination were noted in rats following an IV dose compared with an IM dose of colistimethate. Similar patterns have been reported for rabbits, dogs and humans. In infants aged 4 to 51 days, mean serum half-life after a single IM dose of colistin (unspecified salt) was about 2.5 hours, which was only slightly shorter than that reported for adults (3.0 hours).

Distribution

In vitro binding of colistimethate to dog plasma proteins was substantially less than that for colistin sulphate, with the latter showing concentration-dependence (decreased binding with increasing concentration).

Tissue binding of colistimethate sodium following single intravenous doses of 10 or 30mg/kg to rats showed highest serum and tissue drug concentrations at 0.5 hours (the first sampling time), except for

the contents of the small intestine, which peaked at 1 hour post-dose. No drug was evident in the brain at any time. Tissue concentrations equal to, or above, serum levels were recorded for the kidney, small intestine and the small intestine contents, reflecting the presumed routes of elimination.

Neither polymyxin B sulphate nor colistimethate sodium accumulated in the serum following daily IM administration (2.5mg/kg/day) of the compounds to rabbits for 7 days, but both free and bound polymyxin B persisted in liver, kidney, muscle and brain for 5 days following dosing.

For colistimethate, bound drug concentrations increased in all tissues apart from serum with time, the highest concentrations being detected in the liver and muscle and the lowest concentration in the brain. Bound drug was lost most rapidly from the kidney over the 5-day period after the last dose, but tended to persist longer in the brain than other tissues. Free colistimethate was not found in the brain or lung 24 hours after each administration, but free colistimethate in kidney, liver and muscle declined slowly and was present (>5µg/g, stated to be therapeutic concentrations) for up to four days after the last dose.

In rabbits, colistimethate appears to be incompletely converted to colistin *in vivo*.

Bound colistimethate appeared to reach saturation in rabbit brain, muscle and heart following twice daily dosing of colistimethate sodium for 7 days, with less evidence of saturation in the kidney and lung. Free colistimethate was not detected in the brain or lung, and levels in the heart, kidney, muscle and liver were low.

Tissue binding appears to be the main determinant of the distribution and persistence of colistimethate within the body.

In humans, polymyxins have been reported to persist in the liver, kidney, brain, heart and muscle, with colistimethate binding to a greater extent than polymyxin B to the kidney, lung and liver. The pattern is reversed in the brain and penetration into the CSF in humans is reportedly unpredictable and usually negligible.

No animal studies investigating placental transfer were located in the literature, but colistimethate sodium administered as a single intravenous dose to pregnant human volunteers in labour demonstrate that the drug crosses the placenta, with levels higher than those in maternal serum by 8 hours post-dose.

Intramuscular administration of colistin (unknown form) to cattle and sheep has demonstrated the presence of the drug in milk. Clinical studies have reportedly shown that colistin is secreted into human milk following administration of colistimethate sodium.

Metabolism

Colistimethate appears to undergo limited metabolism. It undergoes hydrolysis to colistin base in vitro and in vivo.

In rabbits, colistin-N-glucuronide was detected following a single IV dose of colistimethate sodium, which accounted for 1.7 and 6.7% of the drug in the urine and bile, respectively, in the 24 hours after administration.

Measurement of the D-leucine content of colistin in dog urine by gas chromatography following IM administration of colistin sulphate indicated that a significantly greater proportion of the dose was present in the urine than was detected by bioassay. This suggests the presence of an (unidentified) inactive metabolite or metabolites.

Excretion

Following oral administration to laboratory animals and humans, colistimethate sodium was excreted in the faeces, mainly in a 'bound' form.

The urine is the major route of excretion following parenteral administration of colistimethate sodium in rats, rabbits, dogs and humans.

In rats, over 60% of an IV dose of colistimethate sodium was recovered in urine during the first 24 hours, the majority of that occurring in the first 12 hours. In rabbits, 74% of a dose was recovered in the urine, with a small proportion (0.12%) recovered in the bile within 24 hours. A similar pattern of urinary excretion was evident in humans (children and adults) but no biliary excretion has been reported in humans.

Glomerular filtration appears to be the main elimination process in dogs and humans. The dosage may require adjustment in patients with renal dysfunction.

Pharmacokinetic drug interactions

No pharmacokinetic drug interaction studies were identified in the literature. Given the limited protein binding and lack of metabolism of colistin, pharmacokinetic interactions resulting from displacement of drug from plasma proteins or inhibition of drug-metabolising enzymes is not considered likely.

Clinical experience with colistimethate sodium and concomitant administration with other drugs commonly used in the treatment of cystic fibrosis has not provided evidence of pharmacokinetic interactions.

Concomitant use of colistimethate with non-depolarising muscle relaxants and medications that are nephrotoxic or neurotoxic should be undertaken with care, as the effects may be potentiated. It is stated in the non-clinical summary that polymyxins may possibly reduce the contraceptive effect of oestrogen but that the risk is probably small. The source of this information was unclear, and the published literature has been further discussed. Some antibiotics decrease the efficacy of oral contraceptives by induction of liver enzymes, whilst others do so by affecting gut bacteria. In general, the failure of oral contraception when taken concomitantly with most antibiotics occurs at a low rate and is similar to the rate of failure without concomitant antibiotics. There are no documented reports of interactions between polymyxins, colistin or colistimethate sodium and oral contraceptives, progesterone or oestrogen; therefore it is not necessary to include a warning in the SmPC.

Nevertheless, the applicant has now conducted a study to verify whether or not colistimethate sodium has the potential to induce liver enzymes. The study showed that concentrations up to 3500 ng/mL of colistin or up to 10500 ng/mL of colistimethate sodium did not induce the activity of CYP enzymes (CYP1A2, 2B6, 2C8, 2C9, 2C19 and 3A4/5) in cultured human hepatocytes. Appropriate prototypical inducers were included as positive controls and ensured the validity of the study. Therefore this in vitro study confirmed that colistin and colistimethate sodium are not inducers of these CYP enzymes. Section 4.5 of the SmPC has been amended to include this information.

2.3.4 Toxicology

Single dose toxicity

Single dose toxicity studies were conducted over 35 years ago and were lethal dose tests. From the LD50 values reported in the literature, colistimethate sodium appears to be more acutely toxic to rats than to mice, but less acutely toxic in both species than colistin sulphate. However, colistimethate sodium shows a low order of acute toxicity, irrespective of the route of administration. Inhalation studies have not been reported. Lethal doses of colistin compounds caused muscular incoordination,

respiratory distress and occasionally strychnine-like convulsions in mice. Paralysis of the respiratory muscles has been attributed to neuromuscular blockade.

Repeat dose toxicity

Inhalation toxicity studies have not been conducted with colistimethate sodium. Studies have been reported using oral and parenteral administration of colistimethate sodium, colistin sulphate and other polymyxins. As was seen in acute toxicity studies, colistin appears to be more toxic to rats than mice on repeated dosing, and colistimethate less toxic than colistin sulphate. In an early study, colistimethate sodium at 35.5mg/kg given twice daily (IM or IP) was lethal to rats. Findings included necrosis of the stomach mucosa and the proximal convoluted tubules in the kidneys.

In more recent studies in rats and mice following repeated IP dosing for at least 30 days, toxic effects included deaths, decreases in spontaneous activity, convulsions and alterations in haematological (haemoglobin, haematocrit, red blood cell count) and clinical chemistry (alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, albumin to globulin ratio) parameters.

One reference noted "reactive symptoms" in liver, spleen and kidney in mice and in liver of rats, with hyperaemia noted in rat spleen. Unspecified histopathological changes in the kidney, liver and spleen were also reported following IP administration of colistimethate sodium to rats for 6 months.

An early subcutaneous dog study in which colistin sulphate was administered at 10000 or 20000U/kg three times daily for 21 days identified renal changes that were considered to be reversible.

The findings confirm those reported in the safety pharmacology section.

Genotoxicity

In vitro and *in vivo* genotoxicity studies have been reported in the literature, most of which were conducted prior to the introduction of GLP standards. According to a report by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 2006, there were three studies (reverse mutation in S typhimurium strains, forward mutation in V79 Chinese hamster cells and an *in vivo* mouse micronucleus test) that were reported in 1992 and stated to be GLP-compliant. These GLP-compliant studies were negative, as were the majority of the other published studies. One study was equivocal and another, an investigation of chromosome damage in human lymphocytes, was positive, although the methodology used in the latter study was questioned. On balance, the published literature suggests that 'colistin' (colistin sulphate or other unspecified salt) is not genotoxic.

Carcinogenicity

Colistin sulphate and colistimethate sodium have been in use for decades in both human and veterinary medicine, without any reports of potential carcinogenic effects being published. Although no formal carcinogenicity studies have been conducted, colistimethate sodium does not appear to have any structural alerts, and the largely negative genotoxicity studies support the conclusion that the compound is unlikely to have carcinogenic potential.

Reproduction Toxicity

A full range of reproductive toxicology studies has been reported in the literature. The studies were published in 1981 in Japanese, with English tables and translation of the abstracts and are stated to be conducted according to pre-ICH Japanese guidelines. The studies comprise male and female fertility in mice and rats; embryofetal development in mice, rats and rabbits, and peri- and postnatal

development in rats. Thus the range of studies conducted is appropriate. However, toxicokinetic analyses were not carried out.

There were no notable effects on fertility or general reproductive performance in rats or mice. In embryo-fetal development studies in mice, resorptions and reduced ossification were seen, and in rats, reduced fetal weights, reduced ossification and at the high dose of 10mg colistin base/day, reduced post natal survival. No effects were reported in rabbits at IV doses of 80mg/kg colistimethate sodium (32mg colistin base/kg). The US labelling mentions a single report of talipes varus in rabbits given intramuscular colistimethate sodium (4.15 or 9.3mg/kg), which was apparently not clearly dose-related and was not seen in the Japanese study at higher doses.

There were no effects on prenatal or postnatal development or on maternal function in rats. Colistin has been shown to pass into milk in cattle, sheep and humans.

Toxicokinetic data

Most of the studies reviewed were carried out in the period 1960-1984 and toxicokinetic analysis is not mentioned. These studies also predated the publication of a reliable HPLC method for the separate determination of colistimethate species and free colistin; previously, biological activity of colistin was assayed. Consequently, comparative systemic exposure levels cannot be provided. The applicant discussed the absence of toxicokinetic data in the context of quality and clinical objections raised on the assay, disposition in the lung and systemic exposure. The applicant proposes to conduct a study in adults and children with cystic fibrosis to obtain PK data to establish the extent of any systemic exposure in the relevant patient population. A non-clinical study to investigate toxicokinetics and lung deposition following inhalation of colistimethate sodium is therefore not considered necessary.

Other toxicity studies

No other toxicity studies have been conducted or reported in the literature

2.3.5 Ecotoxicity/environmental risk assessment

An acceptable justification has been provided for the absence of an environmental risk assessment. Colobreathe is intended as an alternative to the current use of nebulised colistimethate. The introduction of the product will therefore not increase the environmental exposure to colistimethate.

2.3.6 Discussion on non-clinical aspects

Polymyxins are a group of lipopeptide antibiotics isolated from *Bacillus polymyxa*. They are selective cationic agents acting on Gram-negative bacteria by targeting the phospholipids in the bacterial cell membrane.

Nonclinical data reveal no special hazard for humans based on conventional studies of genotoxicity. Animal studies of safety pharmacology, repeated dose toxicity or toxicity to reproduction, employing routes assuring systemic exposure, showed no particular hazard. There were no notable effects on fertility or general reproductive performance in male or female rats or mice. In embryo-fetal development studies in mice, resorptions and reduced ossification were seen, and in rats reduced fetal weights, reduced ossification and at the high dose of 10 mg colistin base per day, reduced post-natal survival. An embryo-fetal study in rabbits reported no effects at intravenous doses up to 80 mg/kg colistimethate sodium (32 mg colistin base/kg).

2.3.7 Conclusion on the non-clinical aspects

The non-clinical aspects of colistimethate sodium have been properly addressed. Data do not reveal special hazards to humans. However, as caveat, colistin is known to have an effect on nerve conduction and can cause bronchoconstriction when nebulised.

2.4 Clinical aspects

2.4.1 Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

A GCP inspection related to the single pivotal study was requested by CHMP to support the validity of the clinical data provided. Two study sites in Poland and a CRO in the UK were inspected. The conduct of the trial was considered to be generally GCP compliant in both clinical sites in Poland. It was the opinion of the inspectors that the data recorded and reported by both of the inspected sites were trustworthy and reliable. There was one finding during the inspection of the CRO that was graded as major/critical. The critical finding pertained to the finding that the processes for assigning patients to ITT and PP datasets were inconsistent. The applicant has adequately addressed the observations made during the inspection and CHMP does not consider that the data are a cause of concern.

- Tabular overview of clinical studies

The clinical development programme for Colobreathe is based on five clinical studies tabulated below:

Table 1: Study overview

Study no.	Study Title	Duration of treatment and dose	No. of Patients	Study design
COLO/DPI/98/01	An open label study to compare tolerance and bronchial response to nebulised colistin and colistin dry powder inhalation in healthy, mildly asthmatic and cystic fibrosis volunteers.	Three study days 2-7 days apart: Day 1: Colistin solution for injection (80mg; 1 million IU) nebulised over 10 minutes; Day 2: Inhaled salbutamol (200µg) and micronised colistin (125mg); Day 3: Inhaled micronised colistin (125mg).	12	Open label, single dose
COLO/DPI/98/02	A randomised, open label study to compare tolerability and bronchial response to nebulised colistin and colistin dry powder inhalation in volunteers with cystic fibrosis.	Four study days 2-7 days apart: Treatment A: Colistin solution for injection (80mg; 1 million IU) nebulised over 10 minutes; Treatment B: Micronised lactose (125mg); Treatment C: Inhaled salbutamol (200µg) and micronised colistin (125mg); Treatment D: Inhaled micronised colistin (125mg).	12	Open label, randomised, four segment, single dose, cross-over
PPL-252	Assessing total and regional lung deposition of colistimethate sodium delivered using a dry powder inhaler and a nebuliser device in volunteers with cystic fibrosis – a pilot study.	The CF patients were randomised to receive a single dose of one of three treatments on separate study days, radiolabelled with 99mTc as follows: Regimen A: Inhalation of 1 million IU (80mg) of Colomycin® Injection, using a Medic-Aid Ventstream® nebuliser with a standard flow rate of more than 8L/min, producing an estimated 80% of the aerosol mass in droplets of less than 5µm diameter. Inhalation continued until the chamber reached at least the minimum volume (approximately 0.5-0.75mL) or until the chamber was dry. Regimen B: Inhalation of 200µg salbutamol from a pressurised MDI device with a spacer attached followed 10 minutes later by inhalation of 125mg colistimethate sodium, from a gelatin capsule size 2, using the Turbospin® DPI device. Regimen C: Inhalation of 125mg colistimethate sodium, from a gelatin capsule size 2, using the Turbospin® DPI device.	12	randomised open-label, three-way crossover study.
COLO/DPI/02/05	A randomised, open label, cross over study to compare the safety of a dry powder formulation of inhaled colistimethate sodium and nebulised colistimethate sodium in child and adult cystic fibrosis patients with *Pseudomonas aeruginosa* lung infection.	Four weeks per treatment (72h wash-out period in-between). Treatment A: Colistimethate sodium DPI (125mg , b.d.) Treatment B: Colistimethate sodium solution for injection nebulised (2 million IU, b.d.).	16	Open label, randomised, multiple dose, cross-over
COLO/DPI/02/06	A randomised, open label study to compare the efficacy and safety of	24 weeks. Treatment A: Colistimethate sodium DPI (125mg , b.d.) Treatment B: Tobramycin nebuliser	380	Open label, randomised, multiple

	a dry powder formulation of inhaled colistimethate sodium and nebulised TNSFI (Tobramycin nebuliser solution for inhalation, TOBI®) in cystic fibrosis patients over 6 years of age with chronic *Pseudomonas aeruginosa* lung infection.	solution for inhalation (TOBI®; 300mg, b.d.).		dose, comparator controlled

2.4.2 Pharmacokinetics

Analytical methods

Colistimethate (CMS) concentrations were determined in blood, urine and sputum using a validated microbiological assay that was developed by the Bristol Centre for Antimicrobial Research & Evaluation (BCARE). Over a concentration range 0.5 – 40 mg/L the mean accuracy was reported to be 93.7% and the intra-assay precision was 3.5 – 18.8%. This method measures total antibacterial activity and then infers concentrations from a standard curve. Hence it cannot differentiate the possible sub-components that might be present in test samples.

Absorption

The applicant attempted to assess absorption of colistimethate sodium from the respiratory tract after administration of Colobreathe in two studies in volunteers (healthy or with CF) and in the Phase 2 and Phase 3 studies in patients with CF who were colonised with P. aeruginosa.

- **DPI 98/01** was an open-label study in healthy volunteers that compared single administrations of colistimethate sodium 1 million IU by nebuliser and as 1,662,500 IU of the micronised dry powder (Colobreathe). Urine was collected 0-2 h post-dose and blood was collected 30 minutes pre-dose and 30 minutes post-dose. No CMS was detected in pre-dose blood or urine samples. Post-dose concentrations in serum were all < 0.5 mg/L whereas concentrations in the 8/24 urine samples from six subjects containing > 0.5 mg/L ranged from 1 to 6.6 mg/L.
- **DPI 98/02** was conducted in volunteers with CF and was of similar design to DPI 98/01. Due to uncertainty in the labelling of the assay results at the laboratory, it could not be confirmed which subject each set of results represented, whether each result was from urine or serum or whether the results were pre- or post-dose. Due to some unexpectedly high concentrations (> 64 mg/L) reported initially and some plate contamination with Pseudomonas species the samples were re-analysed. The majority of re-tests gave concentrations within 1-2 mg/L of those reported initially while the two samples previously reported to contain > 64 mg/L were reported as > 32 mg/L on repeat but it is not known if these were blood or urine.
- In the Phase 2 study **COLO DPI/02/05** there were two 4-week active treatment periods with inhaled dry powder (1,662,500 IU colistimethate sodium twice daily) and with nebulised colistimethate sodium in solution (2 million IU colistin twice daily) in a randomised sequence. In both treatment groups, the number of patients with < 1 mg/L in serum was lower at the end of the respective treatment period than at baseline but values above this were from 1.1 to 2.4 mg/L. Urine concentrations ≥ 4 mg/L were seen in four patients in each group at the end of treatment (46 and 52 mg/L for Colobreathe and 7.9 and 41.3 mg/L for nebulisation).

- In the phase 3 study **COLO DPI/02/06** 1,662,500 IU colistimethate sodium dry powder twice daily was compared with TOBI (3 on/off cycles) over 24 weeks. Serum and urine were collected pre-dose (Day 1), at Week 4 and at Week 24 (Exit Visit).
- Of the 492 plasma samples tested approximately 90% had results below LLQ (either 1 or 2 mg/L) and 479 had results < 3 mg/L. Values in individual subjects were mostly up to 3.8 mg/L but some outliers showed concentrations > 32 mg/L, 29 mg/L and 6.7 mg/L.
- In the urine samples from initial sites all except three subjects had at least one urinary concentration > 2 mg/L reported. Concentrations > 20 mg/L occurred commonly but 30/496 samples gave values of around 30 mg/L or higher and approximately half of these results were in children aged less than 18 years (some had levels > 64 or > 128 mg/L reported).

These data remain unexplained (e.g. they cannot be explained by inadequate inactivation of other antibacterial agents in samples) and therefore the possibility that these unusually high plasma and urine levels indicate that a substantial part of the dose may be absorbed by some patients cannot be dismissed.

The applicant was requested to conduct an additional pharmacokinetic study across the full age range and using two assays (one microbiological) to further evaluate systemic absorption in association with dry powder inhalation. This study had commenced but only very limited data were available before an opinion was reached on the application. The full data will be reported and will be used to update the SmPC as seems necessary. Meanwhile it can only be stated that in subjects with CF aged from 13 years systemic exposure after one week of twice daily dosing with Colobreathe was associated with considerably lower plasma levels than have been reported in published literature after intravenous dosing.

Distribution

Lung deposition and distribution of Tc99-radiolabelled colistimethate sodium after 1,662,500 IU dry powder inhalation (with and without pre-treatment with inhaled salbutamol by MDI) was compared to nebulisation of 1 million IU in study **PPL-252** in 10 volunteers with CF.

Following administration of 1 million IU colistin in solution using a nebuliser (Regimen A) 49.9% of the dose was retained in the nebuliser while an average 5.9% of the dose was deposited in the whole lung. On average, and based on the corrected data, 11.9% of the dose was deposited in the lungs from dry powder inhaled using the Turbospin device following pre-treatment with salbutamol (B) compared to 11.6% without pre-treatment with salbutamol (C). Without any correction being made for the difference in particle size differences the whole lung deposition from the dry powder administered via the Turbospin device averaged 19.3% and 18.7% of the dose with or without pre-treatment with salbutamol, respectively.

The lung penetration index was on average 1.8 $\pm$ 0.5 for the nebuliser, 1.5 $\pm$ 0.5 for the dry powder via the Turbospin device following pre-treatment with salbutamol and 1.2 $\pm$ 0.5 without pre-treatment. Percentages of the dose deposited in the oropharynx were 2.9%, 70.4% and 71.1%, respectively. The FEV_1 data indicated that none of the subjects suffered periods of bronchospasm.

Table 2: Percentage of administered dose deposited in the lung regions (non-corrected data)

Regimen	Percentage of dose deposited (mean ± SD)			
	Whole Lung	Central Lung	Intermediate Lung	Peripheral Lung
A	5.9 ± 3.4	1.4 ± 0.8	2.0 ± 1.1	2.4 ± 1.6
B	19.3 ± 8.5	5.6 ± 3.1	6.4 ± 3.0	7.3 ± 2.7
C	18.7 ± 6.9	5.9 ± 2.7	6.2 ± 2.2	6.6 ± 3.0

From these data the applicant concluded that approximately 5.9% (SD ± 3.4%) of a nebulised dose of 1 million IU colistin (~ 80 mg colistimethate sodium) was deposited in the lungs (i.e. ~ 60,000 units of colistin). On this basis, it is assumed that administration of the UK-recommended dose for CF patients aged at least 10 years (i.e. 2 million IU colistin or ~ 160 mg colistimethate sodium) by nebulisation would result in deposition of ~ 120,000 units of colistin in the lungs.

Following administration of 1,662,500 IU micronised powder with the Turbospin device approximately 11.6% (SD + 4.3%) of the dose was deposited in the lungs (i.e. ~ 180,000 units). The applicant concluded that one capsule of 1,662,500 IU colistimethate sodium dry powder inhaled twice daily and 2 million IU colistin administered by nebuliser twice daily should result in comparable lung deposition and on this basis proceeded with Colobreathe 1,662,500 IU twice daily dosing in Phase 2 and 3.

From the literature, it appears that plasma protein binding of colistin is low. One study in cystic fibrosis patients estimated the steady-state volume of distribution as 0.09 L/kg. Considerable amounts of colistin can cross the placenta and also enter breast milk.

Elimination

Regarding ***metabolism***, colistimethate sodium is converted to colistin and various sulphomethylated derivatives in vitro and in vivo. As somewhere between 40-80% of the intravenous dose (depending on the publication) can be recovered unchanged in the urine and there is no biliary excretion it is assumed that the remaining drug is inactivated in the tissues. The mechanism is unknown. One study in CF patients suggested that pulmonary clearance via sputum may contribute to total clearance.

From the literature it appears that the main ***route of elimination*** of the polymyxins is by renal excretion. It has been reported that in subjects with normal renal function about 40% of a parenteral dose of colistimethate sodium is recovered in the urine within 8 h and around 80% in 24 h.

After inhalation by nebulisation, variable amounts of a colistimethate dose have been reported to appear in urine. Using HPLC to quantify polymyxin E1 one paper reported that a mean of 4.3 ± 1.3% of the inhaled dose of 2 million IU was detected in the urine, with a high variability in the results (range 0.3 – 24.2%). The rate of removal during peritoneal dialysis has been reported to be 1 mg/L but haemodialysate contained no detectable levels.

It has also been reported that whereas colistimethate sodium is renally eliminated and the urinary excretion involves renal tubular secretion, colistin itself is eliminated predominantly by the non-renal route with very extensive renal tubular re-absorption. Another report mentions that after parenteral administration of colistimethate sodium in CF patients the plasma half-life of colistimethate sodium (124 ± 52 min) is approximately one-half that of the colistin generated from it (251 ± 79 min).

Dose proportionality and time dependencies

Not applicable.

Special populations

It has been reported that colistimethate sodium kinetics appears to be similar in ***children and adults, including the elderly***, provided renal function is normal. In the current application the intended age range for dosing is from 6 years upwards. Although ~40% of subjects in the Phase 3 study were aged < 18 years, the PK data generated were not considered sufficiently reliable to determine systemic exposure by age group. It is also not possible to reliably assess any possible differences in systemic exposure between nebulised and dry powder doses in any age group.

Pharmacokinetic interaction studies

No drug-drug interaction studies were conducted. This fact has been stated in the SmPC. A cautious approach has been taken with regard to the wording due to the lack of reliable data on systemic exposure.

2.4.3 Pharmacodynamics

Mechanism of action

Colistin is a cyclic polypeptide antibiotic derived from Bacillus polymyxa var. colistinus and belongs to the polymyxin group. Colistin is a mixture of polymyxin A (E1) and B (E2) and is often just denoted as polymyxin E. In solution there is hydrolysis of colistimethate sodium to E1 and E2.

The polymyxin antibiotics are cationic agents that work by damaging the cell membrane. The resulting physiological effects are lethal to the bacterium.

Primary and Secondary pharmacology

Primary pharmacology

Due to the mode of action, colistin is active only against certain Gram-negative aerobes and Gram-negative facultative anaerobes. Species that are generally susceptible to colistin include Citrobacter spp, Escherichia coli, Haemophilus influenzae and Pseudomonas aeruginosa. The in-vitro results may not correlate with clinical responses in the case of Acinetobacter spp. Acquired resistance in normally susceptible species is currently a potential problem in Enterobacter species and Klebsiella species.

Because of the differences between colistimethate, colistin sulphate and colistin base, the interpretation of MICs is dependent on which entity has been used for testing. In light of variable conversion of colistin methanesulfonate (CMS) and colistin sulphate to colistin, the testing conditions may also be critical to the answer obtained. In a 2003 publication in which the stability of CMS and colistin under various conditions of testing were assayed using HPLC it was found that the formation of colistin in buffer corresponded well with a rapid increase in the antibacterial activity of solutions of CMS over time against Escherichia coli. Other reports have shown that the antibacterial activity of colistin against P. aeruginosa, E. coli, Enterobacter aerogenes and Klebsiella pneumoniae were 3- to 10-fold that of CMS. The EUCAST ECOFF for colistin for most susceptible species is 2 mg/L but the ECOFF for P. aeruginosa is 4 mg/L.

Colistin-resistant bacteria are characterised by phosphate groups of lipopolysaccharide that are substituted with ethanolamine or aminoarabinose. Naturally resistant Gram-negative bacteria, such as Proteus mirabilis and Burkholderia cepacia, show complete substitution of their lipid phosphate by ethanolamine or aminoarabinose. Cross resistance between colistimethate sodium and polymyxin B (the only other polymyxin that is available for clinical use) would be expected.

Since the mechanism of action of the polymyxins is different from that of other antibacterial agents, resistance to colistin and polymyxin B by means of changes in lipid phosphate groups would not be expected to result in resistance to other drug classes. However, some bacteria may show cross-resistance to polymyxins and agents in other classes as a result of impermeability and/or efflux pumps.

The applicant has not conducted any studies of the in-vitro activity of colistin. Literature reports were summarised but in many cases it is not known which substance was used for in-vitro testing or the methodology that was applied. For example, in-vitro activity was assessed against 385 mucoid and non-mucoid strains of P. aeruginosa isolated from 192 sputa that were obtained from 57 adult CF patients during 1998-1999 in Germany. Only 38% of the non-mucoid and 45% of the mucoid strains were susceptible at 2 mg/L. In contrast a recent study in Turkey, which tested isolates from CF patients in Istanbul, the MIC90 for colistin methanesulfonate was 2 mg/L. A survey of P. aeruginosa isolates from CF patients in the UK showed that 96.9% were susceptible to colistin based on the BSAC breakpoints operative at the time.

Secondary pharmacology

Colistin has long been known to exert an effect on nerve conduction that appears to be related to an ability to inhibit acetylcholine release at somatic nerve endings in skeletal muscle. Weakness and paralysis can result if plasma concentrations are allowed to increase unnecessarily and/or if colistin is co-administered with other drugs (e.g. curariform agents) that have this effect. An exacerbation of myasthenia gravis is also possible. However, the effect of colistin on sensory nerves and its ability to trigger vertigo and ataxia seem to be mediated by a different mechanism that has not been elucidated.

The effect of colistin on renal function is not well understood although some studies have shown a decrease in creatinine and urea clearance during therapy.

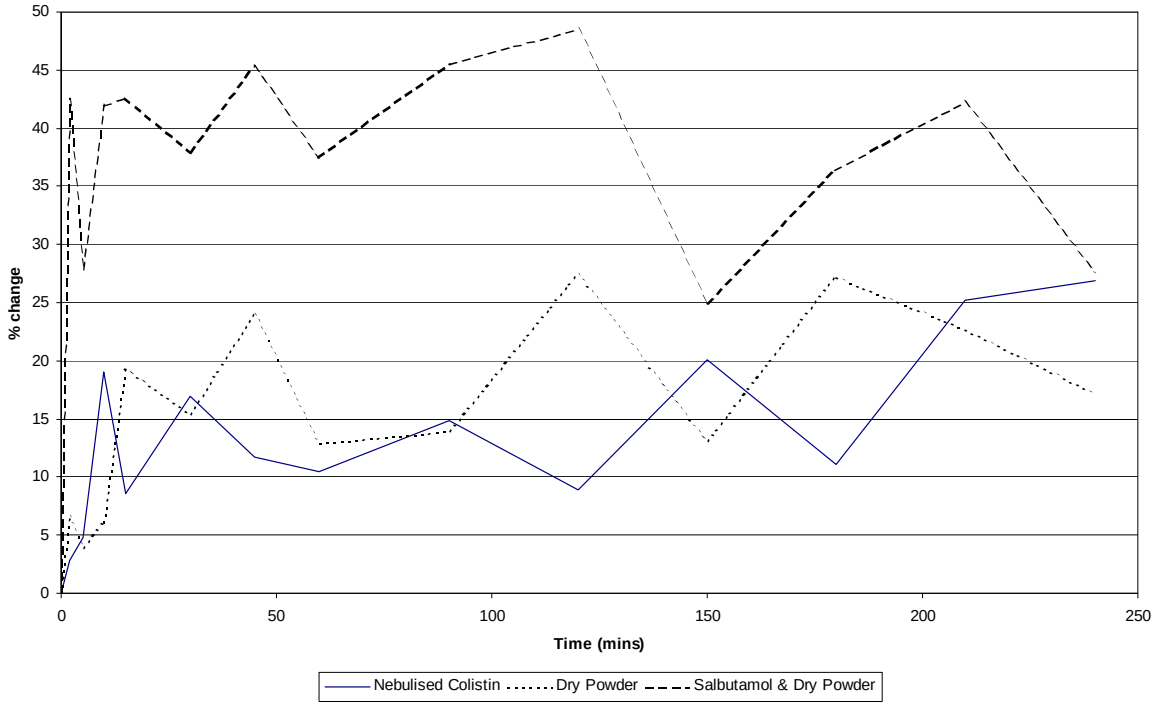
When administered by inhalation of colistimethate sodium in solution via nebulisation local bronchoconstriction has been reported to occur as has been described with other inhaled antibacterial agents. This effect is distinct from the true hypersensitivity reactions that may occasionally occur and may be due simply to a local irritation effect on the mucosa. Published data suggest that a significant drop in FEV1 occurs in < 20% of subjects. The applicant assessed the potential for Colobreathe to trigger bronchoconstriction in two studies:

* In **DPI 98/01** bronchoconstrictive effects were compared following administration of nebulised (1 million IU) and micronised (i.e. 1,662,500 IU dry powder) colistimethate sodium in healthy subjects. The dry powder was administered with and without pre-medication with inhaled salbutamol (by MDI). Subjects underwent continuous specific airways conductance measurements (sGaw) in a whole body plethysmograph at four hours following each dosing. Forced expiratory volume (FEV_1) was measured at baseline and at four hours post-inhalation on each study day.

A mean of 82% of the mass of colistimethate sodium dry powder was delivered when Colobreathe was administered after salbutamol pre-medication (103 mg; SD 44) and 90% was delivered when Colobreathe was administered alone (113 mg; SD 37). There were no clinically significant differences in mean FEV_1 (L) (pre-dose, 4 hours post-dose) between nebulised and dry powder treatment regimens. Mean percentage change in FEV_1 4 hours post-dose (2.7, SD 5.2) was slightly greater for dry powder plus salbutamol pre-medication than for nebulisation (-0.9, SD 6.2) and dry powder alone (-0.2, SD 4.1).

Mean sGaw ($s^{-1}kPa^{-1}$) readings post dose showed no significant differences between groups from baseline to 240 min post-dose. However, the percentage change in sGaw measurements over baseline (up to 200 min post-dose) was greater for dry powder with salbutamol pre-medication than with dry powder alone, showing an improvement in airways resistance.

Figure 2:



Mean Percentage Change in Specific Airway Conductance

In a published study that investigated inhalation of 25 mg dry powder colistin sulphate a decrease in pulmonary function was observed for six healthy volunteers (FEV_1 mean percentage change at 3.5 h of -2.78%) and five patients (FEV_1 mean percentage change at 3.5 h of -6.62%) after dosing. The FEV1 and specific airway conductance readings obtained in study DPI 98/01 indicated that inhalation of nebulised and dry powder colistimethate did not induce any degree of bronchoconstriction in healthy volunteers. This finding is contrary to the published study using the sulphate and would be consistent with lack of hydrolysis *in vivo* of colistimethate to colistin sulphate.

* In **DPI 98/02** an additional control arm (micronised lactose powder) was added compared to DPI 98/01 with the aim of determining whether any bronchoconstriction observed was due simply to the physical properties of inhaling 1,662,500 IU (125mg) dry powder. The study was therefore a four-segment, single-dose cross-over study involving 12 adult subjects with CF.

A mean of 76% of the mass of colistimethate sodium dry powder was delivered when it was administered alone (94 mg, SD 30) compared to a mean of 90% delivered when it was delivered with salbutamol pre-medication (112 mg, SD 40). These results were consistent with the data from DPI 98/01 in healthy volunteers. A mean of 51% of the mass of micronised lactose was delivered (64 mg, SD 43) and it was considered that poor flow from the capsule was a possible explanation for this relatively low delivery.

There was a wide range in baseline pulmonary function with a mean FEV_1% predicted of 50% but a range from 21% - 98%. However, there was no correlation between baseline FEV_1% predicted and the mass of micronised dry powder delivered. The applicant considered that the Turbospin inhaler was reliable in delivering a consistent mass (albeit greater than anticipated from preceding in-vitro studies) of micronised colistimethate sodium irrespective of lung function status.

There were no clinically significant differences of mean FEV_1, FVC, PEF or MMEF (pre-dose up to 240 minutes post-dose) between the four different treatment regimens. The mean percentage change in FEV_1 over 4 h was slightly greater for colistin with salbutamol pre-medication compared with colistin alone. However, no clinically significant decrease in pulmonary function was observed after colistin administration and there were no clinically significant differences in pulmonary function between treatments. It was concluded that the nebulised and micronised powder formulations of colistimethate sodium did not induce bronchoconstriction.

2.4.4 Discussion on clinical pharmacology

The erratic PK results reported in the initial dossier could reflect several factors but it remains impossible to dismiss the possibility that some of the reported high concentrations could be real. The available data do not allow a comparison between systemic exposures during nebulisation vs. DPI treatment. Blood levels reported after IV dosing have been variable, probably reflecting the doses and the biological assay used. However, a range from 6 - 30 mg/L has been reported after dosing within the recommended range using infusions or bolus injections. Study PPL-252 suggested that administration of 1,662,500 IU micronised powder with the Turbospin device deposited ~11.6% (SD $\pm$ 4.3%) of the dose in the lungs (i.e. ~ 180,000 units) so that the average dose delivered by inhalation is perhaps up to 400,000 IU per day. This compares with parenteral doses up to 6 million IU daily in adults and a minimum dose ~750,000 IU/daily for children aged 6 years and at least 15 kg body weight. On this basis, even if the entire dose delivered using Colobreathe (1.6 million IU twice daily) was to leave the Turbospin and get absorbed from the lungs and oropharynx the systemic exposure should be considerably less than that associated with IV dosing.

The applicant has commenced a new study that will generate PK data across age groups and will use biological and non-biological assays. Meanwhile, since theoretical considerations all point to much lower systemic exposure using Colobreathe vs. intravenous dosing it was considered that the outlier results obtained using the microbiological assay most likely reflect unidentified errors. Nevertheless, until such time as the new study provides information on systemic exposure across age groups the SmPC must take a cautious approach.

2.4.5 Conclusions on clinical pharmacology

The CHMP considers the following measures necessary to address the issues related to pharmacology:

Full data to be reported on the ongoing additional pharmacokinetic study across the full age range and using two assays (one microbiological) to further evaluate systemic absorption in association with dry powder inhalation.

2.5 Clinical efficacy

2.5.1 Dose response studies

No formal dose-ranging studies have been performed with Colobreathe. The selection of the dose for main trial is defined by the deposition study using radio labelled colistimethate sodium (Study PPL-252). In this study 125mg colistimethate DP for inhalation was calculated to give similar whole lung deposition to 2-3 Million International Units (160-240mg) colistimethate when given using a Medic-Aid Ventstream® nebuliser. The recommended nebulised dose is 2 million IU (160mg) for children and adults and therefore 125mg (1.6 million IU) was selected as an appropriate dose.

2.5.2 Main study

- **COLO/DPI/02/06** - Randomised, open label study to compare the efficacy and safety of a dry powder formulation of inhaled colistimethate sodium and TOBI (Tobramycin nebuliser solution for inhalation) in cystic fibrosis patients with Pseudomonas aeruginosa lung infection.

This was an open-label randomised and active-controlled study of Colobreathe versus TOBI in CF patients from the age of 6 years upwards colonised with *P. aeruginosa* and was conducted from 2004-2007. There were 66 active study sites spread across 10 EU Member States plus Russia and Ukraine. The study was conducted and monitored on behalf of the sponsor by a UK-based CRO.

This was the single pivotal Phase 3 study in the application. The clinical programme did not evaluate efficacy against placebo.

Methods

Study Participants

Due to differences in the availability and usage of TOBI in participating countries and to ensure that all patients had received at least two cycles of TOBI before the randomised treatment period commenced, a run-in period was incorporated by protocol amendment affecting four countries.

- To be eligible for the run-in period subjects were to be aged at least 6 years with diagnosis of CF from a specialist CF unit (genotype and/or positive sweat tests) and willing to receive TOBI in a cycle of 28 days active therapy followed by 28 days of rest from treatment. Other criteria were as for the main study.
- To be eligible for randomisation subjects were to be aged at least 6 years with a documented diagnosis of CF from a specialist CF unit (genotype and/or positive sweat tests). They were to have received a minimum of two TOBI cycles (on/off; 28 days each and off not to exceed 35 days) immediately prior to randomisation. Patients were non-smokers or had not smoked within 12 months of the first study drug administration (Visit 1).

CF was to be clinically stable in the investigator's opinion with no evidence of acute respiratory exacerbation (according to a standard definition in the protocol) within 28 days prior to Visit 1. FEV1 had to be at least 25% but no more than 75% of predicted value using the Knudson predicted values tables. Lung function had to be clinically stable (investigator's decision) at Visit 1 prior to randomisation. Patients were to have *P. aeruginosa* infection defined as:

(i) ≥ 50% samples (minimum of 3 samples: sputum samples or throat swabs) positive for *P. aeruginosa* over the 12 months prior to Visit 1 OR

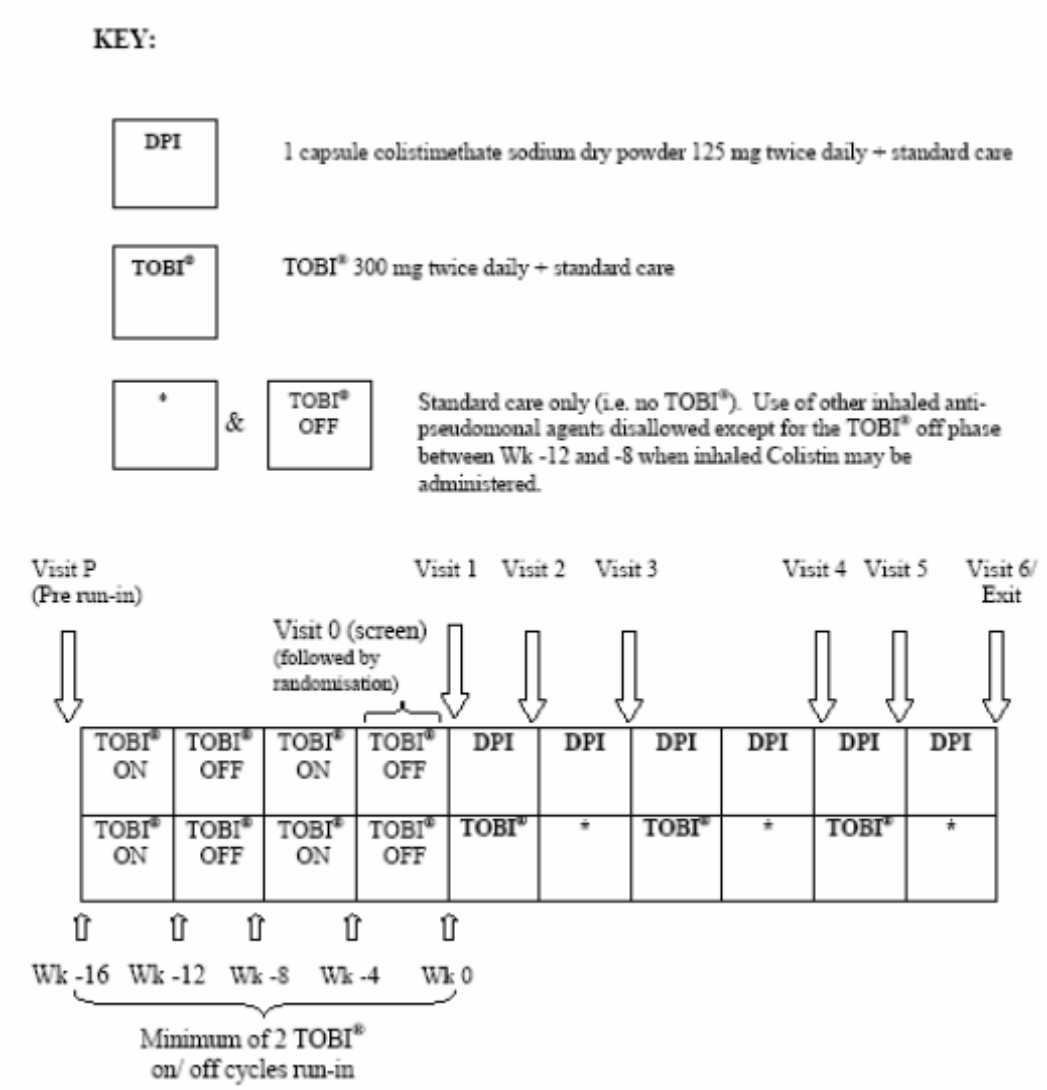
(ii) Two samples (sputum samples or throat swabs) positive for *P. aeruginosa* over the previous 6 months prior to Visit 1.

The exclusion criteria were generally common to the run-in period and to randomisation. Most pertinent of these were evidence of an acute respiratory exacerbation at Visit 1, hypersensitivity or previous intolerance to colistimethate sodium or β2 agonists, pregnancy or breastfeeding, patients receiving anti-pseudomonal agents specifically for the treatment of an exacerbation or pre-scheduled prophylactic courses of oral antibacterial agents at Visit 1 (but see permitted treatments below) and those with allergic bronchopulmonary aspergillosis.

Treatments

Patients of all ages received either 1,662,500 IU Colobreathe (i.e. 1,662,500 IU colistimethate sodium) twice daily for inhalation using a Turbospin device or 300 mg TOBI twice daily by nebulisation using a PARI LC Plus nebuliser. The dose interval was to be as close as possible to 12 hours and not less than 6 hours for both regimens. The general treatment plan over the 24 weeks of the study was as follows:

Figure 3:



Bronchodilator inhalers and pre-existing non anti-pseudomonal CF medications and antibacterial agents (e.g. ciprofloxacin) for prophylaxis or other agents (e.g. azithromycin) if taken for long-term use were permitted during the study. After randomisation patients who needed admission for an acute respiratory exacerbation continued study medication throughout. Rescue medication was allowed under protocol-defined circumstances. All children had to have a responsible adult to supervise (as far as possible) study treatment.

Objectives

The primary objective was to quantify any change in FEV1 % predicted compared to baseline (on entry to the study at Visit 1 [Day 1]).

The secondary objectives were:

i. To quantify changes in antibacterial susceptibility of *P. aeruginosa* isolates (MIC at Week 24)

ii. To compare QoL to establish superior ease of administration

iii. To assess clinical and laboratory safety of 24 weeks of treatment

iv. To compare weight and BMI changes

v. To compare time to first acute respiratory exacerbation and time to first use (and duration of use) of systemic anti-pseudomonal antibacterial treatment for acute respiratory exacerbation

vi. Other pulmonary function tests including FEV1 % predicted at Week 20 and change in FVC, PEFR, FEV1 and FEF25-75

vii. Use of concomitant medication including bronchodilators or rescue medication

viii. To compare the drop-out rates.

Outcomes/endpoints

The primary efficacy variable was the change in FEV1 % predicted from baseline (Visit 1) to Week 24 (Visit 6). The FEV1 % predicted = [Highest FEV1 / predicted FEV1] * 100. The change from baseline to Week 24 of FEV1 % predicted results was summarised separately for patients who completed the study (i.e. with a baseline and a Week 24 result) and for all patients using LOCF imputation to Week 24 for missing data.

Respiratory function tests (spirometry and expiratory curve of the flow volume loop) were measured using suitable equipment (spirometry or body plethysmography) that was capable of printing records that could be stored with the patient's CRF. All testing was performed according to the American Thoracic Society (ATS) criteria. Pulmonary function testing was carried out at each visit by an independent observer who was unaware of the patient's treatment assignment.

For a given patient, pulmonary function testing was performed at the same time of day for each study assessment. There was a minimum time window of 2 hours between inhalation of bronchodilator agents (whether short- or long-acting) and performance of spirometry.

MICs of colistin and tobramycin against *P. aeruginosa* were determined using the E-test system at a reference laboratory (UK HPA). If resistance appeared to develop during the study the isolates from individual patients were investigated by PFGE of DNA macrorestriction digests.

The QoL questionnaires for CF used were those developed in the United States by Quittner, based on versions that were first developed in France. The CFQ-Rs were completed at Visit 1 (study start) and then at Visits 2, 5, and 6. Patients who shifted questionnaire age brackets during the study did not switch CFQ-R version.

Sample size

Based on the publication of Ramsey et al. (1999) with preservative-free TOBI it was assumed that the SD of the primary outcome variable (FEV1 % predicted) was about 16%. To test for this hypothesis, the 95% two-sided CI for the difference between the two groups was computed and if the lower limit was not less than -3.0% then non-inferiority was to be accepted. To detect this difference, with $\alpha=0.05$ and $\beta=0.20$, 162 evaluable patients for the TOBI group and 162 evaluable patients for the Colobreathe group were required. These calculations were based on a 2-group t-test with a 0.05 two-sided significance level and a common SD of 16%, and assumed a difference of 2% in favour of

Colobreathe against TOBI. Assuming a 10% drop-out/non-compliance rate, approximately 360 patients were to be entered into the study (180 TOBI patients and 180 Colobreathe patients) to obtain 324 evaluable patients.

Randomisation

Randomisation and recruitment was as follows:

- At study entry (with or without completion of the run-in period) patients were randomised to treatment (1:1) using an interactive voice response system (IVRS).
- The block size used for each centre's first allocation was 6. A block size of 4 applied thereafter.
- Each centre was to recruit approximately 3 to 10 patients although it was envisaged that certain specialist CF centres (with a significant number of patients routinely nebulising TOBI) would recruit larger numbers of patients.
- The statistical analysis was planned to investigate whether there were any centre effects and whether any particular centres were influencing the outcome.

Blinding (masking)

The study report states that a double-blind design was not feasible in light of obvious differences in the administration method. Using a double-dummy approach would have ruled out an assessment of any potential administration advantages of Colobreathe over TOBI.

Statistical methods

Initially there were three populations defined for the analyses as follows:

- ***Safety population***: all randomised and treated patients.
- **Intent-to-Treat (ITT) population**: all randomised and treated with laboratory-confirmed chronic infection. This population was used for all efficacy analyses.
- **Per Protocol (PP) population**: all randomised and treated patients who met the criteria for efficacy evaluable patients and did not meet the violation criteria. This population was used for the primary efficacy endpoint and other pulmonary function endpoints only.

An additional analysis was performed for the patients with a baseline and week 24 result (i.e. ***completers***).

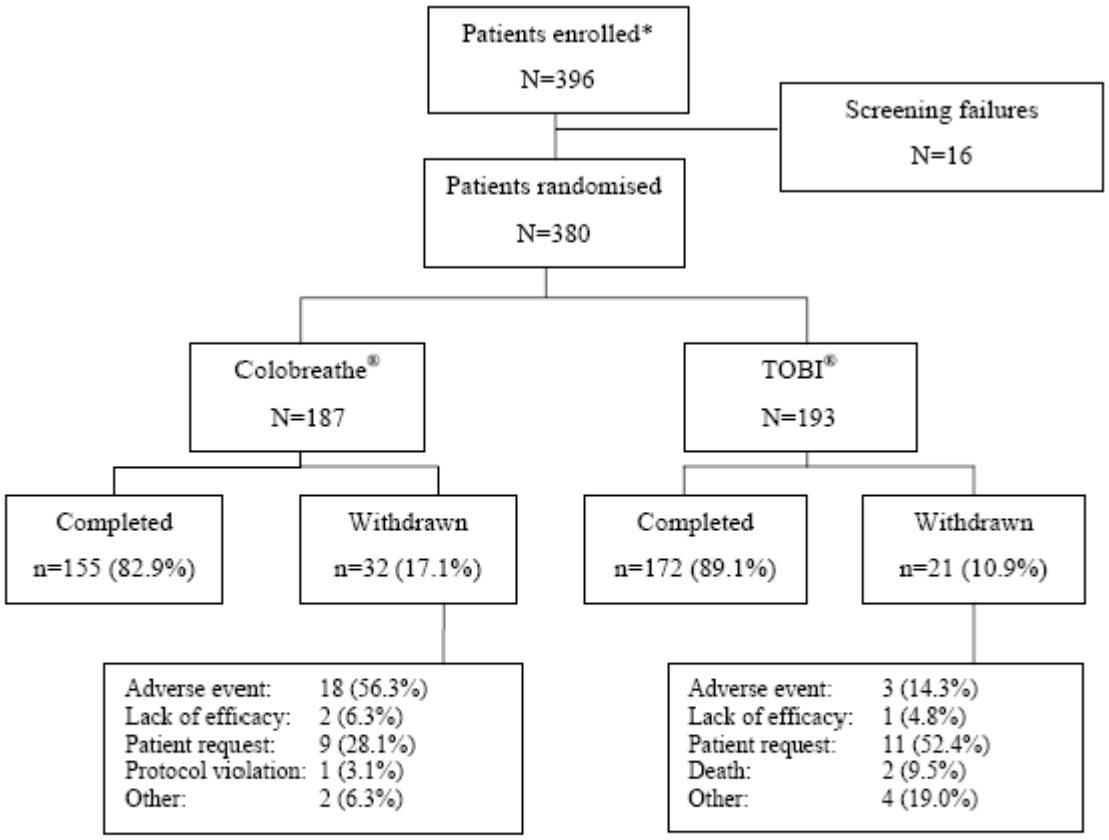
For the analysis of the primary endpoint the applicant calculated the actual difference between treatments in mean FEV1% predicted at week 24 i.e. expressed in difference in percentage points. This approach was in line with the derivation of the non-inferiority margin recommendation by the CHMP. A 95% two-sided CI, based on the ANCOVA model, was computed for the difference of Colobreathe minus TOBI. If the lower bound was no lower than -3% for both the PP and ITT populations it was to be concluded that Colobreathe was non-inferior to TOBI. The analysis of covariance (ANCOVA) was performed using main effects of treatment, baseline FEV1 % predicted and pooled centre. Adjusted means by treatment were presented as well as an estimate of the difference between adjusted means. The analysis was presented for patients who completed the study and also for all patients using a method of LOCF imputation to Week 24 for missing data.

Results

Participant flow

The figure below summarises patient disposition. The percentage of patients who completed the study was numerically higher in the TOBI group, reflecting a higher number of patients in the Colobreathe group whose primary reason for withdrawal was at least one AE. Review of patients who discontinued due to "patient request" included others who experienced adverse reactions and some who did not want to be randomised to TOBI.

Figure 4: Patient Disposition



Note: [1] Only primary reasons for discontinuations are presented. More than one reason could be given per patient withdrawal.
[2] Percentages for the primary reason for discontinuation are based on the number of patients discontinued in each group.
*: Included in the study database

Conduct of the study

There were 9 amendments to the protocol of which 7 occurred after initiation of enrolment on 25 March 2004. The most important reduced the lower age limit from 8 to 6 years and added a run-in for countries where TOBI was not routinely available or used (Russia, Ukraine and UK).

Baseline data

The ITT population comprised 170 (45.5%) female and 204 (54.5%) male patients. The mean age was 21.1 years with a range from 6 to 56 years and overall 59% were aged > 18 years (59%) while 18% were aged 6 to 12 years and 23% were aged 13 to 17 years. However, the distribution of children across sites was uneven. At the Ukraine sites 53/66 (80%) were less than 18 years old, including 34 (52%) aged 6-12 years, 19 (28%) aged 13-17 years and only 13 (20%) adults. In contrast, at the non-Ukraine sites only 104 (33%) were aged < 18 years with 35 (11%) aged 6-12 years and 69 (22%) aged 13-17 years. Therefore, the Ukraine contributed 34/69 (49%) of the total aged 6-12 years in the entire study, 22% of all patients aged 13-17 years and <10% of the adults.

In all three analysis sets, the two treatment groups were comparable with respect to all demographic parameters. There were no statistically significant differences between the treatment groups with respect to disease-related baseline characteristics. In particular, 44.8% and 49.7% per group had a baseline FEV1 % predicted that was < 50% (noting that the "baseline" value was almost always the screening value since most patients had a combined screening/baseline visit).

The actual mean FEV1 % predicted at screening in the ITT population was 52.01 in the Colobreathe group and 50.88 in the TOBI group, with median values of 52.55 and 50.47, respectively. For those aged 6-12 years the mean FEV1 % predicted values at screening were 54.15 and 52.14 per treatment group compared to 51.26 and 52.69 for those aged 13-17 years.

Table 3

	DPI colistin (N=183)	Nebulised TOBI® (N=191)	Overall (N=374)	P-value
Baseline FEV1 % predicted category				
<50% predicted	82 (44.8)	95 (49.7)	177 (47.3)	0.375
>=50% predicted	101 (55.2)	96 (50.3)	197 (52.7)	
Time since diagnosis of Cystic Fibrosis (years)				
n	183	191	374	0.436
Mean (SD)	17.1 (8.77)	17.5 (8.71)	17.3 (8.73)	
Median	16.0	16.0	16.0	
Min, Max	1, 41	2, 46	1, 46	
Time since first ever administration of TOBI® (years)				
n	182	188	370	0.582
Mean (SD)	2.7 (1.90)	2.5 (1.91)	2.6 (1.91)	
Median	2.0	2.0	2.0	
Min, Max	1, 12	1, 15	1, 15	
Number of pseudomonas aeruginosa infective exacerbations in the last year				
n	183	191	374	0.880
Mean (SD)	1.7 (1.66)	1.8 (1.43)	1.7 (1.54)	
Median	1.0	2.0	2.0	
Min, Max	0, 9	0, 8	0, 9	
Mean duration of previous pseudomonas aeruginosa exacerbations in the last year (days)				
n	173	177	350	0.075
Mean (SD)	12.1 (10.00)	14.3 (11.48)	13.2 (10.81)	
Median	14.0	14.0	14.0	
Min, Max	0, 70	0, 98	0, 98	

In the ITT population, comparable proportions in the Colobreathe and TOBI groups were ≥ 75% adherent to study medication (66.7% and 70.7%, respectively). The most frequently used concomitant medication were enzyme preparations (93.4% Colobreathe 94.2% TOBI group), mucolytics (74.3% and 79.1%), selective β2-adrenoreceptor agonists (76.5% and 71.2%), other plain vitamin preparations (59.6% and 55.5%) and macrolides (49.7% and 51.3%). Azithromycin was taken by 85 (46.4%) Colobreathe and 97 (50.8%) TOBI patients while dornase alpha was taken by 51.4% and 55.0%. Azithromycin and/or dornase alpha was used by 72.1% and 75.4% per group.

Numbers analysed

Of 380 randomised patients, six patients (4 Colobreathe) did not have a laboratory confirmed chronic infection and were excluded from the ITT population. Protocol violations in 46 Colobreathe and 35 TOBI patients led to the different proportions included in the PP population and mostly reflected Colobreathe patients given the wrong treatment (3 vs. 0), non-adherence (3 vs. 0), prohibited medication (23 vs. 18) or other violations (2 vs. 0).

Table 4: Data Analysis Sets

	Colobreathe®	TOBI®	Overall
Randomised, N	187	193	380
Safety population, n (%)	187 (100.0)	193 (100.0)	380 (100.0)
ITT population, n (%)	183 (97.9)	191 (99.0)	374 (98.4)
PP population, n (%)	141 (75.4)	157 (81.3)	298 (78.4)

Notes: Percentages are based on the number of patients randomised in each group

Outcomes and estimation

Primary Analysis

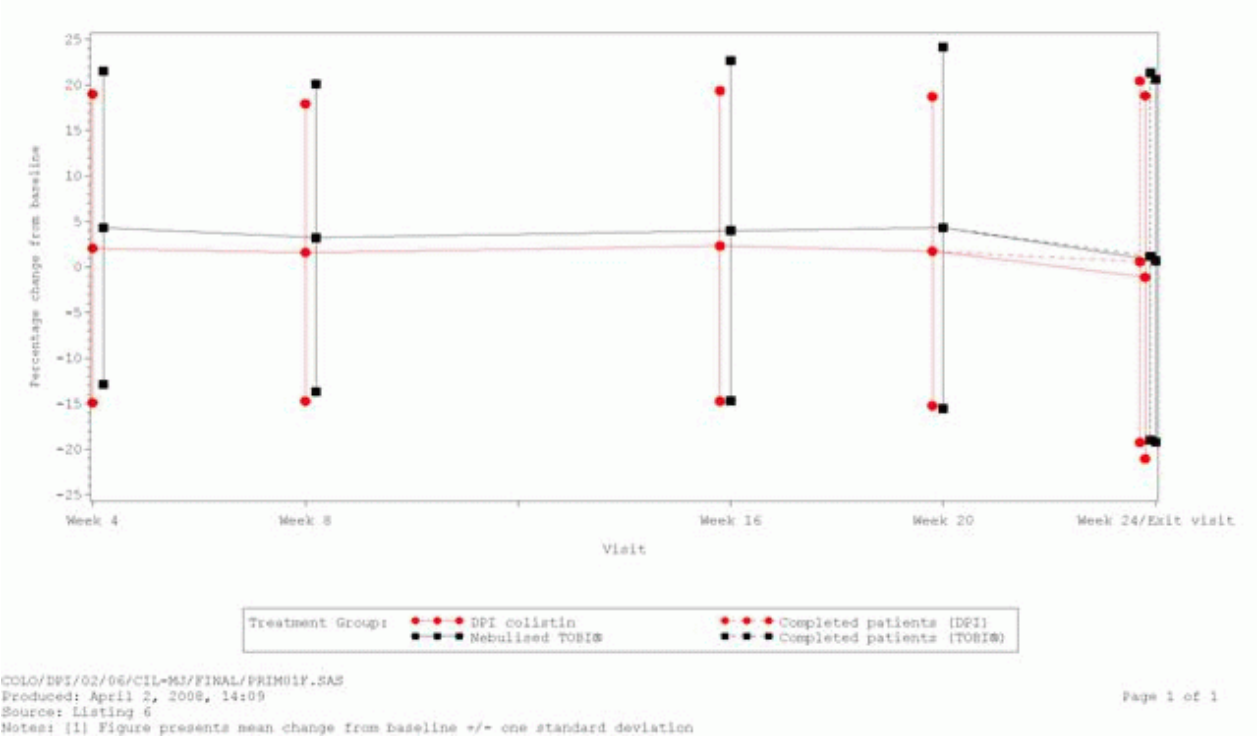
Based on the LOCF approach there was a negative mean change in FEV1% predicted from baseline (-0.9 percentage points) in the Colobreathe group compared to positive mean change (+0.35 percentage points) in the TOBI group. These values gave a difference of -1.25 and an adjusted difference of -1.16 percentage points. The corresponding adjusted difference for the completers was smaller (-0.43 percentage points). The median values were all negative but less so in the TOBI group vs. the Colobreathe group. The minimum and maximum changes indicated that there was considerable inter-patient variability in FEV1% during the course of the study. The lower limits of the 95% CI around the adjusted mean treatment differences were marginally below (-3.15% for ITT LOCF) and above (-2.59% for ITT completers).

Table 5: Change in FEV1 predicted at Week 24 (ITT population)

Patient group	DPI colistin (N=183)	Nebulised TOBI (N=191)	Overall (N=374)	Adjusted difference	95%, CI
All patients using LOCF					
N	183	190	373	-1.16	-3.15, 0.84
Mean (SD)	-0.90 (10.015)	0.35 (10.756)	-0.26 (10.404)		
Median	-1.43	-1.09	-1.27		
Min, max	-32.9, 43.4	-33.6, 49.3	-33.6, 49.3		
Adjusted mean	-1.28	-0.13	-0.69		
Completed patients					
N	153	171	324	-0.43	-2.59, 1.72
Mean (SD)	0.39 (9.715)	0.78 (10.900)	0.60 (10.343)		
Median	-0.70	-0.58	-0.64		
Min, max	-29.0, 43.4	-33.6, 49.3	-33.6, 49.3		
Adjusted mean	-0.36	0.08	-0.12		

Notes:
[1] Adjusted difference (LS Mean difference DPI colistin - Nebulised TOBI®) and confidence intervals were determined using analysis of co-variance with covariates of baseline FEV_1 % predicted and pooled centre
[2] Completed patients are defined as: patients who completed the study; i.e., who have both a baseline and Week 24 result
[3] n=number of patients with available data

Figure 5: Primary endpoint: FEV1 % predicted percentage change from baseline (ITT Population)



In the PP population, the corresponding adjusted difference was -1.49% (95% CI: -3.79%, 0.81%) in the LOCF analysis with -0.99% (95% CI: -3.48%, 1.51%) for patients who completed the study. Therefore the criterion for concluding non-inferiority was not met.

Table 6: Change in FEV1% predicted at Week 24 (PP population)

Patient group	DPI colistin (N=141)	Nebulised TOBI (N=157)	Overall (N=298)	Adjusted difference	95% CI
All patients using LOCF					
N	141	157	298	-1.49	-3.79, 0.81
Mean (SD)	-0.30 (10.306)	1.12 (11.120)	0.45 (10.748)		
Median	-1.28	-0.61	-0.82		
Min, max	-29.0, 43.4	-33.6, 49.3	-33.6, 49.3		
Adjusted mean	-1.02	0.47	-0.24		
Completed patients					
N	120	141	261	-0.99	-3.48, 1.51
Mean (SD)	0.83 (10.236)	1.60 (11.260)	1.24 (10.788)		
Median	-0.51	-0.26	-0.32		
Min, max	-29.0, 43.4	-33.6, 49.3	-33.6, 49.3		
Adjusted mean	-0.26	0.73	0.29		

Notes:
[1] Adjusted difference (LS Mean difference DPI colistin - Nebulised TOBI) and confidence intervals were determined using analysis of co-variance with covariates of baseline FEV_1 % predicted and pooled centre
[2] Completed patients are defined as: patients who completed the study; i.e., who have both a baseline and week-24 result
[3] n = number of patients with available data

The treatment-by-pooled centre interaction was not statistically significant and was therefore not included in the model. Also, no difference in the drop-out rates was detected. However, because of an indication of departures from normality, the ANCOVA using the main effects of treatment, baseline FEV1% predicted and pooled centre was repeated on logarithmically transformed data. Comparisons between treatment groups were presented as ratios. The non-inferiority criterion for the lower limit of the 95% CI of -3% for the treatment difference was equivalent to a lower limit of 0.94 for the treatment ratio. This ratio of 0.94 comes from the fact that as the middle of the inclusion criterion is a predicted FEV1% of 50%, an absolute change of 3% is a relative change of 6%.

In the ITT population, the adjusted mean ratio was 0.980 (95% CI: 0.943, 1.018) in the LOCF analysis and 0.994 (95% CI: 0.955, 1.035) for patients who completed the study. When the treatment ratio was converted to a treatment difference using the unadjusted TOBI geometric mean as the multiplier in the conversion formula, the adjusted mean difference was -0.97% (95% CI: -2.74%, 0.86%) in the LOCF analysis and -0.29% (95% CI: -2.21%, 1.71%) for patients who completed the study. Therefore the criterion for non-inferiority was met. The corresponding results for the PP population showed that the criterion for non-inferiority was marginally missed in the PP LOCF analysis but was met in the PP completers analysis.

Table 7: Change in FEV1% predicted at Week 24 (ITT population) – data logarithmically transformed

Patient group	DPI colistin (N=183)	Nebulised TOBI (N=191)	Overall (N=373)	Adjusted treatment comparison	95% CI
All patients using LOCF		**(Ratio to Baseline)**			
N	183	190	373	0.980	0.943, 1.018 [$]
Mean (SD of logs)	0.964 (0.1994)	0.986 (0.1898)	0.975 (0.1946)	-0.97	-2.74, 0.86[$$]
Median	0.968	0.982	0.978	-0.98	-2.74, 0.86 [$$]
Min, max	0.484, 1.860	0.450, 1.957	0.450, 1.957		
Adjusted mean	0.960	0.979	0.970		
Completed patients		**(Ratio to Baseline)**			
N	153	171	324	0.994	0.955, 1.035 [$]
Mean (SD of logs)	0.988 (0.1916)	0.993 (0.1913)	0.991 (0.1912)	-0.29	-2.21, 1.71[$$]
Median	0.988	0.988	0.988	-0.29	-2.20, 1.70 [$$$]
Min, max	0.502, 1.860	0.450, 1.957	0.450, 1.957		
Adjusted mean	0.977	0.983	0.980		

Notes:
[1] $ Adjusted ratio (DPI colistin / Nebulised TOBI®)
[2] $$ Adjusted difference (DPI colistin - Nebulised TOBI®), obtained using formula (M*(ratio-1)), where M is the unadjusted TOBI® geometric mean
[3] $$$ Adjusted difference (DPI colistin - Nebulised TOBI®), obtained using formula (M*(ratio-1)), where M is the TOBI® geometric mean adjusted for baseline FEV_1 % predicted and pooled centre
[4] Completed patients are defined as: patients who completed the study; i.e. who have both a baseline and Week 24 result
[5] Adjusted values are determined using analysis of variance on logarithmically transformed data with covariates of baseline FEV_1 % predicted and pooled centre

In the logarithmic transformation analyses a significant (just) treatment-by-pooled centre interaction was observed in the ITT LOCF analysis (p=0.0495) but this was not found in the ITT completers (p=0.1192), PP LOCF (p=0.1203) or PP completers (p=0.3070). The interaction was explained by the fact that in some pooled centres the treatment effect was in favour of Colobreathe and in others it was in favour of TOBI. Accordingly additional exploratory analyses were performed on logarithmically transformed data that included the interaction term in the model. In the ITT population, the table shows that the pre-defined criterion for non-inferiority was met in the LOCF and completers analyses when the treatment by centre interaction was included in the model.

Table 8: Change in FEV1 % predicted at Week 24 (ITT population) – Data Logarithmically Transformed – Treatment-by-pooled centre interaction included in model

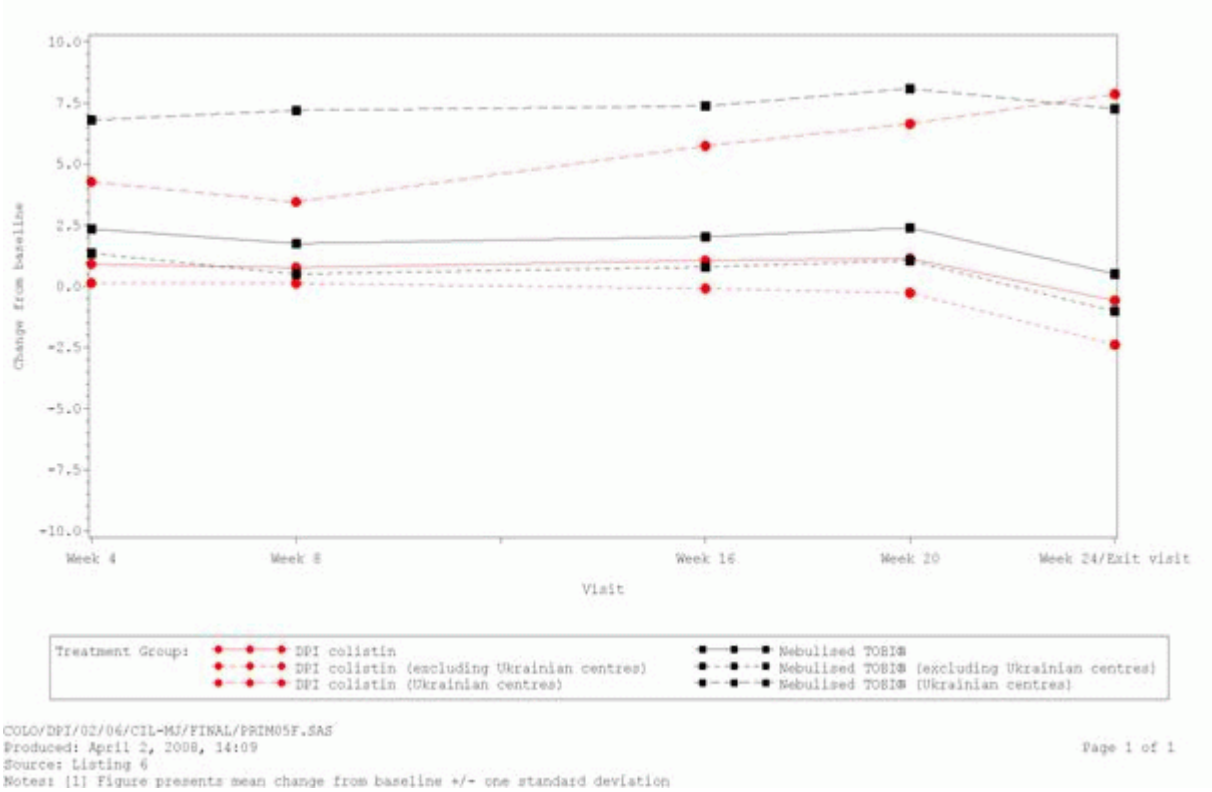
Patient group	DPI colistin (N=183)	Nebulised TOBI (N=191)	Overall (N=374)	Adjusted Treatment Comparison	95% CI
All patients using LOCF		(Ratio to Baseline)			
n	183	190	373	0.980	0.944, 1.017 [$]
Mean (SD of logs)	0.964 (0.1994)	0.986 (0.1895)	0.975 (0.1946)	-0.97	-2.72, 0.84 [$$]
Median	0.968	0.982	0.978	-0.98	-2.74, 0.85 [$$$]
Min, Max	0.484, 1.860	0.450, 1.957	0.450, 1.957		
Adjusted Mean	0.965	0.985	0.975		
Completed patients		(Ratio to Baseline)			
n	153	171	324	0.994	0.955, 1.035 [$]
Mean (SD of logs)	0.988 (0.1916)	0.993 (0.1913)	0.991 (0.1912)	-0.29	-2.20, 1.70 [$$]
Median	0.988	0.988	0.988	-0.29	-2.21, 1.71 [$$$]
Min, Max	0.502, 1.860	0.450, 1.957	0.450, 1.957		
Adjusted Mean	0.989	0.995	0.991		

The assumption of normality was not fully satisfied after logarithmic transformation of the data so a non-parametric analysis was also performed. Firstly, 95% CIs for the difference between treatment groups were determined using distribution-free methods based on the Wilcoxon Rank Sum Test without adjustment for pooled centre. Secondly, 95% CIs for the difference between treatment groups were determined using distribution-free methods based on the Van Elteren Test with adjustment for pooled centre. In ITT (lower 95% CI -2.16 and -1.61) and PP populations (-2.57 and -2.14) the criterion for non-inferiority was met in the LOCF and completers analysis.

Despite the use of a run-in period with TOBI the statistical analyses revealed a highly significant centre effect due to pooled data that corresponded to the Ukrainian centres. Patients at the various Ukrainian centres did not show a uniform pattern of responses to either treatment regimen. The applicant performed a subgroup analysis after exclusion of the Ukrainian patients and compared this to the primary analysis.

- There were 308 patients (Colobreathe 151) in the ITT population after excluding Ukraine.
- There were 236 patients (Colobreathe 111 patients) in the PP population after excluding Ukraine.

Figure 6: Primary endpoint: FEV1 % predicted change from baseline (ITT population)



The figure above shows the FEV1% predicted change from baseline for all ITT patients and for Ukrainian versus non-Ukrainian patients who were included in the ITT population. It becomes clear that across all the Ukrainian centres the change from baseline was greater for both treatments (and despite the TOBI run-in period) compared to the non-Ukrainian patients. After exclusion of the Ukrainian patients the non-inferiority criterion was reached for both (LOCF) ITT (-1.67%) and PP (-2.4%) populations (using type III estimates). The criterion was also met for the completers. An additional analysis of the primary efficacy variable after excluding Ukraine was performed using type II estimates. In the LOCF analysis, the adjusted treatment difference in the change in FEV1 % predicted at Week 24 analysis was -1.36% (95% CI: -3.25, 0.54) for all patients in the ITT population. In completers, the adjusted treatment difference was -0.75% (95% CI: -2.81%, 1.31%) in the ITT population.

The following analyses were performed using the untransformed data.

The change in FEV1 % predicted at Week 24 according to baseline FEV1 subgroups (</> 50% predicted) gave comparable results for the two treatment groups. In the ITT population, the lower limit of the 95% CI was above -3% for the FEV1 <50% predicted subgroup but not the FEV1 ≥50% predicted subgroup. Similar results were obtained for the PP population in the LOCF and completers analysis.

Table 9:

ITT Population	N	Adjusted difference	95% CI
All patients using LOCF			
<50% predicted	176	0.21	-1.88, 2.29
≥50% predicted	197	-1.80	-5.05, 1.44
Completed patients			
<50% predicted	153	0.60	-1.65, 2.84
≥50% predicted	171	-1.25	-4.82, 2.31

The applicant provided additional tabulations of percentages with positive and negative changes in FEV1% predicted from baseline to week 24 by 3, 6 and 9 percentage points for all patients, by the three age groups and also according to baseline FEV1% predicted </> 50%. In the categorical analysis for all ITT patients there was no consistent trend in favour of either treatment. Using the LOCF but not using the completers approach there were more Colobreathe patients with negative changes but this only occurred in the last category (>-9%).

The 6-12 years group showed larger numbers in the Colobreathe group with the greatest positive changes from baseline (12 vs. 7) whereas the opposite occurred in the adolescents (7 vs. 13). Among the adults the results were comparable across all categories of change from baseline. For patients with baseline FEV1 values of < 50% and ≥ 50% there were no consistent trends. However, the subset with higher baseline values showed larger numbers in the Colobreathe with the last category negative change. For the most part the same patterns applied in the tabulations of the PP population data although numbers and differences between groups were mostly smaller.

In the ITT population, the FEV1 % predicted values at Week 24 for the two treatments were comparable within each age sub-group but the lower limit of the 95% CI was above -3% only for adults (59% of the study population). Similar results were obtained for the PP population in the LOCF and completers analysis. Due to the preponderance of children enrolled at the Ukraine sites and in light of the additional tabulations that showed a particular advantage for Colobreathe at the Ukraine sites but not at other sites among those aged 6-12 years it seemed that it was the Ukraine data that was driving the overall finding shown below that the benefit of Colobreathe might be most marked for the youngest group. In contrast, the FVE1% data suggested least benefit for the adolescents and broadly comparable benefit for the adults.

It was considered that these findings merited further exploration and additional questions have been suggested for the D180 LoOI.

Table 10: Change from baseline (untransformed data from CSR)

ITT Population	N	Adjusted difference	95% CI
All patients using LOCF			
6-12 years	67	0.26	-5.96, 6.47
13-17 years	86	-3.04	-8.96, 2.89
≥18 years	220	-0.83	-2.58, 0.92
Completed patients			
6-12 years	64	0.98	-5.40, 7.37
13-17 years	79	-2.00	-8.42, 4.41
≥18 years	181	-0.23	-1.97, 1.51

In the ITT population, the change in FEV1% predicted values from baseline to Week 24 showed slightly greater treatment differences in female patients. The lower limit of the 95% CI was above -3% for the male completer patients only. Similar results were obtained for the PP population in the LOCF and completers analysis, although the lower limit of the 95% CI was below -3% for all analyses.

In the ITT population, the change in FEV1 % predicted values from baseline to Week 24 showed that treatment differences in patients who had not used azithromycin or dornase alpha at baseline were higher than in patients who had. The lower limit of the 95% CI was above -3% for the patients who had used azithromycin or dornase alpha at baseline only. Similar results were obtained for the PP population in the LOCF and completers analysis although the lower limit of the 95% CI was below -3% for each analysis.

The use and timing of use of bronchodilators was comparable between treatments with little change during the 24 weeks of study except that slightly more Ukraine patients started salbutamol during the study period. The applicant was asked to evaluate the possible effects of allowing spirometry to be performed when only 2 h had elapsed since use of a bronchodilator. Further statistical analyses for FEV1 at 24 weeks (logarithmically transformed data) were performed according to use of bronchodilators in the ITT population. Patients were categorised according to no use within 4 weeks of FEV1 measurement or use afterwards only vs. those for whom the CRF indicated bronchodilator use prior to the FEV1 measurement. These additional analyses (for LOCF ITT and PP populations) supported the efficacy of Colobreathe among patients who did not take bronchodilators within 4 hours of pulmonary function testing and/or were not taking bronchodilating drugs.

Other pulmonary function tests

- The adjusted treatment difference for the change in FVC from baseline to Week 24/Exit Visit (Visit 6) was 0.01 L (95% CI: -0.09, 0.10 L) in the ITT population (p=0.886) and -0.02 L (95% CI: -0.12, 0.08 L) in the PP population (p=0.697).
- The adjusted treatment difference for the change in PEFR from baseline to Week 24/Exit Visit (Visit 6) was -3.32 L/min (95% CI: -16.31, 9.67 L/min) in the ITT population (p=0.616) and -8.73 L/min (95% CI: -22.69, 5.22 L/min) in the PP population (p=0.219). The ITT results at weeks 20 and 24 demonstrated differences in mean but not median values, with a large range in both treatment groups.
- The adjusted treatment difference for the change in FEV1 from baseline to Week 24/Exit Visit (Visit 6) was -0.05 L/s (95% CI: -0.12, 0.01 L/s) in the ITT population (p=0.120) and -0.07 L/s (95% CI: -0.14, 0.01 L/s) in the PP population (p=0.077). A detectable treatment difference was observed for the change in FEV1 from baseline to Week 4 (Visit 2) in the PP population (adjusted treatment difference, -0.06 L/s [95% CI: -0.13, -0.00 L/s], p=0.048) but not in the ITT population.
- The adjusted treatment difference for the change in FEF25-75 from baseline to Week 24/Exit Visit (Visit 6) was -0.12 L/s (95% CI: -0.23, -0.01 L/s) in the ITT population and -0.12 L/s (95% CI: -0.26, 0.01 L/s) in the PP population. A significant difference in favour of comparative therapy was detectable in the ITT population (p=0.038) but not in the PP population (p=0.063). Treatment differences (p<0.05) were observed in both populations for the changes in FEF25-75 from baseline to Week 4 (Visit 2), to Week 8 (Visit 3), and to Week 20 (Visit 5) in favour of the comparator.
- For the ITT and PP populations, the analyses of the other pulmonary function tests by paediatric age group showed a small number of detectable treatment differences, which are shown in the table below. These were all in favour of the comparative therapy. However, the actual differences were small.

Table 11: Other pulmonary function tests by paediatric age group

	N	Adjusted difference	95% CI	p-value
ITT Population				
FEF_{25-75}: 6-17 years				
Baseline to Week 4	146	-0.21	-0.40, -0.02	0.033
PP Population				
FVC: 13-17 years				
Baseline to Week 4	69	-0.20	-0.36, -0.04	0.015
Baseline to Week 8	69	-0.20	-0.38, -0.01	0.039
Baseline to Week 16	67	-0.24	-0.43, -0.04	0.020
Baseline to Week 20	63	-0.26	-0.49, -0.04	0.021
FVC: 6-17 years				
Baseline to Week 20	115	-0.17	-0.31, -0.03	0.017

Time to acute respiratory exacerbation and to first additional anti-pseudomonal treatment

In the ITT population, the mean period of time to acute respiratory exacerbation (overall) was slightly longer in the Colobreathe group (63.70 days) than in the TOBI group (59.39 days). The mean period of time to non-protocol-defined acute exacerbations was 83.32 days in the Colobreathe group compared to 67.06 days in the TOBI group.

The mean time to first additional anti-pseudomonal treatment was 55.28 days in the Colobreathe group and 51.79 days in the TOBI group. The results of the PP population were similar and confirmed the ITT results. In the ITT population the mean duration of use of additional anti-pseudomonal agents was slightly lower in the Colobreathe group (13.6 days) than in the TOBI group (14.4 days). The results of the PP population were similar and confirmed the ITT results.

In the 6-12 years ITT and PP populations, the mean time to acute exacerbation was nearly twice as long in the Colobreathe group compared to the TOBI group. There was also a substantial difference between the treatment groups for time to first additional anti-pseudomonal treatment. There was an advantage for TOBI in adolescents and a modest advantage for Colobreathe in adults.

Table 12: Time to Acute Exacerbation and Time to First Additional Anti-pseudomonal treatment, (ITT population)

Age band	Treatment group	Time to Acute Exacerbation Days (n)	Time to first additional anti-pseudomonal treatment Days (n)
≤ 12 yrs	Colobreathe	74.11 (9)	52.83 (12)
	TOBI	40.0 (11)	34.64 (14)
>12 to <18 yrs	Colobreathe	55.05 (20)	57.15 (27)
	TOBI	69.73 (15)	69.16 (19)
≥18 yrs	Colobreathe	65.68 (40)	54.89 (53)
	TOBI	60.57 (49)	50.37 (63)

Change in FEV1 % predicted at Week 20

The adjusted treatment difference for the change from baseline to Week 20 (Visit 5) was -1.40% (95% CI: -3.43%, 0.63%) in the ITT population (p=0.175) and -1.86% (95% CI:-4.19%, 0.46%) in the PP population (p=0.116). The treatment-by-pooled centre interaction was investigated but was found to be not statistically significant and was therefore not included in the model.

The ANCOVA was repeated on logarithmically transformed data. In the ITT population, the adjusted mean difference between the Colobreathe and TOBI groups in the change in FEV1 % predicted at Week 20 was -1.23% (95% CI: -3.03%, 0.64%). In the PP population, the adjusted mean difference between the Colobreathe and TOBI groups in the change in FEV1 % predicted at Week 20 was -1.44% (95% CI: -3.45%, 0.66%). Non-parametric analysis on the data was also performed and the 95% CI fell within -3%.

Quality of life (CFQ-R)

With respect to all CFQ-R domains and at nearly all time points the two treatments were similar. At Week 24/Exit, the QoL assessments were in favour of Colobreathe in the majority of CFQ-R domains in the ITT population.

Table 13: Adjusted mean changes in quality of life (CFQ-R) from baseline to Week 24/Exit Visit (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

In the ITT population, detectable differences were only observed for:

- The change in treatment burden from baseline to Week 4 (Visit 2) with Colobreathe being more favourable (adjusted difference: 6.27; 95% CI: 3.15, 9.40; p<0.001)
- The change in body image from baseline to Week 4 (Visit 2) with TOBI being more favourable (adjusted difference: -4.08; 95% CI: -7.73, -0.44; p=0.028)
- The change in digestion from baseline to last recorded result with Colobreathe being more favourable (adjusted difference: 3.67; 95% CI: 0.27, 7.07; p=0.034).

In the PP population, detectable differences were only observed for:

- The change in treatment burden from baseline to Week 4 (Visit 2) with Colobreathe being more favourable (adjusted difference: 5.57; 95% CI: 2.07, 9.06; p=0.002)
- The change in body image from baseline to Week 4 (Visit 2) with TOBI being more favourable (adjusted difference: -4.30; 95% CI: -8.55, -0.06; p=0.047).

At Week 24/Exit, the QoL assessments for the paediatric subgroups (ITT population) were in favour of Colobreathe in the majority of CFQ-R domains but there were no statistically significant differences.

After exclusion of the data from Ukraine, the ITT population showed changes from baseline to Week 24/Exit Visit that were more positive in the Colobreathe group compared to the TOBI group for the majority of CFQ domains, especially for treatment burden, health perceptions, body image and digestion. The mean change from baseline to Week 4 in treatment burden (ITT: p<0.001 and PP: p=0.004) and health perception (ITT: p=0.047) and for the mean change from baseline to last recorded result in digestion (ITT: p=0.039) were statistically significantly higher with Colobreathe.

Adherence to study medication

In the ITT population, a similar proportion of patients in the Colobreathe and TOBI groups were ≥75% adherent to study medication (66.7% and 70.7%, respectively). In the PP population, rates for adherence ≥75% were slightly higher (68.8% and 72.0%).

Patient ease of use/preference assessment

In the ITT population, 51.9% assessed Colobreathe as 'very easy to use' whereas only 9.9% assessed TOBI as 'very easy to use'. In the Colobreathe and TOBI groups, 38.8% and 44.0% assessed the treatments as 'easy to use' while 2.2% vs. 31.9% assessed them as 'neither easy nor hard to use'. There was a statistical difference (95% CI: 4.684, 15.274; $p<0.001$) in favour of Colobreathe. Overall 43/183 patients (23.5%) randomised to Colobreathe preferred TOBI and 120/183 (65.6%) preferred Colobreathe.

Of the 6-12 year old patients in the in the Colobreathe group, 25/31 (80.6%) preferred Colobreathe.

Of the 13-17 year old patients in the in the Colobreathe group, 24/41 (58.5%) preferred Colobreathe.

Investigator's global assessment

In the ITT population, a slight to marked improvement was reported by the investigators in 84/183 patients (45.9%) in the Colobreathe group and 81/191 patients (42.4%) in the TOBI group. No change was reported for 32.8% and 41.4%, respectively, and a slight to marked worsening for 18.0% and 12.0%, respectively. The differences between the two treatment groups did not reveal a trend.

A slight to marked improvement was reported by the investigator in 26/31 (83.9%) 6-12 year old patients in the Colobreathe group and in 28/36 (77.8%) in the TOBI group.

A slight to marked improvement was reported by the investigator in 21/41 (51.2%) 13-17 year old patients in the Colobreathe group and in 28/46 (60.9%) in the TOBI group.

Antibacterial susceptibility of respiratory tract P. aeruginosa isolates (BSAC breakpoints, 2008)

Based on the 2008 BSAC breakpoints for colistin ($S \leq 4$ mg/L, $R > 4$ mg/L) and the use of E-tests the proportion of colistin-resistant isolates obtained during the 24-week treatment period was low ($\leq$ 1.1%) and did not increase based on patients still in the study at each time point. The findings also applied in the paediatric sub-populations and in each country. The percent resistant to tobramycin did not change substantially during the study.

Summary of main study

The following table summarises the efficacy result from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 14: Summary of Efficacy for trial COLO/DPI/02/06

Title: A randomised, open label study to compare the efficacy and safety of a dry powder formulation of inhaled colistimethate sodium (Colobreathe) and nebulised tobramycin (TNSFI [tobramycin nebuliser solution for inhalation], TOBI™) in cystic fibrosis patients with *Pseudomonas aeruginosa* lung infection.			
Study identifier	COLO/DPI/02/06		
Design	A randomised, open label, multicentre study in subjects ≥ 6 years of age with documented cystic fibrosis (CF) and chronic pulmonary infection with *Pseudomonas aeruginosa*. Subjects would normally be being treated with inhaled antibiotics, and should have an FEV_1 (% predicted) value of 25 – 75% and be inhaling TOBI™ (having had a minimum of two on/off cycles) prior to randomisation. The study objective was to quantify any change in FEV_1 (% predicted) from baseline on entry to the study Visit 1 (Day 1) to Visit 6 (Week 24).		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 weeks At least 8 weeks Not applicable
Hypothesis	Non-inferiority. The 95% two-sided confidence interval was computed for the difference of DPI colistin minus TOBI. If the lower bound is no lower than -3.0 percentage points for both the PP and ITT populations it will be concluded that the experimental drug, dry powder inhaler, is not inferior to the control.		
Treatments groups	Colistimethate sodium dry powder inhaler		One capsule containing 1,662,500 IU (125mg) colistimethate sodium dry powder inhaled twice daily for 24 weeks using the Turbospin™ device(n=187)
	Tobramycin nebuliser solution for inhalation		One ampoule of 5ml containing 300mg tobramycin inhaled via a PARI-LC Plus™ nebuliser twice daily for 24 weeks. Administered as cycles of 4 weeks of treatment followed by 4 weeks of no treatment (n=193)
Endpoints and definitions	Primary endpoint	FEV_1 (% predicted) at week 24	To quantify any change in FEV_1 (% predicted) by comparison to baseline at Visit 6 (Week 24).
	Secondary endpoint	Emergence of resistance	To quantify changes in resistance of *Pseudomonas aeruginosa* isolates to colistimethate and tobramycin as measured by *in vitro* MIC at the beginning and end of the study.
	Secondary endpoint	Quality of life	To compare the quality of life on each treatment regimen as measured by responses to the Cystic Fibrosis Questionnaire – Revised (CFQ-R)

	Secondary endpoint	Other	Additional secondary endpoints to provide supportive evidence by further characterising treatment effects included: 1) Time to first acute respiratory exacerbation and time to first use of additional anti-pseudomonal intravenous or oral antibiotics intended for the management of acute respiratory exacerbation 2) Other pulmonary function tests to include FVC, PEFR, FEV_1 and FEF_{25-75}
Database lock	2^{nd} November 2007		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat, FEV1 % predicted at week 24, logarithmically transformed			
Descriptive statistics and estimate variability	Treatment group	Dry powder colistimethate twice daily	Nebulised tobramycin twice daily	Treatment Comparison Dry powder colistimethate vs. Nebulised tobramycin
	Number of subjects	183	190	
	Ratio to baseline in FEV1 % predicted at week 24 (mean) all patients using LOCF	0.964	0.986	95% CI for treatment ratio 0.943, 1.018 95% CI for treatment difference (back transformed) -2.74, 0.86
	Standard deviation of logs	0.1994	0.1898	
Analysis population and time point description	Per Protocol, FEV1 % predicted at week 24, logarithmically transformed			
Descriptive statistics and estimate variability	Treatment group	Dry powder colistimethate twice daily	Nebulised tobramycin twice daily	Treatment Comparison Dry powder colistimethate vs. Nebulised tobramycin
	Number of subjects	141	157	
	Ratio to baseline in FEV1 % predicted at week 24 (mean) all patients using LOCF	0.974	0.997	95% CI for treatment ratio 0.935, 1.020 95% CI for treatment difference (back transformed) -3.07, 0.96
	Standard deviation of logs	0.2040	0.1957	

Notes	Analysis of variance on logarithmically transformed data with covariates of baseline FEV1 % predicted and pooled centre

Supportive study

- **COLO/DPI/02/05** - Randomised, open label cross-over study to compare the safety of a dry powder formulation of inhaled colistimethate sodium in CF patients with *Pseudomonas aeruginosa* lung infection.

This was a Phase 2 study in which the primary objective was an assessment of safety. However, efficacy data are reported.

This randomised, open label cross-over study in patients aged eight years and over with documented CF who would normally be treated with inhaled antibacterial agents provides a short-term comparison of nebulised and dry powder inhalation of colistimethate sodium. The study was conducted in 2003-2005 at three centres in the UK and enrolled 16 patients (8 aged < 14 and 8 > 14 years).

Patients were to have stable lung function, a history of prior treatment with nebulised colistimethate sodium without showing intolerance or requiring cessation of therapy and FEV1 at least 25% of predicted value. There were two active antibacterial treatment periods of four weeks each, with a wash-out period of 72 h from any anti-pseudomonal therapy (and 28 days off TOBI before study entry) at the beginning and between treatment periods. At randomisation patients were stratified by age to receive either Colobreathe (1) or nebulised treatment (2) first.

No relevant changes in FEV1% predicted and FVC were seen from the baseline to end of the respective treatment period. Additionally, statistical testing (paired t-test) showed no significant differences in changes in FEV1% predicted between the two treatments. FEV1% predicted tended to be higher in those < 14 years vs. > 14 years but within each age stratum no clear differences were seen between the dry powder and the nebulised treatments. There were also no consistent differences in FVC between the two treatments in either age stratum. The results for the per protocol and safety sets were comparable.

All patients with values who received the dry powder first and then the nebulised treatment rated the latter as much harder (62.5%) or a little harder (25%) to use than the former treatment. In line with this finding, all patients with values who received the nebulised treatment first and then the dry powder rated the latter as much easier (62.5% of patients) or a little easier (25%) to use than the first treatment (i.e. nebulised). Patients aged < 14 years were more likely to report better ease of use for dry powder (75% rated dry powder as much easier to use in the safety set and 100% in the per protocol set) than patients aged > 14 years (50% rated dry powder as much easier to use in the safety set and 66.7% in the per protocol set).

When adolescents and adults completed the CFQ the scores remained about the same or decreased from Visit 1 to end of treatment in both treatment groups for most of the domains. A clear increase was only seen for the total treatment score in the dry powder group. When the parents/caregivers completed the CFQ for children a clear increase in mean scores from Visit 1 was seen during treatment with dry powder for the total body score, the total treatment score, the total school score and the total digestion score. With the exception of the total school score where the reverse was the case these increases were greater during dry powder treatment. A pronounced decrease from Visit 1 to end of treatment was seen for the total weight score during both treatments with the decrease being greater on dry powder. For the remaining scores, no major changes were seen.

2.5.3 Discussion on clinical efficacy

COLO/DPI/02/06

Design and conduct of clinical study

The study planned that if the lower bound of the 95% CI around the treatment difference in change in FEV1% predicted at week 24 was within -3% for both the PP and ITT populations, it was to be concluded that Colobreathe was non-inferior to TOBI. This non-inferiority margin was based on the pooled results of two placebo-controlled nebulised tobramycin studies conducted during the 1990s. The published analysis showed that at week 24 the relative change from baseline was by about +8% for TOBI and -2% for placebo. At week 20 the TOBI group had a 10% relative increase in FEV1% predicted compared to -2% in the placebo group.

Since the baseline mean FEV1% predicted was almost exactly 50% in both treatment groups these data equated with approximately 6 and 5 percentage point differences in actual FEV1% predicted mean values at weeks 20 and 24, respectively. Thus, CHMP had considered that a non-inferiority margin not in excess of -2.5% could be supported at week 24 for COLO/DPI/02/06. The changes in treatment of CF and in FEV1% values since the 1990s add to the difficulties raised by possible lack of constancy but there are no other suitable data to assist in defining an appropriate non-inferiority margin from past studies.

Efficacy data and additional analyses

The applicant pre-defined a 3% non-inferiority margin at least partly on grounds that this would be a clinically acceptable difference. In the pre-planned primary analysis the lower bound of the 95% CI was -2.59% for patients who completed the study in the ITT population but for the ITT LOCF and both the PP analyses the lower bound of the 95% CI exceeded -3%. The corresponding analyses using logarithmic transformation of the data gave lower 95% CI from -2.20 to -3.08 and the non-parametric analyses gave lower 95% CI from -1.43 to -2.49.

There are several other observations that need to be taken into account when considering these overall comparisons. For example, at week 24 subjects in the comparative group had been off treatment for 4 weeks and therefore might represent a time point at which a comparison could potentially bias Colobreathe. The comparison of data at week 20 indicated that the lower bound of the 95% CI exceeded -3.5%. As described above, there were clear differences according to age groups with suggestions of an advantage for Colobreathe in those aged 6-12 years, a disadvantage in the adolescents aged 13-18 years and very comparable results in the adults. Most of the children aged 6-12 years had been enrolled at Ukraine sites, where the benefit of Colobreathe was anyway seemingly larger and this could be driving these observations.

The conclusion was that Colobreathe is probably not quite as good as TOBI across pooled age groups but still within a range that would exclude significant clinical differences. In addition, there was a clear patient preference for Colobreathe. Quality of life assessment supported the use of Colobreathe and "Time to exacerbation" also tended to favour Colobreathe. After resolution of all the questions, including the provision of several additional analyses to provide reassurance regarding the robustness of the single pivotal study, it was concluded that making available an alternative dry powder inhalation that requires only two inhalations per day could be regarded as an advantage to patients in terms of convenience and likely without clinical significant disadvantage in terms of lung function..

COLO/DPI/02/05

Regardless of the sequence in which they used dry powder and nebulised colistin, most patients with values found the dry powder easier to use. The tendency for a better ease of use assessment for dry powder than nebulised treatment was more pronounced in children than in adults. Changes in FEV1% predicted appeared to be slightly better with nebulisation, but there was no significant difference between treatments.

2.5.4 Conclusions on the clinical efficacy

Based on all the lung function data the overall picture pointed to a conclusion that Colobreathe may be slightly less optimal than TOBI . However, the fact remains that most differences vs. TOBI were actually quite small (within an acceptable range) whilst there were also some clear advantages noted for Colobreathe in sub-populations. These observations were weighed against patient opinions regarding ease of use and quality of life data that favoured Colobreathe.

2.6 Clinical safety

Patient exposure

Exposure ranged from single doses to 24 weeks treatment with Colobreathe.

Adverse events

In ***COLO/DPI/98/01*** the 12 healthy subjects reported 60 AEs, all of which were of mild intensity. Cough, throat irritation and unpleasant taste were all more common after dry powder inhalations than after nebulised colistimethate sodium. There was no appreciable difference with salbutamol pre-treatment except for nausea and dizziness, which may have been due to use of the beta-agonist by subjects not accustomed to these agents. Similarly, in PPL-252 nine of the 10 subjects reported AEs. These were mainly cough, unpleasant taste and throat irritation. Three subjects also reported wheezing. Most were of mild intensity. In COLO/DPI/98/02 14 AEs were reported by the 12 subjects with CF, all of which were of mild intensity. There was no excess of AEs during dry powder inhalations, with or without salbutamol pre-treatment, compared to nebulised colistin.

In ***COLO/DPI/02/05*** the safety assessments included spontaneously reported AEs and solicited symptoms. All except one patient reported solicited symptoms in the dry powder phase compared to one third in the nebulised colistin phase. The difference was mostly accounted for by reports of unpleasant taste, throat irritation and new cough/increase in cough. There were no major differences in reporting between the adults and the children. The majority of AEs were of mild or moderate intensity. Severe AES were reported by six patients in the dry powder phase and one in the nebulised phase.

COLO/DPI/02/06

The overall comparison between treatment groups is shown in the table. In interpreting these figures it must be remembered that all subjects had already been exposed to the comparative treatment whether pre-study or in the run-in phase.

Table 15: Treatment-Emergent Adverse Events Summary (Safety population)

	DPI colistin (N=187)			Nebulised TOBI® (N=193)		
	n	(%)	E	n	(%)	E
Number of AEs	175	(93.6)	1232	172	(89.1)	1194
Number of related AEs	153	(81.8)	528	90	(46.6)	325
Number withdrawn due to an AE	22	(11.8)	62	5	(2.6)	16
AE severity						
Mild	159	(85.0)	702	165	(85.5)	773
Moderate	123	(65.8)	439	97	(50.3)	388
Severe	48	(25.7)	91	13	(6.7)	33
AE relationship to study drug						
Definitely related	134	(71.7)	352	51	(26.4)	147
Probably related	51	(27.3)	108	35	(18.1)	71
Possibly related	38	(20.3)	68	38	(19.7)	107
Unlikely to be related	56	(29.9)	154	49	(25.4)	158
Not related	129	(69.0)	550	148	(76.7)	711
AE outcome						
Resolved, no sequelae	167	(89.3)	909	163	(84.5)	934
Ongoing	104	(55.6)	319	90	(46.6)	257
Death	0		0	2	(1.0)	2
Lost to follow-up	4	(2.1)	4	1	(0.5)	1

The most common AEs by system organ class were respiratory, thoracic, and mediastinal disorders (occurring in 89.8% of Colobreathe patients and 78.2% of TOBI patients) and the most common individual AEs in this SOC are shown in the table below.

Table 16: Adverse events by system organ class and preferred term (Safety population)

System organ class Preferred term	DPI colistin (N=187) n	(%)	E	Nebulised TOBI® (N=193) n	(%)	E
Number of adverse events	175	(93.6)	1232	172	(89.1)	1194
Respiratory, thoracic and mediastinal disorders	168	(89.8)	758	151	(78.2)	742
Cough	141	(75.4)	193	84	(43.5)	123
Throat irritation	85	(45.5)	94	54	(28.0)	63
Lower respiratory tract infection	53	(28.3)	79	57	(29.5)	85
Dyspnoea	49	(26.2)	81	52	(26.9)	98
Productive cough	38	(20.3)	62	44	(22.8)	76
Wheezing	31	(16.6)	35	38	(19.7)	46
Chest discomfort	26	(13.9)	29	34	(17.6)	41
Dysphonia	22	(11.8)	24	30	(15.5)	35
Haemoptysis	20	(10.7)	26	13	(6.7)	16
Chest pain	13	(7.0)	13	16	(8.3)	23
Crackles lung	13	(7.0)	13	14	(7.3)	18
Increased upper airway secretion	12	(6.4)	12	13	(6.7)	14
Pharyngitis	10	(5.3)	11	14	(7.3)	14
Rhonchi	8	(4.3)	9	10	(5.2)	10
Dyspnoea exacerbated	8	(4.3)	8	8	(4.1)	11
Sputum purulent	7	(3.7)	8	8	(4.1)	8
Respiratory tract infection	8	(4.3)	9	6	(3.1)	7
Upper respiratory tract infection	5	(2.7)	6	7	(3.6)	12
Respiratory tract infection viral	5	(2.7)	6	5	(2.6)	5
Asthma	5	(2.7)	5	2	(1.0)	2
Rales	2	(1.1)	2	5	(2.6)	5
Nasal congestion	2	(1.1)	2	4	(2.1)	4

Forest Laboratories UK Ltd: COLO/DPI/02/06/CIL-MJ/FINAL/AEC01P.SAS
Produced: 11 May 2009, 11:51
Source: Listing 11.1
Notes: [1] All adverse events including serious adverse events are included in summary statistics
[2] If a patient has multiple occurrences of an AE, the patient is presented only once in the respec
[3] Table presents number and percentage of patients (n (%)) and number of events (E)
[4] Percentages are based on the number of patients in the respective group

Gastrointestinal disorders were reported in 65.2% Colobreathe and 38.9% TOBI patients. For other SOCs the total frequencies of reporting were comparable between treatment groups. Individual AEs that were reported with a considerably higher incidence in the Colobreathe group compared to the TOBI group included cough (75.4% vs. 43.5%), throat irritation (45.5% vs. 28.0%), haemoptysis (10.7% vs. 6.7%) and dysgeusia (62.6% vs. 27.5%).

Between 0 and 28 days cough was reported by 58% of patients in the Colobreathe group and 20% in the TOBI group who were still on study. These reporting rates had decreased to 10% and 8% of patients in respective groups for those still in the study after 20 weeks. The nearly 8-fold drop in reporting cough cannot be explained by the numbers who had discontinued due to cough or other respiratory AEs and likely represents habituation of patients to the new treatment.

Relevant to these data patients completed a symptom questionnaire. This showed that at baseline (Visit 1) symptoms reported to be associated with drug inhalation included unpleasant taste (48.1% of Colobreathe patients and 13.5% in the TOBI group), throat irritation (21.4% and 8.3%) and new cough/increase in cough (36.4% and 7.8%). By the time of the Week 24/Exit Visit (Visit 6) the proportions that assessed drug inhalation to be associated with their symptoms had decreased so that unpleasant taste was reported by 34.2% of Colobreathe patients and 5.7% of TOBI patients, throat irritation was reported by 12.8% and 5.2% and new cough/increase in cough by 24.6% and 3.6%. However, there was a slight increase from baseline to Week 24/Exit Visit in the proportion of Colobreathe patients who experienced severe unpleasant taste (from 4.3% to 7.0%).

There were 20 patients treated with Colobreathe who had haemoptysis reported as a TEAE.

Table 17: Safety Population Haemoptysis Reports

Treatment	Medical History (Only)	Run-in (Only)	Treatment Phase (& Medical History)	Treatment Phase (& During Run-in)	Treatment Phase (Only)	Total
Colobreathe	4	3[3]	4[1]	1[1]	15[1]	27
TOBI	3	3[2]	2[2]	2[2]	10[2]	20

[1] = related to Colobreathe treatment; [2] = related to TOBI treatment; [3] = on TOBI during run-in phase before Colobreathe treatment

A prior history of haemoptysis did not correlate with clinically significant differences in severities or durations of the haemoptysis episodes that occurred while on treatment with Colobreathe. Two of the four with a medical history of haemoptysis reported it as ongoing throughout treatment as did three without a prior medical history. Most episodes of haemoptysis lasted for 6 days or less and the maximum duration of those instances that did resolve during study was 36 days. Most patients only experienced one episode of haemoptysis and no episodes resulted in withdrawal from treatment. Co-administered inhaled products which have been associated with reports of haemoptysis include dornase alpha and hypertonic saline. In the Colobreathe group 14/20 with haemoptysis on treatment received one or both of these treatments.

AEs of moderate or severe intensity were reported in a higher percentage of Colobreathe patients compared to TOBI patients. In addition, drug-related AEs were reported more often in the Colobreathe group. Overall 21.9% of patients in the Colobreathe group and 3.1% in the TOBI group had at least one severe AE considered to be drug-related. This difference between groups reflected rates of respiratory AEs (16% vs. 2.1% of patients) and mainly cough (in 11.8% and 2.1% in respective groups). Severe, drug-related gastrointestinal disorders occurred in 10.2% of Colobreathe patients and 1.6% of TOBI patients but these rates were due to dysgeusia. Similar patterns were observed for AEs of moderate severity that were considered drug-related (overall in 43.3% Colobreathe and 20.2% TOBI patients) and mild severity considered drug-related (69.5% and 42% of patients in respective groups).

Adverse reactions (possibly, probably or definitely related or with an unknown relationship to study medication) are summarised in the table below, which expresses rates in terms of percentages of patients reporting an ADR. Cough, unpleasant taste and throat irritation were the most commonly reported ADRs in both treatment groups but were reported more often with Colobreathe. There was no clear trend for these ADRs to increase in frequency with increasing age although adults had the highest rates in each treatment group for many of the AEs listed. Despite this, adults very commonly considered these ADRs to be of mild intensity. The data did not suggest consistent trends for age-related reporting of AEs or ADRs. The types of AEs reported most often in children resembled those reported in adults and rates were often slightly lower in children compared to older subjects.

In order to put the findings into perspective, the applicant pointed out that an increased risk of local irritation from inhalation of a dry powder compared to a nebulised mist was reported in studies that compared these modes of administration for tobramycin. For example, Geller et al (2007) compared tobramycin dry powder (TIP) vs. TOBI. More TIP subjects experienced at least one AE (69% after 112 mg) compared to TOBI (30%). The most common AEs after TIP were cough (13/66 subjects, 20%) and dysgeusia (11/66 subjects, 17%), which were not reported after TOBI but 85% had previously been treated with TOBI. Konstan et al (2011) published results from the EAGER study that compared 24 weeks TOBI with 128 mg TIP given over three on/off cycles in 553 patients. Cough was reported for 48.4% TIP and 31.1% TOBI patients and drug-related cough for 25.3% vs. 4.3%. Approximately 4%

TIP patients discontinued due to cough vs. 1% (2/209) of TOBI patients. Other AEs more commonly reported for TIP were dysphonia (13.6% vs. 3.8%) and dysgeusia (3.9% vs. 0.5%). The highest reporting rates occurred in the first cycle.

Table 18: Adverse reactions by age group as % of patients reporting an event (COLO/DPI/02/06)

	Colobreathe			TOBI		
	≤ 12 yrs (n=32)	>12 to <18 yrs (n=41)	>18 yrs (n=114)	≤ 12 yrs (n=37)	>12 to <18 yrs (n=47)	≥18 yrs (n=109)
Dysgeusia	53%	48.8%	64.3%	21.6%	14.4%	31.2%
Decreased appetite	0%	<5%	0%	5.4%	0%	<5%
Balance disorder	0%	<5%	<5%	8.1%	0%	<5%
Cough	59.4%	51.2%	62.3%	16.2%	8.5%	30.3%
Chest discomfort	<5%	<5%	12.3%	<5%	0%	12.8%
Dyspnoea	6.3%	12.2%	21.1%	8.1%	<5%	18.3%
Haemoptysis	0%	<5%	5.3%	0%	0%	<5%
Dysphonia	6.3%	12.2%	11.4%	10.8%	<5%	17.4%
Throat irritation	34.4%	34.1%	50%	21.6%	8.5%	25.7%
Productive cough	0%	0%	<5%	<5%	0%	5.5%
Wheezing	6.3%	<5%	12.3%	<5%	<5%	16.5%

Hypersensitivity reactions were recorded in a small number of patients in each treatment group.

Serious adverse event/deaths/other significant events

In COLO/DPI/02/06 two TOBI patients had respiratory tract infections leading to death.

Rates of SAEs were not different between treatment groups, were mixed in nature and were not clustered by type or treatment. Of the five SAEs considered to be drug-related by investigators, the three in the Colobreathe group involved a convulsion, asthma and haemoptysis while the two in the TOBI group were both cases of haemoptysis. The Colobreathe patient with a convulsion had a past history of petit mal seizures. The Colobreathe patient with asthma was 14 years old with no history of asthma but had an acute attack requiring hospitalisation on Day 57 of study and 7 hours after the last dose. A patch test performed post-recovery gave a positive result. The patient with haemoptysis at

about one month into treatment was 18 years old and had haemoptysis three years earlier. He also had bronchiectasis and pancreatic insufficiency.

Laboratory findings

COLO/DPI/02/06

Laboratory abnormalities reported as AEs (there were no laboratory SAEs) in the Colobreathe group included increased neutrophil count (n=3 patients), hyperglycaemia (3), increased ALT (2), increased WBC count (2), proteinuria (2), increased hepatic enzymes (1), increased platelet count (1) and blood in urine (1). One AE of proteinuria was assessed as possibly related to study drug by the investigator. There were no notable mean or median changes from baseline to Week 24 in any haematology, biochemistry or urinalysis parameter and no notable differences between the two treatment groups with respect to mean or median laboratory values or shifts from baseline. Clinically significant values were reported in relatively small numbers and there did not seem to be any notable difference between treatment groups in numbers with these various types of events.

Discontinuation due to adverse events

In COLO/DPI/02/05 AEs leading to withdrawal were reported for two patients during treatment with dry powder. Both had completed nebulised treatment in the first treatment period. These involved:

- A 19-year old female with chest discomfort, severe cough, moderate dyspnoea, severe wheezing, unpleasant taste and throat irritation after the first intake of dry powder. No therapy was given and the events resolved. These AEs were considered definitely related to study medication.
- A 9-year old male with moderate cough and severe gastrointestinal disorder after the first intake of dry powder, assessed as definitely related to study medication. No treatment was given and the events resolved.

COLO/DPI/02/06

Of the 27 patients (7.1%) withdrawn from the study due to an AE 22 were in the Colobreathe group and 21 were withdrawn due to one or more respiratory AEs including cough, dyspnoea, haemoptysis and asthma. The timing of withdrawals was as shown below.

Table 19: Number of withdrawals by time band (related adverse events, lack of efficacy and other reasons) (Taken from Appendix 1, Listing A)

	Time band						
Treatment	Day 1	>Day 1 to ≤ 4 weeks	>4 to ≤ 8 weeks	>8 to ≤ 12 weeks	>12 to ≤ 16 weeks	>16 to ≤ 20 weeks	> 20 to ≤ 24 weeks
Colobreathe	2	8	6	2	2	1	1
TOBI	1	0	0	3	0	1	0

Three adults withdrew on days 1- 3, including two due to bronchospasm and one due to abnormal chest sounds, all regarded as probably related and moderate in severity. Up to day 28 a further 7 adults (one was 17 years old) patients withdrew including five due to reasons such as cough, dyspnoea, wheezing and decrease in FEV1 but none appeared to have suffered exacerbations. One withdrew due to haemoptysis and one due to convulsion. In the second 4 week period a further 6 Colobreathe patients (all adults) withdrew for reasons including severe decrease in FEV1, lower respiratory tract infection, asthma, cough with recorded respiratory exacerbation, dyspnoea and cough and haemoptysis. Between days 56 and 84 a child with severe asthma and dyspnoea, an adult with

wheezing being treated with oral antibiotics and an adult with mild dyspnoea on anti-allergy treatment withdrew. In the remaining 12 weeks only 4 patients withdrew.

Thus, 21/22 patients who withdrew from Colobreathe had symptoms that would be associated with pulmonary exacerbation, intolerance to Colobreathe or other manifestations of cystic fibrosis. Only two of these patients were under 18 years even though patients aged < 18 years accounted for half the study population. The rate of withdrawal decreased over time and 16/22 occurred during the first 2 months.

Post marketing experience

There are no post-marketing data on the dry powder. There are many years experience on use of nebulised colistimethate sodium. The applicant provided a satisfactory review of the safety information related to nebulised colistimethate, which suggested that most of the problems that will arise with the DPI will likely be related to immediate or early airways reactivity that should be manageable in the same way that reactions to nebulisation are managed.

2.6.1 Discussion on clinical safety

Cough, throat irritation and unpleasant taste were reported more commonly with Colobreathe compared to nebulised colistimethate sodium or TOBI. There were more withdrawals from Colobreathe than from TOBI due to AEs, almost all which involved cough, dyspnoea, haemoptysis, wheezing or asthma. However, all patients in the Phase 2 study had previously received nebulised colistimethate while all patients in the Phase 3 study had previously received TOBI. Therefore the patients were already pre-selected to a considerable extent such that they were very likely to tolerate nebulised treatments.

It appears that the majority of the problems that can be expected on initiating Colobreathe may be associated with DPI rather than the active substance *per se*. Based on published experience with DPI tobramycin, the picture observed with Colobreathe is not dissimilar. It also appears that the numbers that will withdraw from treatment will decrease over time. This does not necessarily mean that the side effects disappear but more likely reflects early discontinuation by those with severe side effects and increasing tolerance of less severe symptoms.

The analyses of AEs and ADRs by age suggest that the same range of side effects occurs with no marked differences in rates but the severity scoring is more variable.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics

2.6.2 Conclusions on the clinical safety

The overall safety profile of Colobreathe is acceptable. It is likely that a similar profile would be observed when commencing inhalational therapy and also when switching from nebulised to dry powder inhalation antibacterial treatment.

2.7 Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The applicant submitted a risk management plan, which included a risk minimisation plan

Table 20: Summary of the risk management plan

Safety concern	Agreed pharmacovigilance activities (routine and additional)	Agreed risk minimisation activities (routine and additional)
(Identified risks)		
Cough, including coughing out drug substance	o Routine Pharmacovigilance o A study to evaluate systemic exposure following inhalation of Colobreathe is planned to be conducted shortly: This study will include the determination of sputum drug levels and therefore the analysis of these data will be able to correlate the emergence of cough with drug levels. This should provide definitive reassurance that coughing out drug substance has no effect on efficacy. o Post Marketing Surveillance Study: Reports of cough will be closely monitored in a post approval study as well as post-marketing surveillance, and will be the subject of special review in future PSURs	o Sections 4.2 and 4.4 of the SmPC recommend that these symptoms may be ameliorated with appropriate pre-treatment with a bronchodilator (beta2-agonist) prior to inhalation. o Educational material: Preparation of an educational DVD for use by healthcare professionals and patients which will describe clearly the technique for use of the device and provide reassurance with respect to continued use. The complete content of the DVD is currently under consideration and will be finalised prior to launch of the product in the EU
Dysgeusia	o Routine Pharmacovigilance o Post Marketing Surveillance Study: Reports of dysgeusia will be closely monitored in a post approval study as well as post-marketing surveillance, and will be the subject of special review in future PSURs	None
Dyspnoea	o Routine Pharmacovigilance o Post Marketing Surveillance Study: Reports of dyspnoea will be closely monitored in a post approval study as well as post-marketing surveillance, and will be the subject of special review in future PSURs	None
Bronchospasm	o Routine Pharmacovigilance o Post Marketing Surveillance Study: Reports of bronchospasm will be closely monitored in a post approval study as well as post-marketing surveillance, and will be the subject of special review in future PSURs	None

Exacerbation of Myasthenia Gravis	o Routine Pharmacovigilance o Post Marketing Surveillance Study: Reports of exacerbation of myasthenia gravis will be closely monitored in a post approval study as well as post-marketing surveillance, and will be the subject of special review in future PSURs	None
Off-label use	o Routine Pharmacovigilance o Reports of off label use will be closely monitored via the post-marketing pharmacovigilance systems, and will be reviewed independently in future PSURs.	None
Oropharyngeal infection with candida albicans or other yeast like organisms	o Routine Pharmacovigilance, including independent review in future PSURs o Post Marketing Surveillance Study: Reports of oropharyngeal infection will be monitored by review of adverse events reported during post-marketing surveillance,	None
Accidental inhalation of gelatin capsule particles	o Routine Pharmacovigilance, including independent review in future PSURs o Post Marketing Surveillance Study: Reports of accidental inhalation will be monitored by review of adverse events reported during post-marketing surveillance.	o Educational material: Preparation of an educational DVD for use by healthcare professionals and patients which will describe clearly the technique for use of the device and provide reassurance with respect to continued use. The complete content of the DVD is currently under consideration and will be finalised prior to launch of the product in the EU
Accidental Ingestion of whole gelatin capsule	o Routine Pharmacovigilance, including independent review in future PSURs o Post Marketing Surveillance Study: Reports of accidental inhalation will be monitored by review of adverse events reported during post-marketing surveillance.	o Educational material: Preparation of an educational DVD for use by healthcare professionals and patients which will describe clearly the technique for use of the device and provide reassurance with respect to continued use. The complete content of the DVD is currently under consideration and will be finalised prior to launch of the product in the EU
Increased Sensitisation to colistimethate due to inhaled route of administration	o Routine Pharmacovigilance, including independent review in future PSURs o Post Marketing Surveillance Study: Reports of increased sensitisation to colistimethate will be monitored by review of adverse events reported during post-marketing surveillance.	o Section 4.3 of the SmPC specifically contraindicates use in patients with hypersensitivity to colistimethate sodium, colistin sulphate or polymyxin B. This is also fully reflected in the Patient Information Leaflet
Nephrotoxicity	o Routine Pharmacovigilance, including independent review in future PSURs o Post Marketing Surveillance Study: Reports of nephrotoxicity will be monitored by review of adverse events reported during post-	None

	marketing surveillance,	
Hepatotoxicity	o Routine Pharmacovigilance, including independent review in future PSURs o Post Marketing Surveillance Study: Reports of hepatotoxicity will be monitored by review of adverse events reported during post-marketing surveillance,	None
Neurotoxicity	o Routine Pharmacovigilance, including independent review in future PSURs o Post Marketing Surveillance Study: Reports of neurotoxicity will be monitored by review of adverse events reported during post-marketing surveillance,	None
Potential for medication errors due to inappropriate handling of the inhalation device	o Routine Pharmacovigilance o Post Marketing Surveillance Study: Reports of medication errors will be closely monitored in a post approval study as well as post-marketing surveillance, and will be the subject of special review in future PSURs	o The patient information leaflet (PIL) contains clear instruction as to how to administer Colobreathe. The possibility of underdosing as a result of incorrect puncturing of the capsule can be addressed by checking the capsule has been fully emptied following inhalation. This instruction is included in the PIL. o Educational material: Preparation of an educational DVD for use by healthcare professionals and patients which will describe clearly the technique for use of the device and provide reassurance with respect to continued use. The complete content of the DVD is currently under consideration and will be finalised prior to launch of the product in the EU
Foetal Harm	o Routine Pharmacovigilance, including independent review in future PSURs o Post Marketing Surveillance Study: Reports of foetal harm will be monitored by review of adverse events reported during post-marketing surveillance,	o The SmPC Section 4.6 Pregnancy and lactation states: **...**` *Pregnancy* There are no adequate data from the use of inhaled colistimethate sodium in pregnant women. Studies in animals using parenteral administration have shown reproductive toxicity (see section 5.3). Single dose intravenous studies in human pregnancy show that colistimethate sodium crosses the placenta and consequently there is potential for foetal toxicity if administered during pregnancy. Colistimethate sodium should be used in pregnancy only if the benefit to the mother outweighs the potential risk to the foetus. This is also fully reflected in the Patient Information Leaflet
(Missing Information)		

Pregnant or lactating women	Routine Pharmacovigilance, including independent review in future PSURs	o The SmPC Section 4.6 Pregnancy and lactation states: **...**` *Pregnancy* As above. *Breastfeeding* Absorbed colistimethate sodium may be secreted in breast milk. A decision on whether to continue/discontinue breastfeeding or to continue/discontinue therapy with COLOBREATHE should be made taking into account the benefit of breastfeeding to the child balanced against the benefit of COLOBREATHE therapy to the woman. This is also fully reflected in the Patient Information Leaflet
Pharmacokinetic and pharmacodynamic interactions with co-medications other than aminoglycosides	Routine Pharmacovigilance, including independent review in future PSURs	o The SmPC Section 4.5 on interactions states: There is no experience of using COLOBREATHE concurrently with other inhaled antibiotics. Due to the effects of colistimethate sodium on the release of acetylcholine, non-depolarising muscle relaxants should be used with extreme caution in patients receiving COLOBREATHE as their effects could be prolonged. Concomitant use of inhaled colistimethate sodium with other medicinal products that are nephrotoxic or neurotoxic (e.g. cephalothin sodium, aminoglycosides, non-depolarising muscle relaxants) including those which are administered by the intravenous or intramuscular routes should be undertaken with care.
Systemic exposure data in children after inhalation of Colobreathe	A systemic absorption study in cystic fibrosis patients including children is planned to address this issue. The protocol for this study is summarised in section 2.4 of this RMP for reference purposes	None
Metabolism/ Mechanism of inactivation in the tissues	A study of the effect of colistimethate on hepatocytes is planned to investigate inhibition or enhancement of metabolism by colistimethate	None

The CHMP, having considered the data submitted, was of the opinion that the below pharmacovigilance activities in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
Systemic absorption study in cystic fibrosis patients	Final report should be available before end March 2012
Postmarketing surveillance study: Open-label, observational, registry based surveillance study comparing the long term safety of 2 years' treatment with Colobreathe 125mg with the same of	Study to commence Q3 2012. Final

Description	Due date
nebulised Colomycin	report by Q4 2015
Early colonisation study: Multicentre, multiple dose, single-blind parallel group study of the efficacy and safety of Colistimethate dry powder for inhalation in the treatment of early infection with *Pseudomonas aeruginosa* in paediatric patients with cystic fibrosis	Study to commence Q3 2012. Final report by Q4 2016

The following additional risk minimisation activities were required

The Marketing Authorisation Holder shall agree the format and content of the healthcare professional and patient educational pack with the National Competent Authority prior to launch in the Member State.

The Marketing Authorisation Holder shall ensure that all physicians who are expected to prescribe or use Colobreathe are provided with a healthcare professional and patient educational pack containing the following:

- The Summary of Product Characteristics
- The Patient Information Leaflet
- The "Physician DVD"
- The "Patient DVD"
- "Physician DVD" information in "leaflet form" for those physicians who do not have access to a DVD player
- "Patient DVD" information in "leaflet form" for those patients who do not have access to a DVD player

The Physician and patient "DVDs/leaflet forms" should contain the following key elements and messages:

- Introduction to the product: provide information on the contents of the box ie that 28 days treatment is 56 capsules and 1 device. Explain that the device should be discarded after 28 days. Explanation of the Turbospin and how it works.
- Information on the need to comply with the treatment in order to maximise the potential benefits. Explanation that using inhaled antibiotics can reduce the need for intravenous antibiotics.
- Detailed instructions about how to use the medication: starting from unpacking of the product and finishing with disposal of the used capsule and device. Some detail about cleaning the Turbospin device.
- Discussion about common side effects and in particular cough and taste abnormality: Explanation that:
  - These are only of nuisance value for most patients
  - Emphasise that patients should persist with the treatment.
  - that cough decreases with repeated use of the product and should stabilize after the first month or so.

2.8 User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3 Benefit-Risk Balance

Benefits

Beneficial effects

Since a dramatic change in FEV1 would not be expected in such a patient population, the modest improvement in FEV1 achieved by Colobreathe when administered twice daily over 24 weeks to subjects already established on TOBI with no evidence of acute exacerbation at baseline, is considered a sufficient demonstration of efficacy. Overall, the fact that Colobreathe failed to meet the pre-defined criterion for non-inferiority vs. TOBI is not considered critical in light of the overall amount of evidence provided. In terms of respiratory function, the data show that the differences with TOBI were mostly quite small. There were some advantages noted for Colobreathe in sub-group analyses. Secondary outcome measures such as the time to acute respiratory exacerbations and mean time to first additional anti-pseudomonal treatment tended to favour Colobreathe. Also, patients generally preferred the dry powder inhalations instead of nebulisations.

Uncertainty in the knowledge about the beneficial effects

The critical questions are whether subjects satisfactorily maintained on TOBI have a clinically important deterioration in FEV1% if they switch to Colobreathe and whether adequate efficacy could be expected if Colobreathe was used instead of TOBI from the outset in subjects in need of chronic anti-pseudomonal therapy. Regarding the first issue the available data suggest that if there is a deterioration in FEV1% it is likely modest. Since these types of patients are usually closely followed and also would report back to their management centres if there were untoward symptoms any deterioration of significance could be expected to come to light and be dealt with quite quickly. Regarding the second issue, there are no data to answer this question. However, it does seem that Ukrainian patients who had received only a short pre-study run-in with TOBI experienced a benefit on commencing Colobreathe.

Risks

Unfavourable effects

The rate of serious adverse events were not different between treatment groups. However, Colobreathe was associated with higher rates of AEs vs. nebulised comparators. Patients were exposed to a dry powder inhalation for the first time and the available evidence suggests that much of the difference was due to the novel effects of dry powder inhalations rather than Colobreathe *per se* or the active substance. The comparisons are biased against Colobreathe since patients had already been exposed to the comparative treatments and were therefore to some extent pre-selected to be tolerant. Rates of withdrawal decreased considerably after weeks 1-8.

Uncertainty in the knowledge about the unfavourable effects

While it seems unlikely that rates of AEs attributable to Colobreathe would increase during longer-term use there are currently no data on usage beyond 24 weeks of twice daily inhalations.

Benefit Risk Balance

Importance of favourable and unfavourable effects

It is concluded that Colobreathe showed adequate efficacy in the sought indication. The safety data, when viewed in the light of the biases introduced by patient treatment histories are considered acceptable.

Benefit-risk balance

The risk-benefit relationship for Colobreathe is considered to be favourable in the intended indication.

4 Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Colobreathe is not similar to Cayston and Tobi Podhaler within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Colobreathe in the management of chronic pulmonary infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis (CF) aged 6 years and older (see See Section 5.1) is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

Risk Management System and PSUR cycle

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

Conditions or restrictions with regard to the safe and effective use of the medicinal product

The Marketing Authorisation Holder shall agree the format and content of the healthcare professional and patient educational pack with the National Competent Authority prior to launch in the Member State.

The Marketing Authorisation Holder shall ensure that all physicians who are expected to prescribe or use Colobreathe are provided with a healthcare professional and patient educational pack containing the following:

- The Summary of Product Characteristics
- The Patient Information Leaflet
- The "Physician DVD"
- The "Patient DVD"
- "Physician DVD" information in "leaflet form" for those physicians who do not have access to a DVD player
- "Patient DVD" information in "leaflet form" for those patients who do not have access to a DVD player

  The Physician and patient "DVDs/leaflet forms" should contain the following key elements and messages:

- Introduction to the product: provide information on the contents of the box ie that 28 days treatment is 56 capsules and 1 device. Explain that the device should be discarded after 28 days. Explanation of the Turbospin and how it works.
- Information on the need to comply with the treatment in order to maximise the potential benefits. Explanation that using inhaled antibiotics can reduce the need for intravenous antibiotics.
- Detailed instructions about how to use the medication: starting from unpacking of the product and finishing with disposal of the used capsule and device. Some detail about cleaning the Turbospin device.
- Discussion about common side effects and in particular cough and taste abnormality: Explanation that:
  - These are only of nuisance value for most patients
  - Emphasise that patients should persist with the treatment.
  - that cough decreases with repeated use of the product and should stabilize after the first month or so.

Obligation to complete post-authorisation measures

Not applicable

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

The Member States shall agree the final healthcare professional and patient educational pack with the Marketing Authorization Holder (MAH) prior to launch of the product in their territory.

The Member States shall ensure that all physicians who are expected to prescribe or use Colobreathe are provided with a healthcare professional and patient educational pack containing the following:

- The Summary of Product Characteristics
- The Patient Information Leaflet
- The "Physician DVD"
- The "Patient DVD"
- "Physician DVD" information in "leaflet form" for those physicians who do not have access to a DVD player
- "Patient DVD" information in "leaflet form" for those patients who do not have access to a DVD player

  The Physician and patient "DVDs/leaflet forms" should contain the following key elements and messages:

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  - These are only of nuisance value for most patients
  - Emphasise that patients should persist with the treatment.
  - that cough decreases with repeated use of the product and should stabilize after the first month or so.