EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Assessment report

TOBI Podhaler

International Nonproprietary Name: tobramycin

Procedure No. EMEA/H/C/002155

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

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Table of contents

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novartis Europharm Ltd. submitted on 3 December 2009 an application for Marketing Authorisation to the European Medicines Agency (EMA) for TOBI Podhaler, 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 CHMP on 23 February 2009.

TOBI Podhaler, was designated as an Orphan medicinal product EU/3/03/140 on 17 March 2003 for the indication Treatment of *Pseudomonas aeruginosa* lung infection in cystic fibrosis. The calculated prevalence of this condition was 1.3 per 10,000 EU population. On 27 October 2006 the initial designation, which was held by Chiron Corporation Ltd was transferred to Novartis Europharm Limited.

The applicant applied for the following indication "long-term management of chronic pulmonary infection due to *Pseudomonas aeruginosa* in adults, adolescents and children aged 6 years and older with cystic fibrosis"

The legal basis for this application refers to Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

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

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/58/2009 for the following condition "*Pseudomonas aeruginosa* pulmonary infection/colonisation in patients with cystic fibrosis" on the agreement of a paediatric investigation plan (PIP).

The PIP is not yet completed.

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.

Market Exclusivity

Not applicable.

Protocol assistance:

The applicant received Protocol Assistance from the CHMP on 17 March 2004, 19 November 2004 and 26 June 2008. The Protocol Assistance pertained to quality, non-clinical and 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. Steps taken for the assessment of the product

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

Rapporteur: **Barbara van Zwieten-Boot** Co-Rapporteur: Michal Pirozynski; replaced in June 2010 by **Piotr Fiedor**

- The application was received by the Agency on 3 December 2009.
- The procedure started on 23 December 2009.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 March 2010. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 15 March 2010.
- During the meeting on 22 April 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 23 April 2010.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 21 May 2010.
- The summary reports of the inspections carried out at the following sites: Novartis Pharmaceuticals Corporation, San Carlos, CA, USA and SGS Life Sciences Services Lincolnshire, IL, USA 14th – 16th June 2010 and 18th June respectively were issued on 26th July 2010.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 17 July 2010.
- During the CHMP meeting on 22 July 2010, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP list of outstanding issues on 23 August 2010.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding issues to all CHMP members on 08 September 2010.
- The applicant submitted the responses to the remaining outstanding issues on 15 September 2010.
- During the meeting on 20-23 September 2010, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee adopted the CHMP Assesment Report and issued a positive opinion for granting a Marketing Authorisation to TOBI Podhaler. The CHMP adopted also the conclusions on similarity of Tobi Podhaler with Cayston. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 27 September 2010.
- Following the European Commission request from 17 March 2011 and EMA response dated 30 March 2011 the CHMP further substantiated the motivation of its initial opinion. During the meeting on 11-14 April 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive revised opinion for granting a Marketing Authorisation to Tobi Podhaler

2. Scientific discussion

2.1. Introduction

Problem statement

Cystic fibrosis (CF) is an autosomal recessive disorder caused by mutations in the gene encoding for the cystic fibrosis transmembrane conductance regulator (CFTR), a protein that acts as a chloride channel. Disruption of the sodium and chloride ion transport mechanism of epithelial cells, associated with water transport abnormalities results in abnormally viscous secretions in different exocrine tissues, mainly the respiratory tract, pancreas, gastrointestinal tract and exocrine glands. In Europe approximately 25,000 people are affected by CF.

In the respiratory tract the disorder results in progressive, obstructive pulmonary disease. The abnormally viscous mucus interferes with the mucociliary transport mechanism normally responsible for clearance of bacteria and other organisms from the airways. This makes CF patients particularly susceptible to pulmonary infections caused by bacterial pathogens such as *P. aeruginosa* (PA), as well as *Burkholderia cepacia*, and *Stenotrophomonas maltophilia*. Pseudomonas infections are usually established in the first decade of life. Patients infected with *P. aeruginosa* experience episodes of acute pulmonary exacerbation, characterized by worsening respiratory symptoms and acute decline in lung function. The repeated episodes of infection and associated inflammation cause progressive damage of the lungs; *P. aeruginosa* is rarely eradicated. This chronic infection is associated with reduced life expectancy.

The current management of the pulmonary infections in CF patients is comprised of early treatment with a variety of therapies in an effort to prevent exacerbations or management without hospitalisation. It includes in addition to antibiotics a variety of therapies such as bronchodilators, mucolytic and anti-inflammatory agents and airway clearance techniques. Chronic suppressive treatment with inhalational antibiotics in particular tobramycin nebuliser solution [TNS, TOBI] belongs now to the standard therapy in the management of CF patients with chronic pulmonary infection due to *P. aeruginosa*. The recommended dose of TOBI is 300 mg twice daily (morning and evening) for 28 days. After 28 days of therapy, patients must stop treatment for the next 28 days; the rationale for intermittent dosing is to reduce the potential for antimicrobial resistance caused by continuous exposure to drug. More recently the monobactam aztreonam lysine 75 mg powder for nebuliser solution has been approved in the EU also for the same indication. IV antibiotics are usually reserved for the treatment of acute exacerbations or infections that fail to respond to combined oral and nebulized treatment.

As a result of progress in CF care, the demographics of the CF population have evolved. The mean age of CF patients has increased to 17 years in the EU[1].

The applicant (TOBI's MAH) has developed a tobramycin inhalation powder (TIP, TOBI Podhaler) formulation for use in the same target group. The dosage is four capsules (4x 28 mg = 112 mg tobramycin), administered twice daily i.e. then amount per dose is approximately 1/3 of that approved for TOBI. It is administered by using the Podhaler device; each device and its case are used for seven days and then discarded and replaced.

With this formulation the applicant is attempting to address a known problem of compliance with long-term inhalational therapy requiring long nebulization time in CF patients especially those using TOBI.

[1] European Cystic Fibrosis Society, Kerem E, et al. The European Cystic Fibrosis Registry Report on 2003 Data, Summary, 2006: 2 p.

The present powder formulation is intended to offer the same efficacy and safety as TOBI but with decreased dosing time and simpler administration compared with a nebuliser and compressor.

About the product

Tobramycin is a well known bactericidal. It is primarily active against aerobic Gram-negative bacilli. Tobramycin is considered more active than most other aminoglycosides against PA. It is also active against *Citrobacter species*, *E.coli*, *Enterobacter*, *Klebsiella*, *Providencia species*, *Proteus species* (*Pr. mirabilis*; *Pr. morganii*; *Pr. rettgeri* and *Pr. Vulgaris*), *Serratia species and* Staphylococci.

TIP is formed of low density particles (PulmoSpheres). TOBI Podhaler drug-device combination presents a substantial improvement compared to TOBI (TNS) formulation and delivery system resulting in a reduced administration time, a decrease in the complexity of equipment, increased portability, no need for an external power supply and reduced maintenance.

The originally sought indication for TOBI Podhaler was "long-term management of chronic pulmonary infection due to Pseudomonas aeruginosa in adults, adolescents and children aged 6 years and older with cystic fibrosis (CF). Consideration should be given to official guidance on the appropriate use of antibacterial agents".

The approved indication is "suppressive therapy of chronic pulmonary infection due to Pseudomonas aeruginosa in adults and children aged 6 years and older with cystic fibrosis. See sections 4.4 and 5.1 regarding data in different age groups. Consideration should be given to official guidance on the appropriate use of antibacterial agents".

The recommended posology is the same for both adults and paediatric patients 6 years of age and older: four capsules (4x 28 mg = 112 mg tobramycin), administered twice daily for 28 days. TOBI Podhaler is taken in alternating cycles of 28 days on treatment followed by 28 days off treatment. The two doses (of 4 capsules each) should be inhaled as close as possible to 12 hours apart and not less than 6 hours apart.

Treatment with TOBI Podhaler should be continued on a cyclical basis for as long as the physician considers the patient is gaining clinical benefit.

Type of application and aspects on development

The legal basis for this application refers to Article 8.3 of Directive 2001/83/EC, as amended. It is an independent "full-mixed" application, which included a combination of study reports from the applicant studies and bibliographical references relevant to the pharmacology, pharmacokinetics, and toxicology of tobramycin.

The TIP development program was initiated by Chiron Corporation, and continued by Novartis Pharmaceuticals from April 2006, when Chiron was acquired by Novartis.

In March 2003 TIP was granted orphan designation on the assumption of a potential significant benefit over existing treatments. Since TOBI is already authorised, the assumption of significant benefit of TIP is currently based on its potential contribution to patient care. The potential benefit may be related to the administration time, portability, storage, cross contamination, environmental and resistance issues, variability of performance, compliance, lifestyle, and accessibility to inhaled tobramycin. The applicant was advised to consider in the development programme all the above mentioned aspects i.e. through relevant questionnaires; however the comparability of the efficacy and safety of TOBI and TIP should be demonstrated in the MAA.

The applicant requested scientific advice to the CHMP in 2004 and 2008. In the scientific advice letter from November 2004 the CHMP concluded that the pivotal studies C2301 (placebo-controlled) and C2302 (formerly TIP002 and TIP003 respectively) might provide sufficient information for a marketing authorisation The CHMP considered that study C2302 (TIP versus TOBI) was essential for the assessment of the efficacy and should include a minimum of three cycles. Follow up protocol assistance was subsequently sought by the applicant and advice was given by the CHMP in June 2008.

The Phase III studies C2301 and C2302 were conducted following advice from the regulatory authorities although there were concerns with regard to a number of issues e.g. the lack of third arm (placebo), and study delta and alpha values selected (6% and 0.15 respectively) in study C2302, and the small number of patients recruited in study C2301. The limited safety data with TIP were considered acceptable considering the previous experience with TOBI. Additional information on the scientific advice requests is provided in section 3.4.1.

On 27 March 2009 a Decision was granted by the EMA in accordance with Regulation (EC) No 1901/2006 on a Paediatric Investigation Plan (PIP) for TIP in the condition "Pseudomonas aeruginosa pulmonary infection/colonisation in patients with cystic fibrosis". It included also a waiver for the newborn and "less than 3 months of age" paediatric subsets and a deferral to complete some of the studies after the initial MA.

The CHMP "guideline on the clinical development of medicinal products for the treatment of cystic fibrosis" and the "NfG on the Clinical Evaluation Medicinal Products Indicated for Treatment of Bacterial Infections" (CPMP/EWP/558/95 rev.1) have been considered for this application.

2.2. Quality aspects

2.2.1. Introduction

Tobi Podhaler inhalation powder, hard capsules, contains 28mg Tobramycin filled into clear size #2, hypromellose colourless capsules imprinted in blue ink with the text "NVR AVCI" on one half and the Novartis logo on the other half of the capsule. Other ingredients are: sulphuric acid, 1, 2-distearoyl-sn-glycerol-3-phosphocholine and calcium chloride. The components of the capsule shells are hypromellose, carrageenan (E407), potassium chloride, printing ink (blue) and carnauba wax.

The capsules are packed in Aluminium-Aluminium blisters.

2.2.2. Active substance

Tobramycin drug substance is a white to almost white powder which should be visually free from any foreign contamination. Tobramycin is freely soluble in water, very slightly soluble in ethanol and practically insoluble in chloroform and ether. It contains 14 asymmetric carbon atoms. The configuration of the asymmetric carbon atoms is determined by the fermentation process and checked by the specific optical rotation.

Tobramycin free base exists as a crystalline solid with three known forms, two anhydrous forms and one monohydrate form. A fourth solid state form, amorphous tobramycin, can be prepared by any of several means (e.g., melt quenching, spray drying, etc.). Nevertheless, because he active substance is dissolved during the manufacture of the drug product, the polymorphic state of the drug substance is not considered to be relevant.

Tobramycin is a well known active substance. Valid certificates of suitability to the Tobramycin Ph. Eur. Monograph (CEP) have been submitted as part of this application by the active substance manufacturers. The information provided regarding the manufacturing process and the control of the active substance was assessed and approved by the European Directorate for the Quality of Medicines (EDQM). Satisfactory quality of the active substance is ensured through the CEP.

The specification of the applicant includes all relevant tests as described in the Ph.Eur as well as all other tests and limits as described on the CEPs: appearance (Ph.Eur), colour (in house), pH (Ph.Eur), identity by TLC (USP and Ph.Eur), by HPCL (USP) and by colour reaction (Ph.Eur), purity by HPLC (in house and by TLC (USP), related substances by HPLC (Ph. Eur.), water content (Ph.Eur), sulphated ash (Ph.Eur), heavy metal (USP), specific optical rotation (Ph.Eur), residual solvent by GC (in house), microbial enumeration test (Ph.Eur and USP), assay by HPLC (Ph.Eur and USP).

In general the Ph.Eur methods are used. For several parameters in-house methods are used that differ from the methods that are enclosed with the CEPs. In those cases, cross validation has been performed and provided.

Both manufacturers of the active substance conducted stability studies according to ICH guidance at long term (25°C±2ºC/60%RH±5%RH) and accelerated conditions (40°C±2ºC/75%RH±5%RH)

The first manufacturer submitted data for 60 months (long term) and 6 months (accelerated) results on 3 commercial batches with active substance stored in the proposed packaging have been submitted. The parameters tested included: appearance, water content, impurities (TLC and HPLC), assay and bacterial endotoxins

The second manufacturer provided stability results on 7 batches in alternate proposed packaging for up to 36 months under long term conditions and 6 months under accelerated conditions. Appearance, water, specific optical rotation, pH, Impurities (HPLC, conform Ph.Eur. and CEP), and assay were tested.

Both manufacturers have also performed stress testing by treating the drug substance with acid, base, heat light and hydrogen peroxide.

The stability results are within the specifications and justify the proposed retest periods. In accordance with EU GMP guidelines[2], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMEA.

2.2.3. Finished Medicinal Product

2.2.3.1. Pharmaceutical Development

Finished product development

The aim of the development was to propose a pharmaceutical form delivering reproducibly therapeutic dose of antibiotics with a portable inhaler.

At present, the only approved inhaled antibiotic treatments for cystic fibrosis patients with chronic pulmonary *Pseudomonas aeruginosa* infection are nebulised solutions. Yet, cost of use of nebulisers is high and the complex administration can lead to poor adherence to treatment (extended administration time, device cleaning, need for an electrical source…).

[2] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal Products in the European Union

For these reasons, it was decided to investigate the development of a dry powder inhaler; dry powder can, in principle, deliver higher doses than liquid-based systems on a puff-by-puff basis. The ability to deliver antibiotics with a portable inhaler in less time than with a nebuliser is considered as a significant advantage likely to improve patient compliance and quality of life.

A spray-drying process followed by capsule filling was initially investigated. Over the course of the product, the manufacturing process has been continuously improved and optimized, while maintaining the same general sequence and steps.

Tobramycin properties, and especially its solubility, suggested that this well known aminoglycoside might be suitable to develop an inhalation powder in hard capsules formulation manufactured by spray-drying process. It has been demonstrated to be compatible with the emulsion preparation and subsequent spray-drying process.

Excipients have been selected for their suitability to the manufacturing process, aerosol delivery performance, product stability and safe inhalation use. Their choice and relevance in this formulation have been duly justified. In addition to Tobramycin sulfate, the inhalation powder is composed of 1, 2-distearoyl-sn-glycerol-3-phosphocholine (DSPC) and calcium chloride; both were chosen as wall-forming agent and taking into account their satisfactory behaviour in terms of stability. A perfluorocarbon solvent and water for injection are used as processing aids during the manufacturing process and then removed by evaporation.

Sulfuric acid (used as salt forming agent and pH adjuster), calcium chloride dehydrate and water for injection comply with the Ph. Eur. specifications and USP specifications are applied for the perfluorocarbon solvent. The analytical procedures are described in the corresponding pharmacopoeias. DSPC is the only excipient for which no pharmacopoeia monograph is available. The applicant has therefore submitted a set of in-house specifications ad analytical methods as well as the corresponding validation data.

Hypromellose capsule shells were chosen over gelatin capsules due to their superior physical characteristic and low moisture content. No specific monograph exists for the capsule shells but the individual components fulfil their respective pharmacopoeia monographs.

Inhaler development

Tobramycin inhalation powder is delivered with a hand-held, manually operated, breath-activated, single-dose dry-powder inhaler that uses no stored power sources or electronics. The product bears a CE mark as a Class I Medical Device under 93/42/EEC the Medical Device Directive and applicable amendments. It was subjected to controlled extraction studies. No substances from those tests were identified as a safety risk which would need to be monitored during leaching studies.

During development changes were introduced to this inhaler (changes to the functional components, cosmetic changes and manufacturability). Comparisons of aerosol performance between manufacturing locations used during development have also shown equivalence. No changes to the product design have been made since the initiation of the phase III clinical studies.

A number of different studies have been performed to demonstrate the suitability of the device for this product including Delivered Dose Uniformity (DDU) and Fine Particle Mass (FPM) through device life, DDU and FPM over patient flow rate range, single dose fine particle mass, particle size distribution, mouthpiece deposition, cleaning requirements, effect of environmental moisture, robustness and effect of orientation.

2.2.3.2. Adventitious agents

Two materials from animal origin are used in the manufacturing of tobramycin by one of the active substance manufacturer: beef extract paste (bovine origin) and peptone (porcine origin). TSE information as well as relevant CEPs are available for these materials and ensure that criteria for minimizing the risks of transmitting agents of animal spongiform encephalopathy are met. Furthermore a compound derived from bovine origin is used as an additive to the plastic resin used in the manufacture of the inhaler device. The applicant declares that the material was submitted to a treatment that complies with the Note for Guidance on TSE risks.

2.2.3.3. Manufacture of the product

The manufacturing process consists of a spray drying step followed by capsule filling and blistering. It has been described in sufficient details and a flow chart stating the temperatures, mixing speeds and times, filter sizes, environmental parameters… is included. The manufacturing process can be seen as a standard process. Manufacturing of the inhalation powder hard capsules takes place in a strictly controlled area and the capsules are subjected to microbiological release testing.

The proposed in-process controls are in line with the manufacturing development and are considered to be adequate. The proposed in-process control limits for the dry powder particles are also in line with the results obtained for the Phase III clinical batches and the validation batches. Emulsion preparation and spray drying are considered to be the critical steps and are controlled within tight operating ranges.

Three consecutive commercial scale validation batches were successfully manufactured on the commercial equipment at the proposed launch site. All three batches passed in-process material control testing, additional non-routine in process testing, and release testing according to the proposed specification. The microbial attributes of the drug product were assessed through development studies and as part of the long-term registration stability testing.

Overall, the pharmaceutical development has been extensively described and the applicant has adequately justified all aspects applicable to inhalation powders as are mentioned in the Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products.

2.2.3.4. Product specification

The release specification includes relevant tests with methods and suitable limits for: appearance of content, appearance of shell (aspect, imprint and size), fine particle dose (Next generation impactor), identification (HPLC and FTIR), uniformity of delivered dose (HPLC), degradation products (HPLC), water content (Karl Fisher), microbial enumeration tests, assay (HPLC) and uniformity of dosage units (HPLC). All analytical procedures except the visual test for appearance have been satisfactorily validated in accordance with ICH guideline Q2(R1) 'validation of analytical procedures: tests and methodology'. The tests and limits of the specifications at release and shelf life are appropriate to control the quality of the finished product for its intended purpose. Control of impurities has been sufficiently justified and the applicant has committed to tighten some impurities shelf life limits.

Batch analyses data of 12 batches (3 validation batches, 3 registration stability batches and 6 representative clinical batches) of the drug product confirm the satisfactory quality of the product and indicate the manufacturing process is under control.

2.2.3.5. Stability of the product

Stability data has been presented for three production batches packed in the proposed commercial container and stored for up to 24 months under long term condition (25°C/60%RH and 30°C/75%RH), for up to 6 months under accelerated conditions (40°C/75%RH) and under other conditions with more extreme temperatures and/or relative humidity (e.g. -20°C/ambient, 5°C/ambient, 25°C/75%RH, 50°C/ambient and freeze-taw). No significant changes in the results were observed for any of the batches for the reported duration of storage. The capsules were also evaluated for their photostability according to ICH Q1B.

The parameters investigated were: appearance, assay, degradation products, water content, delivered dose uniformity, aerodynamic particle size distribution, microscopic examination, DSPC, degradation product , and microbiological quality. The results of these studies demonstrate that the product is not sensitive to light, refrigeration or freezing and that the primary packaging adequately protects the product from moisture.

Based on the available data, the proposed shelf life and storage conditions as stated in the SmPC are accepted.

In accordance with EU GMP guidelines[3], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMEA.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

In general satisfactory documentation has been provided to confirm the acceptable quality of this medicinal product, and no major objections have been raised during evaluation. The drug substance has been adequately characterized and the specification is acceptable in view of the route of synthesis and the various ICH guidelines. Concerning the finished product the complete control strategy and an established manufacturing process guarantees consistent control of the product quality which should have a satisfactory and uniform performance in the clinic.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the benefit/risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve these as Follow Up Measures after the opinion within an agreed timeframe.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. 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

[3] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal Products in the European Union

2.3.1. Introduction

The non clinical dossier submitted consists of a combination of TIP studies bridged to the TOBI toxicology package, and selected studies performed with tobramycin administered by parenteral routes (e.g. acute and reproductive toxicology). A literature review has also been provided.

All main inhalation toxicology studies performed with TIP, TOBI and excipients, and the carcinogenicity study in rats were performed in accordance with GLP and currently accepted guidelines. Acute and reproductive / developmental toxicity studies with tobramycin drug substance were not completed strictly according to GLP requirements as they were done prior to the issuance of this guidance. The tobramycin reproductive studies were reviewed and considered to meet the accepted criteria as of the time of TOBI assessment.

2.3.2. Pharmacology

Considering the amount of clinical trial data and post-marketing experience available from TOBI, as well as the well-established pharmacodynamic profile of tobramycin in scientific literature from the last three decades, no additional non-clinical pharmacology studies on pharmacodynamics were performed during development of TIP.

No new non-clinical pharmacodynamic studies have been performed for the current application. The applicant has justified it on the amount of clinical trial data and post-marketing experience available from TOBI, as well as the well-established pharmacodynamic profile of tobramycin. Since tobramycin is a well known substance, this is acceptable, as data can be provided using literature publications. As this was a full application, all non-clinical aspects had to be addressed.

Primary pharmacodynamic studies

Tobramycin is a water-soluble aminoglycoside antibiotic. Tobramycin acts primarily by disrupting protein synthesis leading to altered cell membrane permeability, progressive disruption of the cell envelope and eventual cell death. Tobramycin inhibits protein synthesis of numerous Gram-negative bacteria including *Escherichia coli*, the species *Proteus*, *enterobacter*, *Klebsiella*, *Acinetobacter*, *Pseudomonas*, *Serratia*, *Providencia* and Gram-positive *Staphylococcus aureus*.

The parenteral tobramycin resistance breakpoint for *P. aeruginosa* is 4 μg/ml. It must be noted, however, after inhalatory administration of tobramycin the local concentrations that will be achieved will be much higher than after systemic administration.

Data on current European MIC values are limited. MIC90 values from different sources range from 8 to 32 μg/ml for CF isolates, and over 64 μg/ml for isolates from non-CF patients.

In the original submission, an overview of the resistance mechanisms and the current status of resistance rates to tobramycin in CF patient had not been provided. This was requested to the applicant during the evaluation together with a comparison of resistance and susceptibility rates with other commonly used antibiotics. From the data submitted with the responses, resistance rates seem to be variable. For single resistant organisms, resistant rates of up to 13% have been found in Europe, with rates rising to 52% for multiple-resistant non-mucoid isolates from the US (based on a breakpoint of 16 μg/ml). Of note, multiple-resistant isolates from Scotland showed a resistance rate of 13%.

Multiple resistance mechanisms are involved. The main one utilized by *P. aeruginosa* to overcome tobramycin activity are drug efflux and drug inactivation by modifying enzymes. The unique characteristics of chronic *P. aeruginosa* infections in CF patients, such as anaerobic conditions and high

frequency of genetic mutations, may also be important factors for reduced susceptibility of *P. aeruginosa* in CF patients.

No animal studies were performed with the TIP formulation to assess the *in vivo* activity. In respect to PK/PD relation, no information has been provided. The above points are covered by clinical data and therefore no further non-clinical data are required.

Secondary pharmacodynamic studies

A literature review of the secondary pharmacodynamics of tobramycin was provided by the applicant. Tobramycin has been investigated for the treatment of infections other than the lung, specifically otitis media, ocular infection, sinusitis and meningitis. In addition, tobramycin has been investigated in bone cement, for the treatment of wounds and other musculoskeletal infections. No further information is required since tobramycin is a well known substance.

Safety pharmacology programme

Specific safety pharmacology studies were not completed with TIP. However, safety pharmacology has been assessed as part of the repeated dose toxicity studies which have been performed in rats and dogs for the present application. No effect on any parameter was observed, at maximum exposures which were 13-fold (rats) and 2.2-fold (dog) the clinical exposure.

Pharmacodynamic drug interactions

No new pharmacodynamic drug interaction studies have been performed. Given the fact that tobramycin is a known substance which is already marketed as an inhalation formulation for the treatment of CF patients, this is acceptable. Drug interactions are unlikely due to the low systemic exposure resulting from the inhalation administration. However, relevant and potential interactions are described in the SmPC.

2.3.3. Pharmacokinetics

Tobramycin administered parenterally has been used since 1975. Information on the pharmacokinetics in pre-clinical species is available in the scientific literature and has been summarised, along with the pharmacokinetics of tobramycin nebuliser solution (TOBI), in a report included in the application (Heywood, 1998).

The exposure of tobramycin after inhalation of TIP was investigated in rats and dogs as an integral part of the toxicology studies. Tobramycin and its internal standard sisomicin were analysed using high performance liquid chromatographic (HPLC) methods with UV detection that involved pre-column derivatisation with 2,4-dinitrofluorobenzene. Accuracy and precision were within the calibration range. Tobramycin was stable in rat serum and dog serum and lung tissue, indicating a lack of chemical degradation and is assumed to be stable in rat lung tissue.

Absorption was fast with T_{max} occurring within 0.083 to 1 hour of administration of dose. Tobramycin has a short serum half-life and did not accumulate in serum after repeated daily exposure. TIP has a long half life in lung tissues that was highly variable (2 to 124 h). Accumulation in lung tissues was observed upon daily inhalation with tobramycin C_{max} increasing with a factor of approximately 7-fold and AUC0-24h increasing with a factor of approximately 20-fold. In rat, steady state levels would most likely be reached in one month. Increases in systemic exposure, as measured by AUC and C_{max}, were less than dose-proportional. The bioavailability of TIP after inhalation is high in rat (≥85%). The clinical data indicate that the bioavailability in cystic fibrosis patients is lower compared to the non-clinical

species. Cmax and AUC of tobramycin after administration of TIP were lower in humans compared to rat and dog at similar administered dosages (around a factor 2). In contrast, serum half-life was comparable between humans, rat and dog. The pharmacokinetic data indicate that the concentration in lung tissue and serum is higher for TIP than TOBI at the corresponding dosage. This was also observed in the clinical trial in which a dose of 300 mg TOBI led to similar serum concentrations as 112 mg TIP.

Tobramycin has a plasma protein binding of 0% and therefore TIP will have no plasma protein binding after absorption. Tobramycin is widely *distributed* with highest levels observed in the kidney. The distribution of TIP after absorption will be the same as tobramycin and most likely the highest will be found in the kidney in addition to the lung. Tobramycin crosses the placenta and is concentrated in the kidney and urine of the foetus.

Tobramycin is not *metabolised* and no additional studies were performed for TIP.

Tobramycin is primarily *excreted* unchanged in the urine in humans and most likely also in rat and dog. The excretion of TIP was not investigated in animal studies, but will be the same as tobramycin after absorption. No information is available for the excretion via breast milk.

No CYP inhibition and induction studies of TIP were performed. However, *interactions* with CYP substrates have not been reported for tobramycin and are therefore unlikely.

2.3.4. Toxicology

Single dose toxicity

No new single dose toxicity studies have been performed for the current application for TIP, as single dose toxicity studies had been previously conducted with tobramycin administered by oral and IV routes. This was considered acceptable.

The above single dose toxicity studies performed in mice and rats reveal high LD50 values of around 7000 mg/kg after oral dosing, and from 50 to 130 mg/kg for IV dosing.

Repeat dose toxicity (with toxicokinetics)

The applicant has performed bridging studies, to evaluate the toxicity profile of TIP and compare this to what is known about TOBI. Table 1 shows the inhalation toxicology studies performed with the dry powder formulation in rats (1- and 6-months) and dogs (7- and 28-days).

Table 1: Repeated dose toxicity studies performed with TIP

Study ID	Species/Sex/ N./Group	Dose/Route	Duration	NOEL/ NOAEL (mg/kg/d.)	Major findings
N103741 GLP	SD rat 10/sex/dose (5 for recovery)	0, 9.9, 19.7, 72.9 mg/kg/day inhalation	4 weeks	N.D.	≥ **9.9**: peribronchiolar inflammation, degeneration and inflammation olfactory epithelium, chronic submucosal inflammation of trachea ≥**19.7**: ↑ lung weight (M), nephropathy (M), pelvis dilation (M), alveolar macrophage accumilation **=72.9**: ↑ kidney weight (M), ↑ lung weight (F), inflammation, squamous hyperplasia and ulcer/erosion of larynx, bronchiolar/alveolar hyperplasia **After recovery**: ≥ **19.7**: degeneration and inflammation olfactory epithelium
N103748 GLP	SD rat 15/sex/dose (5 for recovery)	0, 6.4, 11, 38 mg/kg/day inhalation	26 weeks	N.D.	≥ **6.4**: squamous hyperplasia of epiglottis base (F), alveolar histiocytosis, inflammation of nose, degeneration olfactory epithelium, hyperplasia of mucosal glands ≥ **11**: ↑ lung weight, ↑ kidney weight (M), nephropathy (M), squamous hyperplasia of epiglottis base (M) **= 38**: ↓ globulin, nephropathy (F), squamous hyperplasia of arytenoids cartilages in larynx, hyperplasia of broncho-alveolar epithelium, inflammation lamina propria (M) **After recovery**: ≥ **6.4**: alveolar histiocytosis, inflammation of nose, degeneration olfactory epithelium, ≥ **11**: hyperplasia of mucosal glands **= 38**: hyperplasia of broncho-alveolar epithelium
MN103743 GLP	Beagle dog 2/sex/dose (1 for recovery)	0, 8.2, 23.8 mg/kg/day inhalation	1 week	23.8 mg/kg/day	No treatment-related findings
N103749 GLP	Beagle dog 3/sex/dose (2 for recovery)	0, 12, 21.4 (M), 38.7 (F), 27.6 mg/kg/day inhalation	4 weeks	N.D.	≥ **12**: Tubular degeneration, inflammation in kidney (M), inflammation in lung and nasal turbinates ≥ **27.6**: Inflammation in kidney (F) **After recovery**: ≥ **12**: Tubular degeneration

The main issue to address is whether there is a difference in toxicological profile between the two formulations, either qualitatively or quantitatively. The effects that are seen in both rats and dogs after TIP treatment can be divided into local effects on the respiratory system, and systemic effects on the kidney.

Local effects on the respiratory system are likely to result from high local concentrations in the lung tissue. It is not known whether the concentrations in the lungs of rats and dogs are in excess of those found in humans. Therefore no conclusions on safety margins can be drawn. However, the qualitative profile of TIP and TOBI seems similar in respect to the respiratory findings in rats. Moreover, at similar

tobramycin lung concentrations, similar respiratory effects are seen for TIP and TOBI. It can therefore be concluded that TIP and TOBI are comparable with respect to local effects.

With respect to systemic effects, the main target organ in rats and dogs is the kidney. For rats, a NOAEL could be determined which corresponds to a safety margin of 1.5 (AUC) and 4 (C_{max}). However, in dogs effects on the kidney were evident at the lowest dose tested, which is below therapeutic exposures.

Nephrotoxicity is a well documented effect of tobramycin treatment both in nonclinical animal species and in the clinic. Trough tobramycin levels of 2 µg/mL are required to induce evidence of renal effects in humans. It must be assumed that once tobramycin is systemically absorbed, it behaves the same way as any other tobramycin product, and systemic effects will depend on exposure.

Whether there is an increased risk of systemic effects of TIP compared to TOBI depends on systemic exposure, which needs to be evaluated clinically. Based on the repeated dose toxicity bridging studies, TOBI and TIP are similar regarding their toxicity profile.

Genotoxicity

Tobramycin does not have any *genotoxic* potential. No additional genotoxicity studies have been performed for the present application. This is acceptable.

Carcinogenicity

A carcinogenicity study with TIP was not performed. However in a 95-week *carcinogenicity study* in rats with the TOBI inhalation formulation, no evidence of a carcinogenic potential was seen.

The lack of a carcinogenic effect in this TOBI study can be extrapolated to TIP. No further studies are considered necessary.

Reproduction Toxicity

Specific reproductive and developmental toxicity studies were not completed with TIP. Tobramycin was however evaluated in previous studies for *reproduction toxicity* in rats and rabbits with subcutaneous administration. Tobramycin is not teratogenic nor embryotoxic in animal studies. Only at maternal toxic doses there is a decrease in live foetuses in rabbits, mainly due to increased mortality of the dams.

No studies on juvenile animals were conducted for the present application. As there is already clinical experience in children, this is acceptable.

Local Tolerance

The local tolerance of inhaled tobramycin is addressed in the repeated dose toxicity studies. Findings observed in the respiratory tract were considered typical of non-specific inflammatory responses to the extended inhalation of particles in animals and represent a low human risk. No other specific studies on local tolerance were conducted. Based on the above findings, this is considered acceptable

Other toxicity studies

Toxicity studies on impurities have also been conducted; conclusions are shown below:

The *excipient* DSPC has been studied in repeated dose toxicity studies in rats and dogs to 6 months. There were no effects that could be related to DSPC. This excipient is therefore safe to use at the intended concentration.

An *impurity* and degradation product of DSPC was evaluated in a 2-week rat study. There were no effects that could be related to the degradation product.

In addition a perfluorocarbon *residual solvent* was present in the batches used for the 1-month repeated dose toxicity studies at high enough levels to be qualified. This residual solvent has no genotoxic potential.

2.3.5. Ecotoxicity/environmental risk assessment

Substance (INN/Invented Name): Tobramycin					
CAS-number (if available): 32986-56-4; 49842-07-1 (sulfate: xH2SO4); 79645-27-5 (sulfate: 5H2SO4)					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	Extracted from 'Clarke's Analysis of Drugs and Poisons'	log K_{ow} -5.8			Potential PBT: N
PBT-statement :	The reported log K_{ow} value of -5.8 can be used for environmental risk assessment. Since this value is clearly below the trigger value of 4.5, tobramycin is not considered to be a PBT, nor vPvB substance.				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, refined (orphan status)	0.007	µg/L			> 0.01 threshold: N
Other concerns (e.g. chemical class)					N
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} = 48945-115185 L/kg for sludge and 90445-657429 L/kg for soil			
Ready Biodegradability Test	OECD 301	not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308				Test not performed
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ Cyanobacteria	OECD 201, 4 days	NOEC E_rC_{50}	0.051 0.349	mg/L	
Daphnia sp. Reproduction Test	OECD 211, 21 days	NOEC	0.36	mg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210, 28 days	NOEC	10	mg/L	No significant effect at highest test concentration
Activated Sludge, Respiration Inhibition Test	OECD 209	EC50	>1000	mg/L	
Conclusion phase IIa	Based on the risk quotients in the phase II tier A assessment, no adverse effects from tobramycin are expected for the aquatic environment.				

Based on the orphan status for tobramycin inhalation powder, the Fpen can be refined using prevalence of cystic fibrosis (worst-case, 1 in 8000 inhabitants) and the prescribed dose regime of 28 days cycles on treatment followed by 28 days off treatment. This results in a worst-case Fpen of 0.000063.

The use of a refined Fpen results in a PEC surface water of 7.02 x 10-3 µg/l. This value is below the trigger value of 0.01 µg/l. Therefore, there is no need for a phase II assessment.

However, the applicant has performed a phase IIa assessment. The studies have been provided but the results are without consequences since the assessment stops at phase I. Therefore, even though tobramycin is not readily biodegradable, a study on aerobic and anaerobic transformation in aquatic sediment systems is not necessary. Furthermore, although the Koc is above 10.000 l/kg, an environmental risk assessment of the drug substance in the terrestrial compartment is not necessary.

The reported log K_{ow} value of -5.8 can be used for environmental risk assessment. Since this value is clearly below the trigger value of 4.5, tobramycin is not considered to be a PBT, nor vPvB substance.

2.3.6. Discussion on non-clinical aspects

Non-clinical aspects of TIP have been assessed to a large extent from previous tobramycin studies conducted with tobramycin administered through oral or parenteral routes. The applicant has performed bridging studies, to evaluate the toxicity profile of TIP and compare this to what is known about TOBI.

No new pharmacology studies have been performed for this application. Reference has been made to the pharmacodynamics of tobramycine which is well known; this is considered acceptable.

In respect to TIP pharmacokinetics, no new non-clinical studies have been conducted with TIP given the information on tobramycin pharmacokinetics after intravenous administration available in the scientific literature. The pharmacokinetics is therefore adequately evaluated. Toxicokinetics were compared between TIP and TOBI, and showed a higher tobramycin systemic and lung exposure at the corresponding dosage.

Inhalation toxicology studies have been completed with TIP in rats (up to 6 months) and dogs (up to 1 month). The effects that are seen in both rats and dogs after TIP treatment are local effects on the respiratory system, and systemic effects on the kidney. At similar tobramycin lung concentrations, similar respiratory effects are seen for TIP and TOBI; both formulations seem to be comparable with respect to local effects. In respect to systemic effects, whether there is an increased risk with TIP compared to TOBI depends on systemic exposure, which needs to be evaluated clinically.

Tobramycin was evaluated in previous studies for *genotoxicity and reproduction toxicity* with other routes of administration; no findings were seen in these studies. In a 95-week *carcinogenicity study* in rats with the TOBI inhalation formulation, no evidence of a carcinogenic potential was seen.

The *excipient* DSPC and its *impurity* and residual product were evaluated in toxicology studies and no effects were seen; the perfluorocarbon *residual solvent* was present in the batches used for the 1-month repeated dose toxicity studies and is therefore qualified in respect to general toxicity at the proposed level.

In summary the TIP formulation has a similar toxicological profile to the TOBI formulation. There are no newly identified risks for humans.

2.4. Clinical aspects

2.4.1. Introduction

This application concerns tobramycin inhalation powder (TIP), a novel drug-device combination which delivers tobramycin topically to the lumen of the lungs, and is intended to increase convenience in cystic fibrosis patients. It is designed for use in CF patients for the same indication and the same twice daily, 28 day on, 28 off dosing schedule as used for TOBI.

The recommended posology for adults and paediatric patients is four capsules (4x 28 mg = 112 mg tobramycin), administered twice daily for 28 days. TOBI Podhaler is taken in alternating cycles of 28 days on treatment followed by 28 days off treatment. Treatment with TOBI Podhaler should be continued on a cyclical basis for as long as the physician considers the patient is gaining clinical benefit.

The applicant requested scientific advice to the CHMP in 2004 and 2008. In the scientific advice letter from November 2004 the CHMP concluded that the pivotal studies C2301 and C2302 (formerly TIP002 and TIP003) might provide sufficient information for a marketing authorisation and acknowledged that more than 1 placebo study would be difficult to justify from an ethical point of view. The CHMP considered that study C2302 versus TOBI was essential for the assessment of the efficacy and should include a minimum of three cycles. The primary objective proposed by the applicant was safety. However, the CHMP advised that the primary objective of this study should be the assessment of efficacy; therefore it was recommended that a formal hypothesis to test for efficacy be included in this comparative study. In addition there should be no indication of deterioration of efficacy in the TIP arm compared to the TOBI arm. In previous protocol assistance a 3 arm study was highly recommended by the CHMP.

Follow up protocol assistance was sought by the applicant and advice was given by the CHMP in the letter dated 26th June 2008. The CHMP considered that the approach taken by the applicant with regard to study C2301 was acceptable, although there was concern about the pre-mature closure of the study with very small number of patients included and the fact that efficacy had remained a secondary endpoint in study C2302; the lack of placebo arm was also considered unfortunate. The chosen delta assumed that the response in TOBI naive and TOBI experienced patients was comparable; however the CHMP stated that more data were needed in this respectively A lenient delta value of 6% was considered eventually acceptable for the sought orphan condition. Stratification was recommended. It was emphasized that the one-sided alpha of 0.15 would not be considered acceptable. The applicant proposed to perform sensitivity analysis to include one-sided 90% and 95% CI in addition to protocol planned 85% CI; however considering the late stage in which the trial was, the issue of the alpha was not pursued any further.

GCP

The applicant declared that all studies were conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice (GCP) and the Declaration of Helsinki. Critical findings during auditing/monitoring process with regard to the conduct of study C2301 especially in some Latin American sites required measures which were adequately addressed by the sponsor (see discussion of study C2301).

Tabular overview of clinical studies

The table below summarises the pivotal studies (table 2)

Table 2. Efficacy and Safety Studies

Protocol No. & Study Dates Investigator & Country	**Study Design & Purpose Population Studied Evaluations**	**Total No.& Race (w,b,a,o) Age Range (mean) Group No. & Sex (m,f)**	**Treatment, Route, Regimen, Duration of Therapy, Dosage**
[TBM100C2301] **invest.:** Konstan M et al **countries:** Argentina, Brazil, Bulgaria, Chile, Lithuania, Mexico, Serbia, United States **start:** 22-Sep-2005 **end:** 28-Feb-2007	**design, goal & population**: Randomized, double-blind, placebo-controlled, multicenter, phase 3 trial to assess the efficacy and safety of tobramycin inhalation powder (TIP) in cystic fibrosis subjects **evaluations**: **efficacy: Lung function (**FEV1, FVC, FEF25-75), *P. aeruginosa* CFU/g sputum, *P. aeruginosa* susceptibility (MIC), antipseudomonal antibiotic use, hospitalization due to respiratory events **safety:** AEs, SAEs, hematology, chemistry, urinalysis, audiology, airway reactivity (FEV1), vital signs (VS), physical examination (PE), serum tobramycin concentration **other:** PK	**total**: 95 (80w, 1b, 0a, 14o) **age:** 6-21 yrs (13.3) **groups**: 2 Cycle 1: 42m, 53f TIP: 46 (19m, 27f) Placebo: 49 (23m, 26f) Cycles 2 and 3: all patients received TIP	Powder-filled hard capsules delivered via T-326 inhaler (DPI) TIP 28 mg Placebo **duration**: 3 cycles of 28 days on treatment and 28 days off treatment **doses**: bid, orally inhaled Cycle 1: TIP 4 x 28 mg Placebo Cycles 2 and 3: TIP 4 x 28 mg
[TBM100C2302] **invest.:** Konstan M et al **countries:** Australia, Canada, Chile, Colombia, France, Germany, Greece, Hungary, Israel, Italy, Mexico, Spain, Switzerland, The Netherlands, United Kingdom, United States **start:** 06-Feb-2006 **end:** 12-Mar-2009	**design, goal & population**: Randomized, open-label, multicenter, phase 3 trial to assess the safety of tobramycin inhalation powder compared to TOBI in cystic fibrosis subjects **evaluations**: **safety** (primary objective): AEs, SAEs, hematology, chemistry, urinalysis, audiology, airway reactivity (FEV1), VS, PE, serum tobramycin concentration **efficacy** (key secondary objective): lung function (change in FEV1 % predicted), treatment satisfaction questionnaire for medication (TSQM), administration time, *P.aeruginosa* suppression, hospitalization	**total**: 517 (468w, 4b, 4a, 41o) **age**: 6-66 yrs (25.6) **groups**: 2 (286m, 231f) TIP: 308 (171m, 137f) TOBI: 209 (115m, 94f)	Powder-filled hard capsules delivered via T-326 inhaler (DPI) TIP 28 mg Nebulized solution delivered via PARI LC PLUS™ Jet Nebulizer and DeVilbiss PulmoAide™ compressor or a suitable alternative TOBI 60 mg/mL (5 mL ampule) **duration**: 3 cycles of 28 days on treatment and 28 days off treatment **doses**: randomized to TIP or TOBI at a 3:2 ratio. Dosing bid, orally inhaled TIP 4 x 28 mg TOBI 5 x 60 mg/mL

2.4.2. Pharmacokinetics

Tobramycin inhalation powder is designed for use in the same indication and with the same dosing cycle as used for TOBI. TOBI has been used as comparator in the pharmacokinetic studies.

To support the application of TIP, the following 3 studies have been submitted:

- study TSB-001: exploratory study in CF patients of varying age and lung function to characterize their inspiratory flow profiles and to assess inspiratory volumes, flows and times using a simulated dry powder inhaler (active drug was not administered in this study).
- study INH-007: exploratory study in healthy subjects using a prototype TIP formulation to compare the lung deposition and pharmacokinetics between TIP and TOBI
- study TPI001: Phase I study in patients with CF to assess the safety, tolerability and pharmacokinetics of ascending single-doses of TIP (up to a dose of 112 mg); the approved 300 mg dose of TOBI was used as the reference in the study.

Furthermore, sparse pharmacokinetic samples were also collected in the Phase III trials (C2301 and C2302) and analyzed as part of the population pharmacokinetic analysis for TIP to determine the influence of various covariates like gender, body mass index, lung function etc on the pharmacokinetics of TIP.

For the analysis of tobramycin in plasma and sputum, fully validated analytical methods were applied, showing acceptable performance with regard to accuracy, precision, and in part stability. In study C2302 samples were stored for 33 months, while stability data only cover 21 months. In response to CHMP request of the missing data the applicant indicated that stability studies were ongoing. The applicant committed to provide the results as a follow-up measure when completed (see follow-up measures section).

Analysis of tobramycin in serum was carried out at 4 study sites. No cross validation was carried out. The applied method was for all study sites the same using the standard kit Abbot diagnostics TDxFLx system. No pronounced differences in outcome between the studies were expected as the observed variability (accuracy/precision) during validation was well within limits and the observed variability in pharmacokinetics was high. This also applied for analysis of tobramycin in sputum.

Absorption

Tobramycin is not absorbed from the gastrointestinal tract after oral administration. The T-326 inhaler has been used in all studies. Lung disposition after TIP administration is ca. 34%, meaning that of the recommended 112 mg dose, 27.6 mg tobramycin had reached the lung. The bioavailability was estimated to be about 30%.

Distribution

Tobramycin bounds less than 10% to plasma proteins. After parenteral administration, tobramycin distributes throughout extracellular water and highly perfused tissues and has an apparent volume of distribution in the range of 7 to 35 L (0.1- 0.6 L/kg).

Elimination

Tobramycin is not metabolized and is excreted unchanged principally by glomerular filtration with some tubular re-absorption. Tobramycin is cleared from serum with a half-life of approximately two hours. This half-life is dependent upon renal function, and increases with decreasing creatinine clearance.

After inhalation of radiolabelled drug, the relative distribution of radiolabel within the central, intermediate, and peripheral airways was comparable for both TIP and TOBI, and the same proportion of the drug delivered to the lung reached the systemic circulation. There is a possibility that the difference in formulations may affect rheology properties of the mucous, which may be clinically relevant.

Dose proportionality and time dependencies

In CF patients, an almost dose proportional increase in AUC and Cmax is observed for TIP over the dose range of 28 – 112 mg. No significant correlation between change from baseline in FEV1 and AUC and Cmax was detected for TIP and TOBI. A comparable systemic exposure was obtained after a 4x28 mg dose of TIP compared to a 300 mg dose of TOBI, which support the recommended dose of 112 mg (4 capsules) b.i.d. Further support is coming from clinical efficacy and safety studies. Administration of 4 capsules of TIP took about 5 min, which is clearly shorter than the time needed for TOBI (approximately 15 min).

Two inhalations should be taken from each capsule. This is in accordance with the outcome of study TSB-001, to ensure that patients at the lower end of the typical CF range of inspired volume inhale the complete dose; all patients receiving TIP were instructed to inhale twice from each capsule. The applicant has confirmed that this posology was used in the pivotal clinical trials.

From TOBI it is known that tobramycin does not accumulate in plasma and sputum. It is expected that this also applies for TIP, taking also into account the short elimination half-life of about 2 to 3 h. Moreover, in study C2301 and C2302, only low Ctrough levels were observed after b.i.d. administration of 112 mg TIP. Therefore, time dependency in pharmacokinetics is not an issue for tobramycin.

Special populations

Tobramycin is excreted renally, and patients with an impaired renal function may have elevated tobramycin plasma concentrations. The SmPC recommends monitoring to avoid toxic levels of tobramycin.

Taking into account that tobramycin is not metabolised and cleared unchanged in the urine, it can be expected that plasma clearance of tobramycin will not be influenced in patients with impaired liver function. No specific dose recommendation is given in the SmPC and it is indicated that no studies have been performed in this patient group.

As tobramycin is excreted unchanged in the urine, clearance is related to renal function. It is not uncommon that elderly patients have the renal function reduced. As a result an increase in systemic tobramycin exposure may occur. The SmPC states that there are insufficient data in this population to support a dose recommendation.

Pharmacokinetic data indicate that pharmacokinetics is not significanly altered in children (age 6 years and older). The SmPC states that the formulation is not indicated for use in the paediatric patients less than 6 years of age.

Gender, weight and race are not identified as factors which may influence tobramycin pharmacokinetics.

Pharmacokinetic interaction studies

Tobramycin is not metabolised and therefore no interactions on cytochrome P450 level are expected.

As tobramycin is excreted renally, a possible interaction may occur with diuretic compounds; in this respect relevant warnings are included in section 4.4 and 4.5.

Population pharmacokinetics

A population pharmacokinetic model for tobramycin inhalation powder in CF patients was developed to characterize the covariates effect of age, body mass index, creatinine clearance, gender, lung function (as FEV1% predicted), and weight on the model parameters. Tobramycin inhalation powder-containing arms of three clinical studies (TPI001, C2301 and C2302) were pooled to generate a pharmacokinetic analysis dataset for modelling. In study TPI001 single doses of 28 mg, 56 mg, 84 mg, and 112 mg were administered, while in study C2301 and C2302 112 mg b.i.d doses were administered. For studies C2301 and C2302, the times of the doses associated with the pharmacokinetic samples are only available at the beginning and end of each cycle. The times of other doses in the cycle were imputed by carrying backward from the dose at the end of the cycle with the assumption that each dose was given 12 h apart.

The developed population pharmacokinetic model described the pharmacokinetics sufficiently. The analysis indicated that for a typical CF patient, CL/F was estimated to be approximately 14 l/h, Vd/F 84 l, and apparent peripheral volume of distribution (Vp/F) 162 l. From the included covariates, BMI and FEV1 were identified to influence pharmacokinetics, however simulations showed that changes in Cmax and C_{min} were small and considered not clinically significant. A few observations indicated concentrations at t=12h of above 2 mg/l. Further analysis performed upon CHMP request indicated that younger children are not subject to such a high exposure.

Comparison of trial formulations with finished product

Two formulations of TIP capsules have been used in the studies: the 25 mg formulation TS-001 has been used in study INH007, which is considered a supportive study; in all other studies formulation CN1-002 has been used. In all cases TIP was inhaled using the dry powder inhaler T-326. TIP formulations are considered comparable.

For commercialisation, the manufacturing process had to be changed to improve the stability of the emulsion before spray-drying and to reduce powder yield variability. However, no changes were made to composition of the formulation, batch size or delivery device. Equivalence was supported by *in vitro* data, like aerosol performance.

Intra- and inter-individual variability

After single-dose administration of TIP to CF patients, inter-subject (n=12) variability in serum Cmax and AUC_{inf} was about 52% and 40%, respectively for the 112 mg dose group (study TPI001). This is comparable to the inter-subject (n=20) variability in Cmax (about 56%) and AUC_{inf} (48%) after a single 300 mg dose of TOBI (study TPI001). The high variability observed in AUC and Cmax is not unexpected for a drug after inhalation.

Study INH-007 was an exploratory study in healthy subjects with normal lung function using a prototype TIP formulation to compare the lung deposition and pharmacokinetics between TIP and TOBI. In this study the observed within subject variability after administration of TIP by the T-326 inhaler was about 18%, indicating that subjects are capable of consistent administrations of tobramycin via this method. For TOBI, whole lung disposition was about 5%, meaning that about 15 mg of the total 300 mg dose was disposed. A total of 56% radioactivity remained in the nebuliser, which may indicate that the nebuliser had not functioned as efficiently as expected and had not delivered the expected dose. The mean lung disposition after TIP administration was ca. 34%, meaning that 27.6 mg

tobramycin had reached the lung, which is considerably higher than the TOBI administration via the nebuliser, even taking into account that for TOBI the full dose was not administered.

The relative distribution of radiolabel within the central, intermediate, and peripheral airways was comparable for both TIP and TOBI.

The dose normalised Cmax and AUC indicate that the same proportion of the drug delivered to the lung reached the systemic circulation.

Data regarding TOBI should be interpreted with care as it seems the nebuliser did not function optimally.

Overall, the pharmacokinetics is sufficiently covered and the applicant has committed to provide further data on stability of subject samples as a follow-up measure.

2.4.3. Pharmacodynamics

Mechanism of action

Tobramycin is an aminoglycoside antibiotic that acts bactericidal primarily by disrupting protein synthesis leading to altered cell membrane permeability, progressive disruption of the cell envelope and eventual cell death. Mechanism of action of aminoglycosides is sufficiently known.

Primary and Secondary pharmacology

The applicant has not conducted formal primary pharmacodynamic studies with TOBI Podhaler as it was considered that the pharmacodynamic experience with TOBI could be extended to TIP and verified in the Phase III studies.

The active substance tobramycin is well known based on the long-standing experience with the systemic (IV) use at higher dose levels than those presently proposed for TOBI Podhaler for the treatment of infections associated with aerobic gram-negative bacteria. Therefore the applicant has not conducted formal pharmacodynamic studies with TOBI Podhaler. Nevertheless, sputum drug concentrations obtained after TIP administration were considered sufficiently high (multiple–folds) to be active against PA present in the lung.

Similar to the experience with TOBI MIC data, PK data, together with the comparable deposition of TIP and TOBI in the lung in healthy volunteers, give assurance that TIP will be expected to be similar to TOBI from the PD point of view. The differences between the two formulations in CF patients are further discussed in the following sections.

2.5. Clinical efficacy

Efficacy data are derived primarily from the following two pivotal Phase III clinical studies (Table 4).

Table 4. Overview of pivotal clinical trials.

Study no.	Study objective, population/design	N. pat./age	Treatment duration	Medication dose/day/duration	Efficacy endpoint
C2301[a4]	Efficacy/safety TIP vs placebo in target population/ RDB *	102/ 6-21 yrs	24 weeks	4x28 mg bid. 3 cycles of 28 days on treatment and 28 days off treatment Cycle 1: TIP 4 x 28 mg or Placebo Cycles 2 and 3: TIP 4 x 28 mg	Change in % predicted FEV_1
C2302[b5]	Safety/efficacy TIP vs TOBI in target population/ ROL **	517/ 6-66 yrs	24 weeks	3 cycles of 28 days on treatment and 28 days off treatment TIP 4x28 mg bid or TOBI 300 mg	Change in % predicted FEV_1

a. Countries: Argentina, Brazil, Bulgaria, Chile, Lithuania, Mexico, Serbia, United States

b. Countries: Australia, Canada, Chile, Colombia, France, Germany, Greece, Hungary, Israel, Italy, Mexico, Spain, Switzerland, The Netherlands, United Kingdom, United States

* RDB= Randomised double blind ** ROL = Randomised open label

See table 2 for additional information on these studies.

In addition supportive data from one study in healthy volunteers (Study INH-007) and two in CF patients (Study TSB-001 and Study TPI001) are provided.

There is also an ongoing Phase III randomised double-blind placebo controlled study (C2303- in Russia, Estonia) in cystic fibrosis patients to assess efficacy, safety and pharmacokinetics of tobramycin inhalation powder from a modified manufacturing process (TIP new). Finalisation of the latter study is planned for December 2010.

2.5.1. Dose response studies

No clinical dose-finding studies were performed since TIP contains the same active component as TOBI (i.e. tobramycin) but has been designed to be delivered more quickly and easily as a dry powder rather

[4] **External participants**
Contract Research Organization (CRO-perform study, data management) were PAREXEL International LLC (perform study in Latin America, data management) and AbCRO, Inc., Business Park Sofia, Bulgaria (perform study in Eastern European countries)
Central laboratory (routine blood analysis and microbiology) was **ICON** Central Laboratories, Inc.
Laboratory (PK analysis) was Anapharm, Québec

[5] **CRO Quintiles UK Ltd,**
Site project management
(except USA and Canada)
Data management Parexel International, UK
Plus ICON Central Laboratories (Ireland) and Anapharm Québec, Canada as for trial C2301

than as a solution. Hence, a dose escalation study (TPI001) was performed in order to determine the dose of TIP that would show equivalent systemic exposure to the current TOBI formulation. This study identified that the 112 mg (4x28 mg) b.i.d dose of TIP gave comparable systemic pharmacokinetics and sputum concentrations to the approved 300 mg dose of TOBI. The efficacy and safety of the chosen dosage are discussed in the pivotal clinical studies described below.

2.5.2. Main studies

C2301 ***A randomised, double-blind, placebo-controlled, multicenter, phase 3 trial to assess the efficacy and safety of tobramycin inhalation powder in cystic fibrosis subjects***

This was a superiority study of TIP vs. placebo (for cycle 1) with patients being enrolled in 1:1 ratio, followed by an open-label treatment with TIP for Cycles 2 and 3, in all patients.

C2302. ***A randomised, open-label, multicenter, phase 3 trial to assess the safety and efficacy of tobramycin inhalation powder compared to TOBI in cystic fibrosis subjects***

This was an open-label randomised study designed to show comparative safety and efficacy with TIP vs. TOBI for 3 cycles (6 months) with patients being enrolled in 3:2 ratio.

The double-blind superiority (vs. placebo) design in study C2301 was limited to the first cycle, although a double-blind design for all 3 cycles of treatment would have been preferred. This had been discussed with the CHMP in the protocol assistance requested by the applicant. From the ethical point of view in this orphan condition a longer placebo treatment would not have been feasible. The results of the first cycle can be considered as proof of concept phase and provided the results of the other 2 treatment cycles and profile of the effect on the objective efficacy parameter % predicted FEV1 in these patients are consistent and supportive, the design of this pivotal trial would be acceptable.

The open-label design of study C2302 was justified due to the obvious differences between the inhalation devices and unfeasible burden on the patients in case of a double-dummy design for this CF disease.

Methods

Study Participants

In study C2301 the inclusion and exclusion criteria were such to allow the selection of a patient population similar to that used in the original TOBI pivotal registration studies, naïve to TOBI treatment. Diagnosis of CF was confirmed by the presence of one or more clinical features of CF in addition to a quantitative pilocarpine iontophoresis sweat chloride test of ≥ 60mEg/L, or identification of well-characterized disease causing mutations in each CFTR gene, or abnormal nasal transepithelial potential difference characteristic of CF. PA must have been present in a sputum/throat culture (or BAL) within 6 months prior to screening, and in the sputum culture at the screening visit.

At entry in the study patients with lung PA infection had not to have used inhaled anti-PA within 4 months prior to entry. The study enrolled CF patients, aged between 6 and 21 years (inclusive), with FEV_1 values from 25% to 80% (inclusive) predicted.

In study C2302 the similarly diagnosed (as in C2301) CF patients with lung PA infection had not to have used inhaled anti-PA within 28 days prior to entry in the study; patients were not naïve to anti-PA treatment systemic or inhalational antibiotics. The study enrolled patients aged 6 years and older with a baseline FEV_1 of between 25% and 75% of predicted normal.

In both studies patients were to be clinically stable in the opinion of the investigator.

In both studies patients with a history of sputum culture or deep-throat cough swab (or BAL) culture yielding *B. cepacia* within 2 years prior to screening and/or sputum culture yielding *B. cepacia* at screening were excluded. Furthermore, patients with haemoptysis more than 60 cc at any time within 30 days prior to study drug administration were excluded.

Treatments

In study C2301, TIP was provided as 28 mg capsules (total weight about 50 mg) in blister packs, 4 to be inhaled b.i.d. using the T-326 dry powder inhaler (DPI) for 28 days. Patients randomized to placebo were to inhale the contents of 4 matching placebo capsules (containing the two TIP excipients, DSPC and $CaCl_2$). All capsules were to be stored at room temperature.

In study C2302, TIP was administered as in study C2301. TOBI was administered as 5 ml of a 60 mg/ml solution via the PARI LC Plus nebuliser twice daily using the same dosing cycles as TIP.

Capsules were to be stored between 2- 8°C, but could be stored at room temperature by the patient for the 28 day treatment period.

Study treatments in both studies were each to be taken b.i.d. approximately 12 hours (but not less than 6 hours) apart.

Treatments were to be delivered in the following order: Bronchodilator (15-60 minutes prior to study drug inhalation)--->Chest physiotherapy--->Other inhaled medicine--->Study drug administration.

On the days of clinic visits, sputum samples and spirometry were to occur after bronchodilator administration, but prior to study drug administration (airway clearance techniques and other inhaled medications were to be administered prior to visiting the clinic with the exception of hypertonic saline which was to be consistently administered at home or at the clinic, but not within 30 minutes of conducting pulmonary function tests, PFTs).

In both studies, the concomitant use of mucolytics (including dornase alfa and hypertonic saline), bronchodilators (including β_2-agonists), inhaled corticosteroids, and macrolides was permitted provided that the doses were kept stable (and initiated during the study). The use of other (systemic) anti-PA antibiotics (other than inhaled) was permitted as a treatment option if necessary to treat symptoms of pulmonary exacerbation. Inhaled anti-PA antibiotics other than the study drugs were prohibited. The study drug was administered after all other respiratory treatments (including physical chest therapy) had been completed. There were no restrictions with regard to the use of other medications as part of current standards of care for CF patients (e.g. pancreatic enzyme replacements, nutrients).

Objectives

In study C2301, the primary objective was to evaluate the efficacy of 28-day bid dosing of TIP versus placebo, as measured by the relative change in FEV_1 percent predicted from baseline (Day 1) to the end of Cycle 1 dosing (Day 28).

The secondary objectives were to assess the safety and efficacy of TIP when administered to patients who were dosed for more than one cycle.

In study C2302, the primary objective was to evaluate the safety of 28-day bid dosing of TIP delivered with the T-326 inhaler versus TOBI delivered with the PARI LC PLUS jet nebuliser and DeVilbiss PulmoAide compressor or suitable alternative. The secondary objectives were to evaluate the efficacy of TIP compared to TOBI using a relative change in FEV_1 percent predicted at the end of Cycle 3 dosing

period compared to baseline, and to evaluate patient-reported treatment satisfaction through the use of the Treatment Satisfaction Questionnaire for Medication (TSQM).

These objectives had been previously discussed with the CHMP in the protocol assistance requests. In particular, the fact that efficacy was a secondary objective and not a primary objective together with the lack of a placebo arm in study C2302 was of concern for the CHMP, who agreed that non-inferiority of TIP vs. TOBI would have to be demonstrated in this study. In the placebo-controlled study C2301 it was critical to demonstrate that the efficacy of TIP in anti-PA inhaled antibiotic naïve CF patients gave similar results as the original registration studies for TOBI in similarly treatment naïve patients when treated for 1-3 cycles. Both studies are considered pivotal for this MAA for the sought indication.

Outcomes/endpoints

In line with EMEA CF guideline, the chosen primary efficacy endpoint in both pivotal studies is relative change from baseline in % predicted FEV_1 at day 28 of each treatment cycle in study C2301 and after 3 treatment cycles in study C2302.

FEV1 was measured in liters, and was converted to FEV1 % predicted using the Knudson (1983) Normal Value (KNV) equations. The relative change in FEV1 % predicted from baseline to *pre-dose* day X of cycle Y = ((predose day X FEV1 % predicted – baseline FEV1 % predicted) / baseline FEV1 % predicted) x 100. i.e., relative change = ((predose day X – baseline) / baseline) x 100**.**

In the present pivotal clinical studies quantitative efficacy primary endpoint (in % predicted FEV_1) for spirometry was supported by microbiological outcomes (as secondary endpoint).

Additional lung function parameters were also evaluated such as relative change in FVC % predicted and FEF25-75 % predicted from baseline to each post baseline visit was summarized descriptively by treatment group.

In C2302 Patient Reported Outcome (PRO) assessment was also used as a secondary efficacy endpoint.

The PRO analysis for treatment satisfaction was based on the ITT population. Patient's self-reported satisfaction or dissatisfaction with study drug (medication and delivery device) was measured using the Treatment Satisfaction Questionnaire for Medication (TSQM), a validated instrument (Atkinson 2004).

The TSQM has a total of 14 items with responses to nearly all items rated on a five-point or 7-point rating scale; with a higher rating indicating a higher level of satisfaction. The questionnaire was modified by Chiron (the original sponsor of the study) with the addition of 4 questions and the rewording of instructions and adjusted wording.

Convenience and Global Satisfaction. Treatment satisfaction scores (Items 1-14) were summarized descriptively by treatment group and time point. The scale scores were transformed into continuous data scores, with a possible range of 0% to 100%, where a higher scale score indicates higher satisfaction for that scale, e.g. convenience.

Microbiology endpoints included change in PA sputum density, treatment-emergent isolation of other bacterial respiratory pathogens, and change in susceptibility of PA to tobramycin. The PA density analysis was based on logarithm scale as log10 (log10 colony-forming units [CFU] per gram of sputum). Absolute change from baseline to each post-baseline time point in cycles 1-3 are summarized descriptively by treatment group. No statistical testing is performed. Sputum was collected preferably from the first morning specimen; if the subject was unable to produce a sputum specimen, a deep-throat cough swab or induced sputum was to be done, at the investigator's discretion.

Exacerbations and hospitalizations related to respiratory events were collected to support the data for the relative change from baseline in % predicted.

Compliance was evaluated as follows in both studies: on the days that the patient was dosed in the clinic, the study coordinator recorded the total study-drug administration time on the source documentation and CRF. Assessment of compliance with the dosing schedule was based on completed subject dosing logs, number of used and unused capsules returned per patient, and percentage of completion of scheduled study visits.

In Study C2302 full TIP compliance was based upon the inhalation of four capsules for TIP (inhalation of one TIP capsule counted as 25% compliance for that dose). Compliance for TOBI was assessed by one ampoule being empty (but without data collection to assess whether the full intended dose had been successfully nebulized and delivered to the patient).

Both studies measured also serum concentrations of tobramycin from blood samples (from a peripheral site) obtained before, and 60 minutes following the administration of the dose (in study C2301) on start and end of cycle 1 and cycle 2. In study C2302 one sample before dosing, one sample between 0 and 2 hours and two samples between 2 and 5 hours after the completion of dosing. See PK sections in this AR.

Safety assessments consisted of collecting all adverse events (AEs), serious adverse events (SAEs), with their severity and relationship to study drug, and pregnancies. They included the regular monitoring of haematology, blood chemistry and urine performed at study centre / central laboratory and regular assessments of audiology (at selected centres), change in airway reactivity (FEV1), vital signs, physical condition and body weight. Serum tobramycin concentrations were also considered to be a safety variable.

FEV_1 is a well documented, quantitative measurement of lung function. It is the strongest clinical predictor of survival among CF patients. Measuring sustained benefit to the patient as measured by lung-function especially FEV_1 after multiple courses of inhalational antibiotic therapy is considered as an important pivotal evaluation in the assessment of such products. Because lung volume is related to age, gender and height, absolute measures of FEV_1, measured in liters, do not provide a useful means to compare pulmonary function among patients who may differ in size and other relevant anthropomorphic variables. Therefore, FEV_1 (L) is often converted to values adjusted for age, gender and height using an equation developed by Knudson and has been the most commonly used outcome measure for CF clinical trials. Results across age groups and by baseline FEV1 % predicted stratification will normally be present to clarify further the overall change in FEV1 % predicted (compared to baseline) in a treatment arm. Such analyses are provided (see results).

The microbiological outcome measure related to suppression of PA growth in anti-PA treatment in CF patients with chronic PA infection of the lung is also an accepted outcome measure.

The PRO questionnaire took into account aspects to be evaluated in relation to the significant benefit for patients using the new formulation of inhalational tobramycin in combination with the new delivery device as compared to the marketed TOBI and recommended approved delivery device.

Overall, the outcomes/endpoints together with the supportive microbiological outcome measure and the adjusted PRO questionnaire are acceptable for the evaluation of the efficacy of TIP in the sought indication.

Sample size

Study C2301 planned to enrol 140 CF patients, aged between 6 and 21 years (inclusive), with FEV_1 values from 25% to 80% (inclusive) predicted. A sample size of 140 subjects (70 per group) was

estimated to be needed to provide 90% power to detect a treatment difference of 11% in the mean relative change of FEV1 % predicted from baseline to the end of Cycle 1 dosing, at a two-sided .05 significance level, under an assumption of a 20% standard deviation for the primary efficacy endpoint. This took into account observations derived form 3 previous studies with TOBI (PC-TNDS-002;-003 and -101) for the relative change in FEV1 % predicted from baseline to Cycle 1 day 28, for TOBI-treated subjects aged 6 to 19 years with baseline FEV1 from 25% to 75% predicted.

An interim analysis was planned when 80 patients had completed Cycle 1, in order to refine the sample size (based on the estimated effect and standard deviation of the primary endpoint measurement).

Study C2302 planned to enrol 500 patients aged 6 years and older with a baseline FEV_1 of between 25% and 75% of predicted normal. A total of 553 patients were randomized and 517 received study drug (308 to TIP and 209 to TOBI). With a sample size of 300 TIP patients, there was a 99.8% chance of observing at least one adverse event with a true incidence rate of 2% from the TIP arm, and a 95% chance of observing at least one adverse event with a true incidence rate of 1% from the TIP arm. The inclusion of 200 TOBI patients would provide 96% power to demonstrate non-inferiority of TIP to TOBI with regard to efficacy, based on a non-inferiority margin of 6% and a one-sided significance level of p= 0.15, assuming that the true TOBI – TIP treatment difference is 1% and that the standard deviation of the relative change in FEV1 % predicted is 20%.

The sample size per study in relation to the objective is considered acceptable.

Randomisation

Study C2301 was a randomized, three-cycle, two arms trial. The first cycle was double blind placebo controlled with eligible patients randomized to TIP or placebo at a 1:1 ratio using a biased coin, adaptive randomization procedure to achieve balance between the 2 treatment groups with respect to the following covariates: region (Europe, United Sates/Canada, Latin America), age (≥ 6 to < 13, ≥ 13 to ≤ 21), screening FEV1 (≥ 25% predicted to < 50% predicted, ≥ 50% predicted to ≤ 80% predicted). The investigator or designee was to complete a randomization worksheet at Visit 1.5 and follow the instructions for randomization using an interactive voice response system (IVRS). The IVRS assigned each patient a unique kit number for the first cycle of therapy.

Upon completion of the first cycle, all patients received TIP for cycles 2 and 3.

Study C2302 was a randomized, open-label, active-controlled, parallel-arm trial. Eligible patients were randomized to TIP or TOBI at a 3:2 ratio using a biased coin, adaptive randomization procedure to achieve balance between the 2 treatment groups with regards to age (≥ 6 to < 13, ≥ 13 to < 20, and ≥ 20), screening FEV1 (≥ 25% predicted to < 50% predicted, ≥ 50% predicted to ≤ 75% predicted), and chronic macrolide use (yes/no). Once the patient's eligibility was confirmed, a randomization worksheet was completed and the patient received a patient number and treatment assignment via an interactive voice response system (IVRS).

The randomisation and balancing for mentioned different important strata are acceptable. The practically absent adult category in study C2301 is understandable based on the evolution of the management of CF patients with PA infection of the lung.

Blinding (masking)

In Study C2301 the first cycle was double blind placebo controlled. Packaging and labelling of TIP and placebo materials were identical, assay results for tobramycin serum concentrations were maintained in confidence until after database lock, and only the Data Monitoring Committee members were permitted to see the interim analysis.

Study C2302 was a randomized open–label study due to differences in study drug administration.

Statistical methods

In study C2301, a pre-planned interim analysis was conducted in November 2006 by an external (with no sponsor involvement) independent Data Monitoring Committee Contract Research Organization (DMC CRO), and the results were reviewed by an external, independent Data Monitoring Committee (DMC).

The Committee comprised three members of the Cystic Fibrosis Foundation's standing Data Safety Monitoring Board (DSMB). The DMC members were joined by an independent statistician.

The primary objectives of the interim analysis were to (a) estimate the common standard deviation for sample size re-estimation, (b) evaluate efficacy of TIP versus placebo for potential stopping of the study, and (c) assess safety in terms of adverse events, airway reactivity, and bronchospasm.

The interim analysis meeting was conducted as called for by the protocol when the 80th randomized patient completed Cycle 1 dosing. The clinical database was locked on 02-Nov-2006 and the DMC interim analysis meeting was held on 20-Nov-2006. The DMC reviewed interim analysis results on 89 randomized subjects with 79 subjects (TIP & placebo) included in the safety and intent-to-treat (ITT) populations (10 subjects were not included due to no dosing information of study drug or withdrawal of consent). This interim analysis is referred to as Original Interim Analysis (OIA).

In the sensitivity interim analysis (SIA) a covariance model with factors of treatment, baseline % predicted FEV_1, age and region was used. Supportive analysis was also provided based on data of All ITT population using a t-test (that is, including spirometry data from all patients). The treatment-by-covariate interactions were assessed by testing the treatment-by-covariate interactions as appropriate, each at the 10% significance level.

The primary analysis for claiming superiority is based on the SIA ITT population using an analysis of covariance model with factors of treatment, baseline FEV_1 % predicted, age and region. Due to interim analysis, the statistical significance level is 0.0044 at the SIA.

In study C2302, the principal efficacy analysis was performed using an inferential analysis and confidence interval approach. The non-inferiority margin of 6% was pre-defined in the protocol. A claim of non-inferiority efficacy was based on the one-side 85% confidence interval in the ITT population (lower limit greater than -6%). Sensitivity analyses based on one-sided 90% and 95% confidence intervals from the same ANCOVA model were provided. Sensitivity analyses were conducted to assess the impact of patient discontinuation on the non-inferiority comparison. These used various data imputation techniques. The single imputation methods included e.g. Last Observation Carried Forward, Baseline Observation Carried Forward. In addition, the non-inferiority inferential analysis was performed for PP population.

In this study, an independent, external data monitoring committee (DMC) was established to monitor certain safety variables during the study. The DMC was comprised of experienced cystic fibrosis clinicians who were not investigators in the trial, and statisticians experienced in the interim evaluation of safety data. The operation procedure was detailed in the DMC charter. The chairperson of the DMC conducted quarterly reviews of SAEs, and the DMC and Novartis had one open meeting when approximately 100-150 patients had been enrolled in the trial. Following this meeting the DMC received monthly updates on SAEs and conducted an annual review in Dec-08.

The 6% non-inferiority margin had been discussed with the CHMP (TBM100C EMEA Protocol Assistance Correspondence 2008), as had been the use of 90% and 95% confidence intervals in addition to the 85% CI. The non-inferiority margin was selected on the basis of it being approximately half of the

expected difference from placebo and also with due regard to the trial feasibility in the comparatively small CF patient population.

Results

Participant flow

Disposition of patients in the pivotal clinical studies is displayed in table 5.

Table 5. Study participation and withdrawals in C2301 and C2302

	C2301		C2302	
	TIP/TIP/TIP n (%)	**PLB/TIP/TIP n (%)**	**TIP/TIP/TIP n (%)**	**TOBI/TOBI/TOBI n (%)**
Randomized	48 (100.0)	54 (100.0)	329 (100.0)	224 (100.0)
Treated	46 (95.8)	49 (90.7)	308 (93.6)	209 (93.3)
Completed	39 (81.3)	40 (74.1)	225 (68.4)	171 (76.3)
Discontinued	8 (16.7)	12 (22.2)	104 (31.6)	53 (23.7)
Reason				
AE or death	0 (0.0)	1 (1.9)	44 (13.4)	20 (8.9)
Withdrawal of consent	0 (0.0)	5 (9.3)	28 (8.5)	12 (5.4)
Inappropriate enrolment	2 (4.2)	2 (3.7)	4 (1.2)	2 (0.9)
Protocol violation	1 (2.1)	1 (1.9)	12 (3.6)	6 (2.7)
Lost to follow up	0 (0.0)	1 (1.9)	5 (1.5)	6 (2.7)
Administrative reason	1 (2.1)	0 (0.0)	1 (0.3)	1 (0.4)
Unable to classify	4 (8.3)	2 (3.7)	10 (3.0)	6 (2.7)
Discontinued by cycle				
Cycle 1	5 (10.4)	8 (14.8)	44 (13.4)	28 (12.5)
Cycle 2	2 (4.2)	1 (1.9)	30 (9.1)	9 (4.0)
Cycle 3	0 (0.0)	0 (0.0)	9 (2.7)	1 (0.4)

% is calculated based on all randomized patients.
The data summaries for the cited source tables were based on the treated patient population and not on the all randomized patient population as provided in this table.

In study C2302, the main reason for discontinuation in both treatment groups was an adverse event.

There were major protocol deviations which resulted in exclusion from the per protocol (PP) population. Overall, the extent of the major protocol deviations was well matched between the treatment groups, with a 1% or less difference between groups with few exceptions to this such as the improper use of chronic macrolides (Tip 6% vs. 2% in TOBI group), compliance less than 80% i.e. a failure to take at least 80% of the study drug (Tip 18% vs. 9% in TOBI group).

Recruitment

In study C2301 patients were recruited in the following centres: Bulgaria (2), Lithuania (1), Serbia (1), Argentina (5), Brazil (3), Chile (3), Mexico (2); and United States (16).

First patient enrolled: 22-Sep-2005

Last patient completed: 28-Feb-2007

In study C2302 patients were recruited in the following centres: USA (78), Chile (1), Colombia (2), Mexico (1), France (4), Canada (1), Germany (9), Hungary (2), Switzerland (1), Italy (6), Netherlands (3), Spain (5), UK (5), Australia (4), Israel (4),

Greece (1)

First patient first visit: 06-Feb-2006

Last patient completed: 12-Mar-2009

Conduct of the study

Study C2301

The study protocol was amended once in relation to aspects such as broadening of the inclusion/exclusion criteria in order to facilitate enrolment (to increase upper limit of FEV1 % predicted from 75% to 80%; increase upper age limit from 19 to 21; allow the use of chronic macrolide antibiotics (provided therapy was initiated 28 days prior to study drug administration) and eliminate the restriction on the use of chronic inhaled anti-PA drugs prior to screening from 12 to 4 months. Other amendments related to altering the treatment sequence order for clinic visits, with patients receiving chest physiotherapy and other inhaled medications prior to the visit; and some other minor amendments.

In August and September 2006, Novartis personnel conducted site audits at three active sites in the Latin American region and two active sites in Europe. Findings from two of the sites in Latin America raised concerns regarding compliance with acceptable pulmonary function test (PFT) calibration practices.

Novartis took a series of measures to assure the quality of the Latin American PFT data. These steps were endorsed by the DMC prior to implementation:

- Novartis set up an external, independent Expert Panel of pulmonologists to review, in a blinded manner, the source PFT data from all Latin American centres in the Original Interim Analysis.
- An assigned independent contract research organization (CRO), in conjunction with Novartis and the chair of the Expert Panel, created a spirometry calibration checklist which was used to document adherence with acceptable PFT calibration practices and to the technical criteria of the American Thoracic Society (ATS)/National Lung Health Education Program (NLHEP).
- Using the spirometry calibration checklist, the assigned CRO conducted an audit of all Latin American study centres in the Original Interim Analysis to assess overall adherence to the study protocol for spirometry equipment calibration.
- The independent Expert Panel, using the completed spirometry calibration checklists, determined the acceptability of calibrations in a blinded manner.
- The Expert Panel reviewed the source PFT data from those Latin American patients with acceptable calibration, and rated their PFT quality using the previously defined quality criteria developed by the Panel members. Those with unacceptable PFT data according to these criteria were excluded.

- A Sensitivity Interim Analysis (SIA) of the OIA data was performed by the DMC CRO (data monitoring committee contract research organization), following a revised statistical addendum to the DMC charter, to ensure robustness of statistical inference from the original interim analysis. The following criteria were used in deciding if subjects were included in the SIA:

  – Subjects must have acceptable calibrations at screening day, day 1, day 8 and day 28.

  – In addition to calibrations, subjects must satisfy quality review at baseline (screening day or day 1 pre-dose) and post-baseline (day 8 or day 28 pre-dose of Cycle 1).

- The DMC reviewed the SIA results, and provided a recommendation to Novartis on whether to stop or continue the study.

- Following the SIA in November 2007, the DMC again recommended that study be stopped based on pre-defined criteria from DMC charter.

The DMC driven stop of study C2301 based on pre-defined criteria from the DMC charter is understandable, although the number of remaining patients in the study became smaller. The latter was also affected by the quality conservation policy disqualifying results from unreliable sites (mainly Latin American). Nevertheless, this can be supported as the relevant sensitivity analyses have been provided.

Study C2302

There were several (4) amendments of the protocol for this study. These included among others flexibility measures to allow patients to adhere to study procedures as specified in the protocol; expand the acute airway reactivity safety endpoint to include an analysis of acute airway reactivity at Visits 3, 5, 7, 8, 9, and 10; and guidelines on the use of inhaled hypertonic saline in study patients and its timing in relation to study drug administration were provided.

All amendments were made before database lock and were not considered to affect the interpretation of study results.

Baseline data

In Study C2301, patient baseline demographics were comparable between treatment groups for the all randomized safety population. See relevant characteristics in the table 6.

Table 6. Baseline disease characteristics (Study C2301-all randomised safety population)

	TIP (N=46)	Placebo (N=49)	Total (N=95)
Age group (years)			
≥6 - <13	21 (45.7%)	24 (49.0%)	45 (47.4%)
≥13 - <22	25 (54.3%)	25 (51.0%)	50 (52.6%)
Age (years)			
n	46	49	95
Mean	13.4	13.2	13.3
SD	4.42	3.91	4.14
Min	6.0	6.0	6.0
Median	14.0	13.0	13.0
Max	21.0	21.0	21.0
Sex			
Male	19 (41.3%)	23 (46.9%)	42 (44.2%)
Female	27 (58.7%)	26 (53.1%)	53 (55.8%)
Race			
Asian	0 (0.0%)	0 (0.0%)	0 (0.0%)
Black	0 (0.0%)	1 (2.0%)	1 (1.1%)
Caucasian	37 (80.4%)	43 (87.8%)	80 (84.2%)
Hispanic	8 (17.4%)	4 (8.2%)	12 (12.6%)
Other	1 (2.2%)	1 (2.0%)	2 (2.1%)
FEV1% predicted at baseline			
n	32	37	69
Mean	54.7	58.5	56.7
SD	18.89	20.03	19.46
Min	24.1	23.4	23.4
Median	56.4	61.0	59.3
Max	96.2	98.2	98.2
FEV1 % predicted at baseline distribution n (%)			
<25	1 (3.1%)	3 (8.1%)	4 (5.8%)
≥ 25 - <50	13 (40.6%)	11 (29.7%)	24 (34.8%)
≥ 50 -≥ 80	16 (50.0%)	18 (48.6%)	34 (49.3%)
>80	2 (6.3%)	5 (13.5%)	7 (10.1%)

Baseline was defined as the last measurement prior to the first dosing of study medication (screening or predose day 1 of Cycle 1); for example, if predose day 1 was missing, the non-missing screening value was used.

Concomitant treatments such as with mucolytics (especially dornase alfa) were used by approximately 2/3 of patients in both treatment groups (58.7% for TIP group and 73.5% for placebo), selective β2-adrenoreceptor agonists in about half of patients in both treatment groups and in particular salbutamol (41.3% for the TIP group and 46.9% for placebo). Macrolides were used by 9.5% of the patients in Cycle 1 (Azithromycin: 4.3% in TIP group and 12.2% in placebo group, Erythromycin: 2.2% in TIP group and none in placebo group).

The compliance was generally high for both CF treatment groups, being close to or above 90% during Cycle 1.

In Study C2302, the treatment groups had similar demographic and disease characteristics (ARS, ITT and PP populations). Adults represented more than 2/3 of the population and most patients were extensively and recently pre-treated with anti-PA therapy (the majority used tobramycin). Most patients had predicted FEV_1 at baseline ≥50%. Approximately ¼ of the patient population had PA tobramycin MIC> 8 µg/ml (see table 7).

Table 7. Selected Demographic & Disease characteristics (ARS population)

	TIP	**TOBI**
	N=308	**N=209**
Age group (years)		
≥ 6 - <13	28 (9.1)	18 (8.6)
≥ 13 - <20	66 (21.4)	48 (23.0)
≥ 20	214 (69.5)	143 (68.4)
Age (years)		
Mean (SD)	25.9 (11.36)	25.2 (10.20)
Chronic macrolide use		
Yes	187 (60.71)	125 (59.81)
No	121 (39.29)	84 (40.19)
Screening FEV1 % predicted		
≥ 25% - < 50%	128 (41.56)	89 (42.58)
≥ 50% -≤ 75%	180 (58.44)	120 (57.42)
Baseline FEV1 % predicted1		
Mean (SD)	52.9 (14.20)	52.8 (15.95)
Last use of anti-PA antibiotics prior to first dose (month)		
0 to 1	78 (25.32)	46 (22.01)
> 1 to 3	171 (55.52)	112 (53.59)
> 3 to 6	33 (10.71)	24 (11.48)
> 6	11 (3.57)	9 (4.31)
never used	15 (4.87)	18 (8.61)
PA tobramycin MIC		
> 8 µg/mL	68 (22.08)	48 (22.97)
≤ 8 µg/mL	240 (77.92)	160 (76.56)

The compliance rate (over all three cycles) was ≥80% in the TIP group, and 91% in the TOBI group.

Overall the treatment groups had similar demographic and disease characteristics per study. Prior therapy with tobramycin was mentioned for approximately 80% of the patients per group in study C2302. There were some differences between treatment arms regarding concomitant medication with mucolytics especially in study C2301.

Numbers analysed

In study C2301, 102 patients were randomized (as a result of the interim analysis it was not necessary to reach the planned sample size), 95 (93%) of whom received study drug (see table 8).

Table 8. Analysis populations by treatment group

	Number of patients				
	Randomized	**All Randomised Safety**	**All ITT**	**SIA Safety**	**SIA ITT**
TIP	48	46	32	29	29
Placebo	54	49	37	32	32

Following the original pre-planned interim analysis (OIA) performed in a population of 79 patients, the Data Monitoring Committee (DMC) recommended stopping the study according to its charter, as the stopping boundaries for efficacy had been met and superiority to placebo had been established. However, following audit findings on calibration practices at two sites in the Latin America region, an independent expert panel (blinded to the treatment assignment) was appointed to review and exclude all pulmonary function test data of unacceptable quality and a sensitivity interim analysis (SIA) was performed on the remaining 61 patients. The DMC assessed the results of the SIA and re-affirmed its recommendation to stop the study.

In study C2302, a total of 517 received study drug (308 to TIP and 209 to TOBI). See analysis populations in table 9.

Table 9.

Analysis population	**TIP N=329 n (%)**	**TOBI N=224 n (%)**
Intent-to-treat	308 (93.6)	209 (93.3)
All Randomised Safety	308 (93.6)	209 (93.3)
Per protocol	200 (60.8)	149 (66.5)

The intent to treat (ITT) population was the main efficacy population. The per protocol (PP) population was used for sensitivity analysis.

In both studies (unless otherwise specified), the following analysis populations were defined for analysis purposes:

- Randomized: all patients who were randomized to study drug (TIP or TOBI).
- All Randomized Safety (ARS): all randomized patients who received at least one unit of study drug (one capsule for TIP or placebo in C2301, one capsule for TIP or one ampoule for TOBI in C2302).
- Intent to Treat (ITT): the same as ARS.
- Per protocol (PP): in C2302, all ITT population patients who adhered to the protocol without any major deviations.

Specific for C2301:

- SIA Safety: all randomized patients who received at least one capsule of study drug and were included in the SIA (61 subjects).
- SIA Intent-to-treat (ITT): all SIA Safety patients who received at least one dose (four capsules) of study drug and were included in the SIA (61 patients).
- All Safety: all SIA Safety patients plus additional treated patients (at least one capsule) from North America / Europe whose data are not available at the time of the OIA/SIA database lock.

- All ITT: all SIA ITT patients plus additional treated patients (at least one dose) from US / Europe whose data were not available at the time of the OIA/SIA database lock.

In both studies, patients who did not receive any study drug are excluded from all analyses.

Outcomes and estimation

Study C2301. The principal efficacy results are displayed in table 10.

Table 10. Relative change in percent predicted FEV_1 from baseline to end of dosing in Cycle 1 – Study C2301 (SIA ITT population)

	TIP N=29	Placebo N=32	Difference (SE)	95% CI of difference	P-value
n	27	31			
Mean (1)	13.21	-0.57	13.79 (3.95)	(5.87, 21.70)	0.0010
LS Mean (2)	13.97	0.68	13.29 (3.98)	(5.31, 21.28)	0.0016

(1) Mean, p-value, mean difference, and its 95% confidence interval are calculated from ANOVA with treatment in the model.
(2) Least square mean, p-value, least square mean difference, and its 95% confidence interval are calculated from ANCOVA with treatment, baseline value, age and region in the model.
SE = standard error, n is number of patients with value at baseline and Day 28.
The analysis is based on observed data only; no imputation is performed for missing data.
Source: [Study C2301–Table 11-4]

TIP treatment was superior to placebo with respect to the % predicted FEV_1 end point on Day 28 of Cycle 1 in the SIA ITT population. After this analysis, data from an 8 additional patients from North America and Europe became available. The supportive analyses of ALL ITT population showed results consistent with those in the SIA ITT analysis.

Pulmonary function data from eight patients from Latin America also became available since the OIA and SIA. Because the quality of these data could not be confirmed by the expert panel these data were not included in the above analysis. This analysis approach was pre-specified prior to database lock/unblinding.

The results of study C2301 are reminiscent of those of TOBI versus placebo in the registration trials more than 10 years ago in a similar patient population, although then there were markedly more adult patients included.

Study C2302, the principal efficacy results (improvements in % predicted FEV_1 obtained with TIP and TOBI treatments) are displayed in table 11.

Table 11. Relative change in percent predicted FEV_1 from baseline to pre-dose day 28 Cycles 3 – Study C2302 (ITT population)

	TIP/TIP/TIP N=308	TOBI/TOBI/TOBI N=209	Difference (SE)	85% one-sided CI of difference	95% one-sided CI of difference
N	227	171			
LS Mean [(1)]	5.8	4.7	1.1 (1.75)	(-0.67, 2.96)	(-1.74, 4.03)
Mean [(2)]	3.1	2.3	0.8 (1.92)	(-1.22, 2.77)	(-2.39, 3.94)

(1) Least square mean, least square mean difference (TIP - TOBI), and its one-sided 85% and 95% confidence interval are calculated from ANCOVA with treatment, baseline % predicted FEV1, age, chronic macrolide use, and region in the model.
(2) Mean, mean difference, and its one-sided 85% and 95% confidence interval are calculated from ANOVA with treatment in the model.
SE = standard error, n is number of patients with values at baseline and Day 28 of Cycle 3.
The analysis is based on observed data only, no imputation is performed for missing data.
Source: [Study C2302–Table 14.2-1.3a]

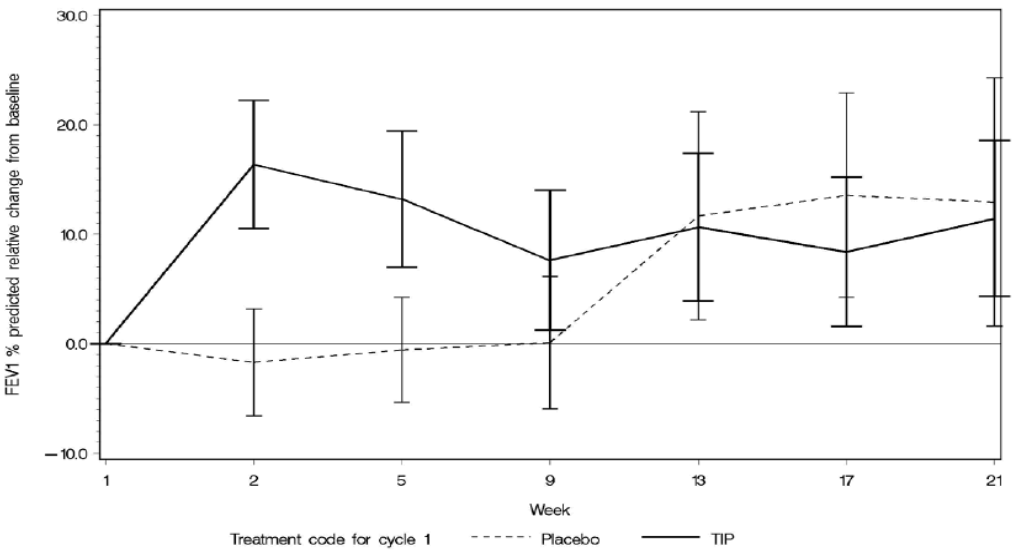
Non-inferiority of TIP to TOBI was shown at the 6% margin with the LS mean one-sided 90% CI (-1.10, 3.39) and the one-sided 95% CI (-1.74, 4.03) in the ITT population with PP analysis being consistent with this conclusion.

The overall observed smaller degree of change of FEV_1 in C2302 compared to study C2301 could be expected because the included patients were generally TOBI "experienced" whereas in Study C2301 the patients were TOBI naive patients

Ancillary analyses

In study C2301, the improvement in % predicted FEV_1 obtained in the first cycle of TIP treatment decreased slightly and was stabilised over subsequent cycles of treatment, see the figure 1.

Figure 1. Relative change in FEV1 % predicted from baseline in Cycles 1-3 (SIA ITT population)



Note: The vertical bar is 95% confidence interval.
Off-treatment phases: from week 5 to 9, week 13 to 17 and week 21 to 25.

The results of subgroup analyses for the different age groups and pulmonary function categories are shown in table 12.

Table 12. Subgroup analysis of relative change in FEV_1 % predicted from baseline to end of dosing in Cycle 1 – Study C2301 (ITT population)

Subgroup	TIP N=32			Placebo N=37			Difference (TIP- Placebo)	
	n	Mean (SD)	LS Mean	n	Mean (SD)	LS Mean	LS Mean (SE)	95% CI
Age								
< 13	10	15.2(15.01)	15.0	13	-2.0(14.94)	-0.9	15.9(6.2)	(3.3, 28.4)
> 13	18	12.6(17.25)	12.0	21	-0.3(12.12)	-0.4	12.4(4.7)	(2.9, 21.8)
Baseline FEV1% pred.								
< 50%	13	15.8(18.18)	15.8	12	-0.1(15.67)	-0.1	15.9(5.9)	(4.1, 27.7)
> 50%	15	11.5(14.72)	11.5	22	-1.4(11.80)	-1.4	12.9(4.9)	(3.0, 22.8)

LS mean, LS mean difference, and its 95% CI are from ANCOVA model (Relative change in FEV1% predicted = treatment + baseline FEV1 % predicted (continuous) + subgroup + subgroup-by-treatment interaction). Note when subgroup is baseline FEV1 % predicted (<50%, >=50%), baseline FEV1 % predicted (continuous) won't be included in the model.

Subgroup analysis by region, age, baseline % predicted FEV_1, gender and race showed the relative change in % predicted FEV_1 to be greater in the TIP treatment group compared with placebo for all subgroups.

The analysis by region revealed the highest mean difference (TIP versus placebo) in relative change in % predicted FEV_1 to be in Latin America (23.3) but the sample size was very small (n=3 on TIP and 5 on placebo). In the region Europe, the difference observed was greater than in the USA, 18.5 and 4.2 respectively (n=38 and 23), possibly due to a lower mean % predicted FEV_1 at baseline in Europe.

TIP treatment decreased the sputum PA CFU density during Cycle 1 compared to placebo: change from baseline of 1.91 and 0.15 $\log_{10}$ CFU for TIP and placebo for the dry biotype-2, respectively; and a change from baseline of 2.61 and 0.43 $\log_{10}$ CFU for the mucoid biotype-1 for TIP and placebo, respectively. During Cycles 2 and 3 all patients in both arms received TIP and the sputum PA decreased from baseline for both treatment groups. Generally, the PA CFU density rebounded after 28 days off-treatment and then decreased again after 28 days of active treatment.

The percentage of patients using anti-PA antibiotics in Cycle 1 and the duration of usage were greater in the placebo group than that in the TIP group (32.7% vs 19.6% and 31.3 days vs 17.0 days, respectively).

The percentage of patients with respiratory-related hospitalizations in Cycle 1 was greater in the placebo group than that in the TIP group (12.2% vs 0). The average number of days of hospitalization in Cycle 1 was 12.3 in the placebo group.

Relative change in FVC % and FEF25-75 % predicted from baseline was also analysed. The general pattern of relative change in FVC % or FEF25-75 % predicted from baseline for TIP compared to placebo was consistent with the observed pattern of improvements for FEV1 % predicted: for FVC % predicted, a 11% improvement in TIP arm vs. placebo at day 28 was obtained as compared to baseline; and for FEF25-75 %, the improvement in TIP arm vs. placebo at day 28 was 38.9% as compared to baseline.

The results of the present pivotal placebo-controlled trial C2301 were consistent with the pattern of results obtained after 1 or 3 cycles with TOBI. The apparent differences in the results between studies can be explained to a great extent by the age and disease characteristics (e.g. baseline lung function, anti-PA pre-treatment) of the recruited patients.

In study C2302, the improvement in % predicted FEV_1 obtained in the first cycle of TIP treatment was maintained over subsequent cycles of treatment; a similar pattern was seen in the TOBI group (see figures 2 and 3 for the ITT and PP populations respectively).

Figure 2. FEV_1 percent predicted relative change from baseline by treatment group (C2302-ITT population)

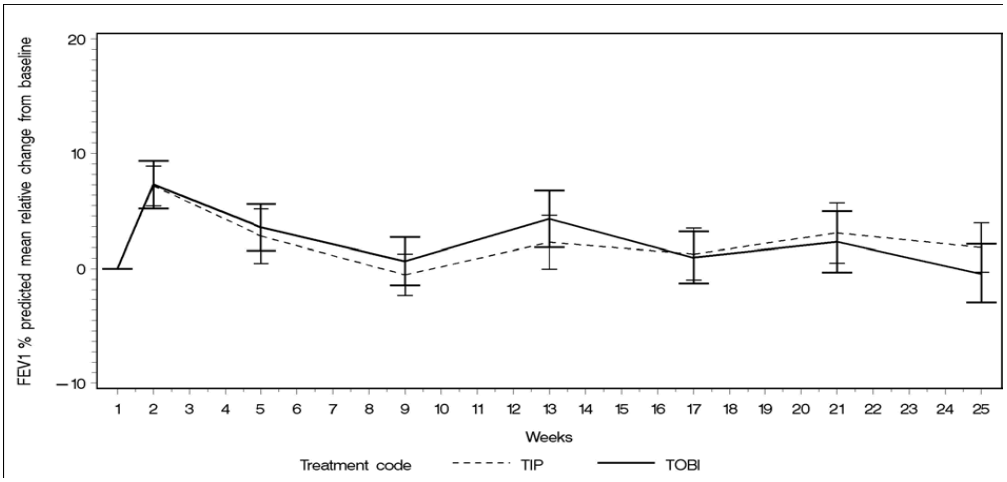
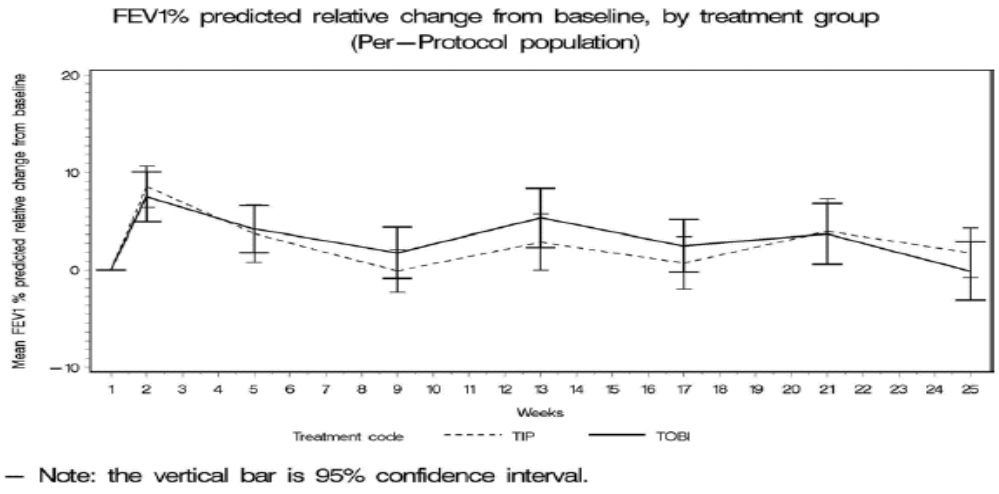


Figure 3. FEV_1 percent predicted relative change from baseline by treatment group (C2302-PP- population)



The sensitivity analyses generally led to the same conclusion as for the ITT and PP populations.

Subgroup analyses for the different age groups and pulmonary function categories are shown in table 13 for the ITT population.

Table 13. Subgroup analysis of relative change in FEV_1 % predicted from baseline to end of dosing in Cycle 3 – Study C2302 (ITT population)

Subgroup	TIP N=308			TOBI N=209			Difference (TIP- TOBI)	
	n	Mean (SD)	LS Mean	n	Mean (SD)	LS Mean	LS Mean (SE)	95% CI
Age								
< 13	28	10.4(25.91)	12.8	15	9.4(18.92)	8.2	4.7(5.74)	(-6.6, 15.9)
≥ 13 - <20	55	6.8 (18.49)	8.4	40	3.9(19.38)	4.8	3.7(3.71)	(-3.6, 11.0)
≥ 20	144	0.3 (18.65)	-0.5	116	0.9(16.60)	0.3	-0.8(2.23)	(-5.2, 3.6)
Baseline FEV1% pred.								
< 50%	77	10.1(25.42)	10.1	76	6.1(19.83)	6.1	4.0(2.99)	(-1.9, 9.8)
≥ 50%	150	-0.5(15.31)	-0.5	95	-0.7(14.94)	-0.7	0.2(2.42)	(-4.5, 5.0))

LS mean, LS mean difference, and its 95% CI are from ANCOVA model (Relative change in FEV1% predicted = treatment + baseline FEV1 % predicted (continuous) + subgroup + subgroup-by-treatment interaction). Note when subgroup is baseline FEV1 % predicted (<50%, >=50%), baseline FEV1 % predicted (continuous) won't be included in the model.

TIP appeared to be generally similarly efficacious as TOBI in these subgroups studied. The results suggest that TIP and TOBI are more suitable for the management of sought indication in patients 6-20 years of age, given the lower performance of TIP in the large group of adults concerning the relative change in % predicted FEV_1 and the observed higher discontinuation rate due to AEs in this group compared to TOBI. In response to the CHMP request for additional data, the applicant analysed the results taking into account baseline lung function parameters and tobramycin resistant PA baseline status. This analysis seemed to indicate that, though not statistically significant, there was a trend towards a slightly higher rate of hospitalizations and need for additional anti-pseudomonal antibiotic treatment in the TIP group aged ≥ 20 years as compared to TOBI. With respect to FEV1 % predicted relative change from baseline in patients colonized with resistant *PA* (MIC > 8 µg/mL), the outcome of TIP and TOBI seems to be different (mean change was 1.4% and 3.6% in the TOBI Podhaler group for those with a MIC > 8 µg/mL and ≤ 8 µg/mL at baseline, compared with 3.0% and 2.2% in the TOBI group). Colonisation with a resistant PA likely reflects the presence of more advanced disease with limited lung function. This might predispose such patients to benefit more from effective anti-pseudomonal therapy compared to those harbouring susceptible strains. The counter-intuitive effects of TIP and TOBI, as the applicant addressed, may be caused by a more limited lung tissue exposure to tobramycin (resulting in overall lower tissue levels) in case of TIP whereas TOBI may still achieve levels > 8 µg/mL. Based on the available data it cannot be dismissed that the resistance breakpoint (i.e. MIC > 8 µg/mL) is a truly relevant factor involved in the disease and has impact on lung function measurements. The applicant acknowledged that resistance is not adequately defined for inhaled antibiotics in chronic pulmonary infection but the concerns related to this issue can be appropriately managed in clinical practice by monitoring patient's clinical response to therapy.

Based on the assumed delta values being of clinical relevance for both studies concerning relative change in % predicted FEV_1 (11% in C2301 and 6% in C2302) the applicant was requested to provide analyses of the percentage of patients who responded by 3%, 6%, 9% and 12% with regards to % predicted FEV_1 in the treatment groups differentiated (i.e. for age and baseline % predicted FEV_1) during the 3 treatment cycles in both studies. A summary of the results is shown in table 14.

Table 14. Percentage of patients achieving a 3%, 6%, 9% and 12% change in FEV1 % predicted by baseline stratification factors on day 28 of and treatment cycle 3 – C2302

	≥ 3%		≥ 6%		≥ 9%		≥ 12%	
	TIP	**TOBI**	**TIP**	**TOBI**	**TIP**	**TOBI**	**TIP**	**TOBI**
	n %	n %	n %	n %	n %	n %	n %	n %
Age group (years)								
6-12	16 57.1	11 73.3	14 50.0	8 53.3	12 42.9	7 46.7	11 39.3	7 46.7
13-19	33 60.0	19 47.5	27 49.1	16 40.0	21 38.2	13 32.5	19 34.5	11 27.5
>=20	55 38.2	48 41.4	43 29.9	42 36.2	37 25.7	32 27.6	27 18.8	27 23.3
Baseline FEV1 % predicted								
< 50	40 50.0	31 43.7	33 41.3	28 39.4	31 38.8	25 35.2	26 32.5	23 32.4
≥ 50	64 43.5	47 47.0	51 34.7	38 38.0	39 26.5	27 27.0	31 21.0	22 22.0
Chronic macrolide use								
Yes	50 36.5	44 43.1	37 27.0	36 35.3	31 22.6	29 28.4	28 20.4	24 23.5
no	54 60.0	34 49.3	47 52.0	30 43.5	39 43.3	23 33.3	29 32.2	21 30.4

The data trended to favour TOBI above TIP in the adult subgroup with regard to lung function response to treatment. About 30% versus 36% of the adult patients in the TIP and TOBI group respectively achieved 6% improvement in % predicted FEV1 after 3 cycles of treatment with TIP. In the younger patients the response was comparable (in the order of 50% on both treatments). However, the data are not unequivocal due to small size of the subgroups and the heterogeneity of the responses in the different subgroups which deserve a cautious interpretation.

Therefore, even if it is acknowledged that these clinical data may suggest that TOBI Podhaler and TOBI are not entirely comparable in specific subgroups, in the total ITT heterogeneous population TOBI Podhaler was statistically non-inferior to TOBI. Indeed they show that with described differences both treatments are of value in an important proportion of patients across evaluated age categories and strata defined by baseline FEV1 % predicted and macrolide use.

The FEV1% results in adult naïve patients or in patients who were anti-PA treatment off for more than 3 or 6 months in study C2302 do not allow meaningful conclusions (although a trend in favour of TOBI was apparent) because of the very small numbers of patients of this category included in the study.

There were some regional differences in the spirometric results. In the Latin American sub-population, FEV1 percent of predicted values were lower than for the total ITT population and the previous exposure to tobramycin was lower compared to the North America and Europe/ROW regions. Relative change from baseline was consistently greater for TIP than TOBI at all post baseline time points. These observations should be interpreted with caution because of the small patient numbers (less than 10 for each treatment group).

Several other evaluations of lung function parameters were conducted and assessed, these included:

- AUC of FEV1 percent predicted, FVC percent of predicted, FEF25-75 percent predicted. The pattern of performance with regard to these parameters was similar in both treatment groups.
- PA sputum CFU density for both dry and mucoid biotypes decreased in both TIP and TOBI treatment groups at the end (Day 28) of each treatment cycles and increased to almost baseline value in the off-treatment period. The mean decrease from baseline was numerically greater in the TIP than in the TOBI group on Day 28 of all three treatment cycles.

New anti-PA antibiotic use was greater in the TIP treatment group than in the TOBI treatment group (64.9% of TIP patients and 54.5% of TOBI patients); the duration of new anti-PA antibiotic treatment was 30.9 days in the TIP group compared with 33.4 days in the TOBI treatment group.

Antibiotic use associated with hospitalization was 22.1% of TIP treated patients and 21.5% of TOBI treated patients. The rate of use of oral antibiotics was 55.5% for TIP and 39.7% for TOBI.

Newly inhaled antibiotics were used by similar proportions of the patients (8.4% and 7.7% in the TIP and TOBI treatment groups respectively). Ciprofloxacin was the most frequently used new anti-PA antibiotic during the study (47.7% of TIP patients and 34.0% of TOBI patients), followed by tobramycin (26.3% and 24.4% of patients in the TIP and TOBI treatment groups, respectively). These data suggest that the difference seen for new anti-PA antibiotic use is largely driven by the use of oral ciprofloxacin for milder events (i.e. those not needing i.v antibiotics and/or hospitalization). Furthermore, this difference of 10% of mainly oral antibiotic use did not seem to result in clinically important differences in outcomes (see above).

The impact of additional new antibiotic use on the outcome of the study was analysed in post hoc analyses. A post-hoc analysis to assess FEV_1 and PA CFU reduction outcomes in patients treated with TIP or TOBI who had received no additional anti-PA antibiotics (assessing this by cycle and cumulatively) indicated that patients who did not receive additional anti-PA antibiotics had comparable outcomes to the overall study population during treatment with TIP and TOBI for both FEV_1 and *PA* CFU reduction. Furthermore, a post-hoc FEV_1 non-inferiority analysis conducted by adding the effect of new anti-PA antibiotic use and the treatment by new anti-PA antibiotic interaction in the analysis of covariance model showed that the one-sided 95% CI is closely comparable to the original non-inferiority analysis.

With regard to Patient Reported Outcome (PRO) LS mean assessments of effectiveness, side effects, convenience and global satisfaction were similar at Weeks 5, 13 and 21 within each treatment group, indicating that patient satisfaction did not alter over the duration of the study. Assessments for effectiveness, convenience and global satisfaction were consistently greater for the TIP group than TOBI at all visits, indicating a higher level of satisfaction, and for these domains the differences were statistically significant for the mean of all visits assessment (LS mean difference of 9.36 for effectiveness, 24.35 for convenience and 5.20 for global satisfaction). As expected significant difference between the TIP and TOBI treatment groups were noted for questions related to portability and administration duration. TIP administration time was approximately 70% shorter than that for TOBI at all weeks. With regard to side effect ratings, no difference between treatment groups were noted suggesting that in the patient's opinion the unwanted effects had a similar impact upon their lives. However, this rating system is not consistent with the overall higher rate of AEs and discontinuations due to AEs in the TIP group compared to TOBI.

Analysis performed across trials (pooled analyses and meta-analysis)

Because of the difference of design and populations between both pivotal studies no pooled analysis was performed.

Clinical studies in special populations

No special studies were provided. See further paediatric data in the pivotal studies.

Supportive studies

Supportive data from one study in healthy volunteers (Study INH-007) and two in CF patients (Study TSB-001 and Study TPI001) are provided.

There is also an ongoing Phase III randomised double-blind placebo controlled study **(**C2303- in Russia, Estonia) in cystic fibrosis patients to assess efficacy, safety and pharmacokinetics of tobramycin

inhalation powder from a modified manufacturing process (TIP new). The final study report is anticipated for December 2011.

2.5.3. Discussion on clinical efficacy

The present results from study C2301 indicate that TIP treatment is superior to placebo in the so-called inhalational tobramycin naive (i.e. no use of TOBI within 4 months prior to entry) patients 6-20 years of age. The results of this study are also consistent with the pattern of results obtained after 1 or 3 cycles with TOBI in so-called inhalational tobramycin naive patients.

In both pivotal studies the improvement in % predicted FEV_1 in the TIP group appeared to be maintained after the second and 3rd treatment cycles. Supportive results were observed for other lung function parameters such as FVC percent of predicted, FEF25-75 percent predicted in both pivotal studies. As expected TIP treatment decreased the sputum PA CFU density during Cycle 1 markedly more compared to placebo for the dry biotype-2 and for the mucoid biotype-1. This effect was maintained during the successive 2 treatment cycles. The PA CFU density rebounded after 28 days off-treatment and then decreased again after 28 days of active treatment. A similar pattern was observed for TOBI in study C2302, although the impact of TOBI on PA CFU density was less pronounced compared to TIP.

Furthermore, in this study the PRO questionnaire favoured TIP above TOBI especially with regard to convenience to the patient; however this was less pronounced with regard to global patient satisfaction. As expected, TIP was preferred with regard to aspects of portability and duration of administration.

The principal efficacy results in study C2302 concerning relative change in percent predicted FEV_1 from baseline to pre-dose day 28 Cycles 3 showed non-inferiority of the efficacy of TIP to TOBI in the overall ITT heterogeneous population. However, in adults (being the largest subgroup in this population) this does not seem as robust as the data in the age group 13-19 years old might indicate. Additional post-hoc analyses provided by the applicant seem to suggest that the two products are not comparable in specific subgroups even if the presented differences do not seem to be always consistent and amenable to clear interpretation. Whilst results by stratified categories for age and baseline % predicted FEV_1 show a comparable response with both treatments in the younger patients, they seem to favour TOBI above TIP in the adult subgroup with regard to lung function response (see ancillary analysis section). The pattern towards a lower efficacy in adults compared to younger patients is observed with both treatments. However, these data from post-hoc analyses need to be interpreted with caution and it is not possible to conclude unequivocally on any apparent difference highlighted in limited subgroups.

The additional analyses included data from patients harbouring tobramycin resistant PA which were compared to those with tobramycin susceptible PA at baseline and took into account the baseline lung function parameters. They show that both treatments are of value in specific subgroups of patients when age, baseline FEV1 % predicted and macrolide use are taken into account.

Colonisation with a resistant PA likely reflects the presence of more advanced disease with limited lung function. Considering available data it cannot be dismissed that the resistance breakpoint (i.e. MIC > 8 µg/mL) is a relevant factor involved in the disease and has impact on lung function measurements. Whilst it is acknowledged that resistance is not adequately defined for inhaled antibiotics in chronic pulmonary infection, this issue can be appropriately managed in clinical practice by monitoring patient's clinical response to therapy.

It is also known that for the deposition of aerosolized powder the steady flow inspiratory rate besides PIF is also important; this factor could be a critical point in clinical efficacy in smaller children or adults

with low FVC. This might affect the compliance especially in the younger children group who will not be able to generate the required flow to aerosolize the powder and who will not be able to take so many doses of aerosolized product. The applicant stated that the minimum flow rate required to fluidize and disperse TBM100 capsules using the T-326 Inhaler according to the instructions for use is ≤ 35 LPM (L/min) based on an *in vitro* study. Although in this study one third of the patients were children 6-10 years of age and thus not fully representative of the whole CF population, all patients were able to generate PIF of 30 L/min.

Finally, the applicant was requested to collect long-term efficacy data for TIP like those documented for TOBI (6-12 cycles or more). The applicant has committed to generate this data for TOBI Podhaler with the on going study C2303 open extensions, and the new uncontrolled study C2401 (see follow up measures). Study C2401 should recruit a sufficiently large number of patients to generate meaningful results and include treatment duration of a minimum of 6 cycles to better evaluate long-term tolerance and emergence of resistance.

2.6. Clinical safety

The *primary safety population* defined by the applicant included patients who received at least one dose of study drug and were randomized to either the TIP/TIP/TIP group or the TOBI/TOBI/TOBI group in Study C2302. Pooling with data from C2301 was not done because of the differences in study design, population demographics, disease characteristics and previous tobramycin exposure between the two studies.

Nevertheless, a Supportive Safety Population was also defined and analysed; this included all patients who received at least one dose of study drug in Studies C2301 and C2302. Pooled analyses were performed on this population to provide an overall assessment of exposure and safety with TIP, TOBI and placebo.

This Report will rely primarily on observations per study because of mentioned differences above between the studies.

Patient exposure

An overview of the duration of exposure for the Primary Safety Population is given in table 15.

Table 15. Duration of exposure to study medication (Primary safety population- based on C2302)

Duration of treatment (Days)	TIP/TIP/TIP N=308			TOBI/TOBI/TOBI N=209		
	Cycle 1	Cycle 2	Cycle 3	Cycle 1	Cycle 2	Cycle 3
Total	308	264	234	209	178	171
1 - 7	5 (1.6)	6 (1.9)	1 (0.3)	2 (1.0)	1 (0.5)	1 (0.5)
>7 - 14	9 (2.9)	4 (1.3)	2 (0.6)	1 (0.5)	0	0
>14 - 21	11 (3.6)	4 (1.3)	3 (1.0)	3 (1.4)	2 (1.0)	2 (1.0)
>21 - 28	114 (37.0)	89 (28.9)	66 (21.4)	71 (34.0)	47 (22.5)	48 (23.0)
>28	169 (54.9)	161 (52.3)	162 (52.6)	132 (63.2)	128 (61.2)	120 (57.4)
Mean (SD)	27.6 (4.72)	27.8 (4.60)	28.9 (3.69)	28.4 (3.41)	28.7 (2.38)	28.9 (2.47)

The denominator for each cycle is the total number of patients exposed to treatment for each treatment group i.e. 308 TIP and 209 TOBI patients.
A subject is counted in only one duration range, per treatment group.
Duration = last dosing date of study medication in on-treatment cycle - first dosing date of study medication in on-treatment cycle+1 day.

An overview of the duration of exposure for the Safety Population in study C2301 is given in table 16.

Table 16. Duration of exposure to study medication (based on C2301)

Duration of treatment (Days)	TIP/TIP/TIP (N=46)			PLB/TIP/TIP (N=49)		
	Cycle 1	Cycle 2	Cycle 3	Cycle 1	Cycle 2	Cycle 3
Total	46	41	39	49	41	40
1 - 7	2 (4.3%)	1 (2.2%)	0	2 (4.1%)	0	0
>7 - 14	2 (4.3%)	1 (2.2%)	0	3 (6.1%)	0	0
>14 - 21	2 (4.3%)	0	0	2 (4.1%)	0	0
>21 - 28	14 (30.4%)	8 (17.4%)	7 (15.2%)	15 (30.6%)	8 (16.3%)	9 (18.4%)
>28	26 (56.5%)	31 (67.4%)	32 (69.6%)	27 (55.1%)	33 (67.3%)	31 (63.3%)
Mean (SD)	26.3 (6.20)	27.9 (4.40)	28.9 (0.50)	25.9 (6.82)	28.8 (0.51)	28.9 (0.69)

Note: Subjects randomized to TIP were treated with TIP in Cycles 1-3, while those randomized to placebo received placebo only in Cycle 1 followed by TIP in Cycles 2-3.
- A subject is counted in only one duration range, per treatment group.
- Duration = last dosing date of study medication in on-treatment cycle – first dosing date of study medication in on-treatment cycle + 1 day.
PLB = placebo

The mean exposure to medication for each cycle ranged between approximately 26 and 29 days per cycle in both pivotal studies. This is consistent with the high compliance noted for the study populations

Adverse events

The majority of patients in both the placebo and TOBI Podhaler treatment groups experienced at least one AE of any causality (see table 17).

Table 17 . Summary of AEs: Individual Pivotal Studies

Patients Reporting AEs	C2301			C2302	
	Placebo (n = 49) n (%)	**TIP (3 cycles)[1]** (n = 46) n (%)	**TIP (2 cycles) [2]** (n = 41) n (%)	**TIP[3]** (n = 308) n (%)	**TOBI[3]** (n = 209) n (%)
Any AE	37 (75.5%)	34 (73.9)	30 (73.2)	278 (90.3)	176 (84.2)
Drug-related AE[a]	10 (20.4%)	10 (21.7)*	11 (26.8)*	157 (51.0)	42 (20.1)
Respiratory, thoracic & mediastinal disorders				133 (43.2)	29 (13.9)
SAE	7 (14.3%)	5 (10.9)	6 (14.6%)	85 (27.4)	61 (29.2)
Drug related Cough[a]	5 (10.2)	4 (8.7)	3 (7.3)	78 (25.3)	9 (4.3)

a) Drug-related AEs are those with a causality of possible or probable by the investigator.
(1) AEs in all 3 cycles with 3 cycles of TIP treatment in the TIP group.
(2) AEs in last 2 cycles with 2 cycles of TIP treatment after the first placebo exposure in the placebo group.
(3) AEs in any of the 3 cycles.
* For cycle 1 this was 7 (15.2%)

The most frequently affected system organ class was respiratory, thoracic and mediastinal disorders, for TIP treated and TOBI treated groups. This is also true for the placebo-controlled study.

Drug-related AEs (DR-AEs) were reported by a slightly higher proportion of patients treated with 3 cycles of TIP than placebo treated patients although the proportion of patients with drug-related AEs in patients treated with TIP for the first cycle was lower than for placebo (15.4 vs. 20.4%). Cough was the most frequently reported DR-AE in the placebo group (10.5% vs. 6.5% for TIP), although cough was more commonly reported as a baseline symptom for TIP patients than in the placebo group (13.0% in TIP arm, 8.2% in TOBI arm). In the TIP group dysgeusia was reported by 6.5% of the patients vs. none in the placebo group; similarly for oropharyngeal pain the rates were 4.2% and 0% respectively In study C2302 DR-AEs such as cough, dysphonia, oropharyngeal pain and dysgeusia were also more frequently reported in the TIP compared to TOBI; the corresponding percentages were 25.3%, 12.7% 4.5% and 3.9% vs. 4.3%, 3.3%, 1% and 0.5% in these groups respectively.

The Kaplan-Meier analysis of time to first event for cough and dysphonia suggested that cough was reported in excess in the TIP groups as an AE in the first few days, and thereafter the TIP and TOBI curves followed similar trajectories. However, no cough AEs led to discontinuation during the first 28 days of study C2302. In the latter study, cough events were reported by a greater percentage of patients in the on treatment periods than in the off-treatment periods in the TIP group, especially during Cycles 2 and 3. In the TOBI group, there was hardly any difference between on and off-treatment periods for cough events and the rate of cough reporting in the TOBI arm during the off period of each cycle was similar to the TIP arm.

Cough was reported as being severe in 2.6% of TIP treated patients and 1.9% of TOBI treated patients, moderate in 22.4% and 14.4% of TIP and TOBI patients, and mild in 23.4% and 14.8% of TIP and TOBI patients.

Of note, in the evaluations of airway reactivity, only a few patients in study C2301 (2 on TIP treatment and 4 on placebo) in both treatment groups showed a relative change ≥20% decrease in FEV1% predicted from pre-dose to 30-minute post-dose (indicative of clinically significant bronchospasm). Similar observations were made in the comparison with TIP vs. TOBI in study C2302 with equal percentages of reporting of such an effect (5.2-5.3% in any cycle). None of the instances was reported as AE or did lead to the study discontinuation of a patient in study C2301 vs. 3 in the TIP group in study C2302. However, all of them had variations between pre-post dose FEV1 measurements of less than 10%. The investigators suspected a relationship between the events and the study drug.

Haemoptysis was reported as DR-AE in equal frequencies (approximately 3%) in trial C2302 in the TIP and TOBI arms. Of note, patients with haemoptysis more than 60 mL at any time within 30 days prior to study drug administration were excluded from the pivotal studies. Inhalation of a dry powder may induce a cough reflex. The applicant recommends in section 4.4 of the SmPC that the use of TIP in patients with active, severe haemoptysis should be undertaken only if the benefits of treatment are considered to outweigh the risks of inducing further haemorrhage.

Serious adverse events and deaths

The most frequently reported SAE in both treatment groups in study C2302 was lung disorder (e.g. pulmonary exacerbations or exacerbations of CF) followed by haemoptysis, cough, bronchitis, dyspnoea, and productive cough consistent with the underlying disease condition. In less than 5% of

the patients they were considered drug-related SAE by the investigator (3% [n=10] on TIP vs. 0.5% [n=1] on TOBI), however, they were all related to underlying disease condition.

In study C2301 cycle 1 SAEs were reported more frequently for placebo (14.3%) vs. 6.5% for TIP.

Five patients enrolled in the completed studies died. There were no patients with treatment related deaths in studies C2301 and C2302. 4 TIP patients died in study C2302, 3 had occurred more than 30 days after the last dose of study medication and were consistent with cystic fibrosis comorbidities; 1 death occurred 4 days after randomisation (and prior to dosing) to TIP.

Laboratory findings

There were no major changes from baseline to specified time points or between-treatment differences observed in study C2301 for any biochemical, haematology parameter and vital signs. Audiology function testing in a subgroup of patients in study C2301 (23%) revealed no evidence of TIP induced sensorineural hearing loss.

In study C2302 there was a decrease from baseline in audiology testing (in selected 25.3% of patients) for both TIP and TOBI treatment groups. The decrease was of a similar degree in both treatment groups, but reported for a higher percentage of patients in the TIP treatment group (25.6% vs. 15.6% for TOBI).

In the TOBI audiology population hearing complaints reported were 2 tinnitus, 1 with a humming noise, 1 with pressure, and 1 unspecified complaint. Hearing complaints tended to be intermittent and transient, with many patients who had abnormal hearing at baseline or a history of hearing complaints.

In this study, 28-33% of patients in the treatment groups had elevations in white blood cell counts and in 41-46% neutrophil counts above normal range at baseline. Similarly, 20-27 of the patients also had serious increased platelet counts above normal range at baseline. In both treatment groups the post-baseline shifts occurred at similar frequencies. The same holds for clinical chemistry values (including serum transaminases and serum creatinine and BUN values).

Microbiological effects

In both studies, there was a tendency toward increased MIC (at least 4-fold) at the end of treatment. In study C2301, end of Cycle 3 treatment the percentage was 10.9% vs. 2.2% end of cycle 1. In study C2302, the percentage of patients with a 4-fold increase in tobramycin MIC at Week 25 was 16% in the TIP treatment group vs. 9% in the TOBI group. At the termination visit, the distribution of tobramycin MIC more closely resembled that seen at baseline.

Pathogens other than PA identified in the sputum of the CF patients were mostly pathogens present in only a small percentage of patients. The organisms which were present in sputum of more than 10 patients in each treatment group at baseline were: Methicillin resistant *Staphylococcus aureus* (MRSA), Methicillin susceptible *Staphylococcus aureus* (MSSA), *Aspergillus fumigans*, *Aspergillus fumigatus* and *Haemophilus parainfluenzae*. The relationship of observed shifts to low or heavy growth to TIP and TOBI treatments is difficult to derive since the population in study C2302 received also other intravenous and oral antibiotic treatments. Therefore, mentioned observations should be interpreted with caution.

Resistance

The use of any antibiotic (oral, intravenous, or inhaled) is associated with selection of pathogens with *in vitro* resistance by standard testing. Nevertheless, CF patients with chronic *P. aeruginosa* infection

harbouring resistant PA detected in sputum cultures may still derive clinical benefits from aerosolized tobramycin. It is hypothesized that this may be due to the high concentrations of drug that can be delivered to the site of infection. The use of inhaled tobramycin for the long term management of chronic *P. aeruginosa* infection is still being advocated by CF learned societies after more than a decade of its use in the target group.[6] However, the duration of long-term benefit is not known. As described for study C2302 above, the percentages of patients with an increase in tobramycin MIC at Week 21 and Week 25 were greater in the TIP treatment group than the TOBI group. At the termination visit, the distribution of tobramycin MIC more closely resembled that seen at baseline. The majority of samples had a tobramycin MIC of between 0.5 µg/mL and 8 µg/mL. Long-term data beyond the presently documented 6 month (3 cycles) experience were not available. Therefore the applicant has committed to monitor the development of resistance to inhaled tobramycin within the context of the RMP. Since there is no established definition and threshold for resistance in the context of inhaled therapy and elevated MICs are not predictive of an absence of lung function response, the terms *susceptibility* and *resistance* should be used appropriately in the monitoring activities as they are not synonymous. The clinical interpretation of the resulting data should be based on the obtained measurements and clinical findings.

Safety in special populations

Gender

The incidence of patients with cough, lung disorders and dysphonia was slightly higher in females than males treated with TIP in study C2302.

Age

The overall numbers of children in the pivotal trials exposed to TIP is appreciable (≥6 - <13: 45 and 28 in C2301 and C2302 respectively; ≥13 - <20: 45 and 66 in C2301 and C2302 respectively). Furthermore, the present data together with the experience obtained from the use of TOBI do not seem to suggest new safety issues in patients exposed to TIP. The earlier mentioned higher incidence of patients with cough and dysphonia with TIP were shown across all age subgroups, while lung disorders were more common for TIP in the ≥13 - <20 years and ≥20 years age subgroups, but higher for TOBI in the smaller 6-12 years age subgroup in study C2302.

Race

As expected the overwhelming majority (approximately 90%) of the included patients in the pivotal studies was Caucasian. No meaningful race based comparisons of the AEs are possible.

Baseline disease severity

In both studies (C2301 and C2302) the majority of the patients had baseline FEV1 % predicted ≥50%. The patients in C2301 were practically naïve to inhalational anti-PA drug whereas the overwhelming majority of patients in C2302 were exposed earlier to such treatment. The baseline sputum tobramycin MIC was > 8 µg/ml in approximately 22% of the patients in the latter study vs. approximately 10% in the former study.

Renal and Hepatic Function

Tobramycin is excreted renally. Serum tobramycin concentrations after inhalational therapy with tobramycin are generally very low. The highest average concentration seen in Phase III studies after twice-daily inhalation of TIP for 4 weeks was 1.99 ± 0.59 µg/mL (mean ± SD, n=32, in serum samples taken 60 minutes after inhalation). These compared favourably with the recommended avoidance of

[6] Cystic Fibrosis Foundation (Flume et al 2007), Cystic Fibrosis Trust (2009)

values greater than 12 µg/mL, which are associated with the toxicity of intravenous tobramycin therapy. The mean trough concentrations after bid TIP administration were also in the safe range (at least four-fold lower than 2 µg/mL trough levels recommended for a safe systemic therapy with tobramycin).

The same precautions hold for TIP as those documented for TOBI in relation to patients with pre-existing disorders such as renal impairment and neuromuscular disorders

Pregnancy and breast feeding

A report of pregnancy has been received during the follow-up Phase in study C2302; the foetus was diagnosed in utero with congenital diaphragmatic hernia and congenital cystic lung. The reported anomalies were found not related to study medication. The same precautions hold for TIP as those documented for TOBI in cases of pregnancy and breast feeding.

Safety related to drug-drug interactions and other interactions

The same contraindications and precautions hold for TIP as those documented for TOBI in relation to patients with hypersensitivity to aminoglycosides and avoidance of concurrent and/or sequential use of TIP with other drugs with neurotoxic, nephrotoxic, or ototoxic potential.

Discontinuation due to adverse events

Discontinuations due to AEs were more frequently reported for the TIP treated patients in study C2302.

However, younger patients ≥ 6-<13 years of age had overall a low discontinuation rate due to AEs (only 1 patient), compared to 5 patients in the ≥13-<20 age category and 37 (17.3%) in the ≥20 years of age. Such a trend was not apparent for the patients in the TOBI arm. In patients ≥13 years of age more patients discontinued due to AEs in the TIP arm compared to the TOBI arm. The higher frequencies of AEs like cough, chest discomfort, bronchospasm and dysphonia in the TIP group compared to the TOBI group were the most frequently distinguishing AEs associated with the use of TIP.

In Europe/ROW there was a greater difference in the percentage of patients discontinuing from the study between TIP and TOBI groups (28.8% versus 14.1%) than in the All Randomized population, with the main difference being as a result of an AE or death.

In study C2301 no AE discontinuations were reported for TIP treated patients.

Post marketing experience

No post-marketing experience is available.

2.6.1. Discussion on clinical safety

Cough, oropharyngeal pain, dysgeusia and dysphonia appear to be most frequently associated DR-AE with the use of TIP in both studies and more frequently reported for TIP than for TOBI. The difference is probably caused by TIP being a powder formulation and not due to the excipients (such as sulfuric acid which is present in a much lower quantities than in the TOBI dose). An alternative explanation coud be that surfactants enhance the penetration of drug particles through the mucous layer, which

enables the particles to interact with the epithelium and cilia causing irritation of the cough receptors or other receptors localized in the epithelium, ultimately resulting in increased haemoptysis risk.

In this respect it is not clear whether DSPC (an endogenous lung surfactant) may contribute to cough induction by slightly increasing the sputum transport. On the other hand, the dry aspect of the TIP powder formulation is more relevant for the observed increased cough potential of the TIP formulation.

Other so-called DR-AEs in study C2302 should be more critically evaluated as to their relatedness to TIP or TOBI beyond the reporting investigators assessment, a number of the listed DR-AEs (e.g. lower respiratory tract infection, pulmonary function test decreased etc.) in the corresponding table can be questioned as to their true drug-relatedness. Sponsors should try their utmost to re-assess the causality of certain DR-AEs especially when the true drug-relatedness raises questions and does not appear to be more frequent than the symptoms related to the underlying condition. To that purpose the placebo-controlled trials and external independent expert assessments especially for the open non-inferiority trials can be used. Such an assessment will increase the correct information value of DR-AE which are listed in section 4.8 of the SmPC, reducing the risk of blurring information.

Haemoptysis was reported as DR-AE in equal frequencies (approximately 3%) in trial C2302 in the TIP and TOBI arms. Of note, patients with haemoptysis more than 60 ml at any time within 30 days prior to study drug administration were excluded from the pivotal studies. Severe (or massive) haemoptysis is usually associated with acute pulmonary bleeding >240mL/d and moderate with >100mL/d. Severe haemoptysis is a serious complication in CF patients, occurring more commonly in older patients with more advanced lung disease.[7] In this respect a relevant warning has been included in section 4.4 of the SmPC, similarly to TOBI's, which includes a precaution intended for patients with severe active haemoptysis.

In study C2302, discontinuations due to AEs in patients $\geq$ 20 years of age occurred at a higher rate in the TIP group (33%) compared to TOBI treatment (19%). These findings, which suggest that TIP is less tolerated than TOBI in a subgroup of the targeted adult patients, are reflected in section 4.4 of the SmPC. The higher frequencies of AEs like cough, chest discomfort, bronchospasm and dysphonia in the TIP group compared to the TOBI group were most frequently distinguishing AEs associated with the use of TIP. The induction of acute bronchospasm and cough should be monitored in the future (see Risk Management Plan).

Side effect ratings in PRO showed no difference between treatment groups. However, it is not clear how this rating is reconcilable with the overall higher rate of AEs and discontinuations due to AEs in the TIP group compared to TOBI. The fact that different items were measured by the AE report and by the used PRO questionnaire assessing the impact of side effects, may justify the different results. However the results of PRO at least with regard to side effects should be interpreted with caution.

In this study the frequency of serious adverse reactions was similar in both treatment arms.

Notwithstanding differences observed in frequencies of specific adverse reactions, overall no new safety issues were observed in patients exposed to TIP compared to TOBI.

In both studies there was a tendency toward increased MIC (at least 4-fold) during treatment with TIP (or TOBI in C2302). At the termination visit, the distribution of tobramycin MIC more closely resembled that seen at baseline in study C2302. However, the applicant did not present long-term data and therefore has committed to monitor the development of resistance to inhaled tobramycin within the RMP.

[7] Flume PA, Yankaskas JR, Ebeling M, Hulsey T and Clark LL. "Massive Hemoptysis in Cystic Fibrosis". *Chest* 2005;128;729-738.

In regard to the shifts observed to low or heavy growth to TOBI Podhaler and TOBI in other pathogens than PA (e.g. MRSA, MSSA, *Aspergillus*), no conclusions can be drawn as to their relationship to study treatment, since the population in study C2302 received also other antibiotic oral and intravenous treatments. Therefore, these observations should be interpreted with caution.

No data on the long-term effect on lung function are available. In this respect the applicant has committed to obtain long term data from an open extension of the on going study C2303 with additional cycles of TIP treatment (6-12 cycles or longer) and from the new study C2401 (see follow-up measures section).

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 MAA submitted a risk management plan, which included a risk minimisation plan.

Table Summary of the Risk Management Plan

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
Important identified risk		
Cough	Routine pharmacovigilance	This risk is adequately addressed and communicated in the SmPC Adverse drug reactions (Section 4.8 of the SmPC) Table 1: Cough – Very Common "*Description of selected adverse drug reactions* *Cough was the most frequently reported adverse reaction in both clinical studies. However, no association was observed in either clinical study between the incidence of bronchospasm and cough events*." Warnings and precautions (Section 4.4 of the SmPC) "Cough can occur with the use of inhaled medicinal products and was reported with the use of TOBI Podhaler in clinical studies. *Based on clinical trial data the inhalation powder TOBI Podhaler was associated with a higher reported rate of cough compared with tobramycin nebuliser solution (TOBI). Cough was not related to bronchospasm. Children below the age of 13 years may be more likely to cough when treated with TOBI Podhaler compared with older subjects.* *If there is evidence of continued therapy-induced cough with TOBI Podhaler, the physician should consider whether an approved tobramycin nebuliser solution should be used as an*

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		alternative treatment. Should cough remain unchanged, other antibiotics should be considered."
Bronchospasm	Routine pharmacovigilance	This risk is adequately addressed and communicated in the SmPC Adverse drug reactions (Section 4.8 of the SmPC) Table 1: Bronchospasm: Common Warnings and precautions (Section 4.4 of the SmPC) "*<u>Bronchospasm</u>* *Bronchospasm can occur with inhalation of medicinal products and has been reported with TOBI Podhaler in clinical studies.* *Bronchospasm should be treated as medically appropriate.* *The first dose of TOBI Podhaler should be given under supervision, after using a bronchodilator if this is part of the current regimen for the patient. FEV1 should be measured before and after inhalation of TOBI Podhaler.* *If there is evidence of therapy-induced bronchospasm, the physician should carefully evaluate whether the benefits of continued use of TOBI Podhaler outweigh the risks to the patient. If an allergic response is suspected, TOBI Podhaler should be discontinued.*"
Hemoptysis	Routine pharmacovigilance Targeted follow-up with the use of a hemoptysis questionnaire/checklist for all serious and non-serious spontaneous cases	This risk is adequately addressed and communicated in the SmPC Adverse drug reactions (Section 4.8 of the SmPC) Table 1: Haemoptysis – Very Common Warnings and precautions (Section 4.4 of the SmPC) *"<u>Haemoptysis</u>* *Haemoptysis is a complication in cystic fibrosis and is more frequent in adults. Patients with haemoptysis (> 60 ml) were excluded from the clinical studies so no data exist on the use of TOBI Podhaler in these patients. This should be taken into account before prescribing TOBI Podhaler, considering the inhalation powder TOBI Podhaler was associated with a higher rate of cough (see above). The use of TOBI Podhaler in patients with clinically significant hemoptysis should be undertaken or continued only if the benefits of treatment are considered to outweigh the risks of inducing further haemorrhage."*
Important potential risk		
Nephrotoxicity	Routine pharmacovigilance	This risk is adequately addressed and communicated in the SmPC Warnings and precautions (Section 4.4 of the SmPC) *"<u>Nephrotoxicity</u>* *Nephrotoxicity has been reported with the use of parenteral aminoglycosides.* *Nephrotoxicity was not observed during TOBI Podhaler clinical studies. Caution should be*

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		exercised when prescribing TOBI Podhaler to patients with known or suspected renal dysfunction. *Baseline renal function should be assessed. Urea and creatinine levels should be reassessed after every 6 complete cycles of TOBI Podhaler therapy."*
Ototoxicity	Routine pharmacovigilance Targeted follow-up with the use of an ototoxicity questionnaire/checklist for all serious and non-serious spontaneous cases	This risk is adequately addressed and communicated in the SmPC Adverse drug reactions (Section 4.8 of the SmPC) Table 1: Hearing loss – Common; Tinnitus - Common Warnings and precautions (Section 4.4 of the SmPC) "*Ototoxicity* *Ototoxicity, manifested as both auditory toxicity (hearing loss) and vestibular toxicity, has been reported with parenteral aminoglycosides. Vestibular toxicity may be manifested by vertigo, ataxia or dizziness. Tinnitus may be a sentinel symptom of ototoxicity, and therefore the onset of this symptom warrants caution.* *Hearing loss and tinnitus were reported by patients in the TOBI Podhaler clinical studies (see section 4.8). Caution should be exercised when prescribing TOBI Podhaler to patients with known or suspected auditory or vestibular dysfunction.* *In patients with any evidence of auditory dysfunction, or those with a predisposing risk, it may be necessary to consider audiological assessment before initiating TOBI Podhaler therapy.* *If a patient reports tinnitus or hearing loss during TOBI Podhaler therapy the physician should consider referring them for audiological assessment*."
Fetal Harm	Routine pharmacovigilance	This risk is adequately addressed and communicated in the SmPC Pregnancy and breastfeeding (Section 4.6 of the SmPC) "*Pregnancy* *There are no adequate data on the use of tobramycin via inhalation in pregnant women.* *Animal studies with tobramycin do not indicate a teratogenic effect (see section 5.3).* *However, aminoglycosides can cause foetal harm (e.g. congenital deafness) when high systemic concentrations are achieved in a pregnant woman. Systemic exposure following inhalation of TOBI Podhaler is very low, however TOBI Podhaler should not be used during pregnancy unless clearly necessary, i.e. when the benefits to the mother outweigh the risks to the foetus.* *Patients who use TOBI Podhaler during pregnancy, or become pregnant while taking TOBI Podhaler, should be informed of the potential hazard to the foetus*."
Decreased	Routine pharmacovigilance	This risk is adequately addressed and

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
Pseudomonas aeruginosa susceptibility to tobramycin (MIC)	Targeted follow-up with the use of a decreased susceptibility/increased resistance questionnaire/checklist for all serious and non-serious spontaneous cases	communicated in the SmPC Warnings and precautions (Section 4.4 of the SmPC) *"The development of antibiotic-resistant P. aeruginosa and superinfection with other pathogens represent potential risks associated with antibiotic therapy. In clinical studies, some patients on TOBI Podhaler therapy showed an increase in aminoglycoside minimum inhibitory concentrations (MIC) for P. aeruginosa isolates tested. MIC increases observed were in large part reversible during off-treatment periods.* *There is a theoretical risk that patients being treated with TOBI Podhaler may develop P. aeruginosa isolates resistant to intravenous tobramycin over time (see section 5.1). Development of resistance during inhaled tobramycin therapy could limit treatment options during acute exacerbations; this should be monitored."*
Potential drug-drug interactions with diuretics and other drugs affecting renal clearance, nephrotoxic, neurotoxic and ototoxic drugs (class effect of parenteral use of aminoglycosides).	Routine pharmacovigilance	This risk is adequately addressed and communicated in the SmPC Warnings and precautions (Section 4.4 of the SmPC) "*Other precautions* *Patients receiving concomitant parenteral aminoglycoside therapy (or any medication affecting renal excretion, such as diuretics) should be monitored as clinically appropriate taking into account the risk of cumulative toxicity. This includes monitoring of serum concentrations of tobramycin. In patients with a predisposing risk due to previous prolonged, systemic aminoglycoside therapy it may be necessary to consider renal and audiological assessment before initiating TOBI Podhaler therapy.* *See also "Monitoring of serum tobramycin concentrations" above.* *Caution should be exercised when prescribing TOBI Podhaler to patients with known or suspected neuromuscular disorders such as myasthenia gravis or Parkinson's disease. Aminoglycosides may aggravate muscle weakness because of a potential curare-like effect on neuromuscular function.*" Interactions (Section 4.5 of the SmPC) "*No interaction studies have been performed with TOBI Podhaler. Based on the interaction profile for tobramycin following intravenous and aerosolised administration, concurrent and/or sequential use of TOBI Podhaler is not recommended with other medicinal products with nephrotoxic or ototoxic potential.* *Concomitant use of TOBI Podhaler with diuretic compounds (such as ethacrynic acid, furosemide, urea or mannitol) is not recommended. Such coumpounds can enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue.*

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		See also information on previous and concomitant use of systemic aminoglycosides and diuretics in section 4.4. *Other medicinal products that have been reported to increase the potential toxicity of parenterally administered aminoglycosides include:* - *amphotericin B, cefalotin, ciclosporin, tacrolimus, polymyxins (risk of increased nephrotoxicity);* - *platinum compounds (risk of increased nephrotoxicity and ototoxicity);* - *anticholinesterases, botulinum toxin (neuromuscular effects).*"
Important missing information		
Patients with moderate or severe renal failure not included in clinical studies	Routine pharmacovigilance	This is adequately addressed and communicated in the SmPC Dosage and administration (Section 4.2 of the SmPC) *"Patients with renal impairment* *Tobramycin is primarily excreted unchanged in the urine and renal function is expected to affect the exposure to tobramycin. Patients with serum creatinine 2 mg/dl or more and blood urea nitrogen (BUN) 40 mg/dl or more have not been included in clinical studies and there are no data in this population to support a recommendation for or against dose adjustment with TOBI Podhaler. Caution should be exercised when prescribing TOBI Podhaler to patients with known or suspected renal dysfunction*. *Please also refer to nephrotoxicity information in section 4.4*"
Patients on diuretics and other drugs affecting renal clearance, nephrotoxic, neurotoxic and ototoxic drugs (class effect of parenteral use of aminoglycosides) generally not included in clinical studies	Routine pharmacovigilance	This is adequately addressed and communicated in the SmPC Interactions (Section 4.5 of the SmPC) "*No interaction studies have been performed with TOBI Podhaler*". *Based on the interaction profile for tobramycin following intravenous and aerosolised administration, concurrent and/or sequential use of TOBI Podhaler is not recommended with other medicinal products with nephrotoxic or ototoxic potential.* *Concomitant use of TOBI Podhaler with diuretic compounds (such as ethacrynic acid, furosemide, urea or mannitol) is not recommended. Such compounds can enhance aminoglycoside toxicity by altering antibiotic concentration in serum and tissue*"
Patients post organ transplantation not included in clinical studies	Routine pharmacovigilance	Dosage and administration (Section 4.2 of the SmPC) "*Patients after organ transplantation* *Adequate data do not exist for the use of TOBI Podhaler in patients after organ transplantation. No recommendation for or against dose adjustment can be made for patients after organ transplantation*."
Potential adverse effects of long-term	Routine pharmacovigilance	Should routine pharmacovigilance activities and/or open-label study (CTBM100C2401) and

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
use (other than listed as potential risks)	Two sequential open-label extension studies (CTBM100C2303E1 and CTBM100C2303E2) of the ongoing CTBM100C2303 study An open-label study (CTBM100C2401)	open-label extension studies (CTBM100C2303E1 and CTBM100C2303E2) uncover additional data, this risk will be communicated through the IB, CDS, and EU-SmPC and additional risk minimization activities may be proposed if necessary.
Pregnant or lactating females	Routine pharmacovigilance	This risk is adequately addressed and communicated in the SmPC Pregnancy and breastfeeding (Section 4.6 of SmPC) "*(...)Systemic exposure following inhalation of TOBI Podhaler is very low, however TOBI Podhaler should not be used during pregnancy unless clearly necessary, i.e. when the benefits to the mother outweigh the risks to the foetus.* *Patients who use TOBI Podhaler during pregnancy, or become pregnant while taking TOBI Podhaler, should be informed of the potential hazard to the foetus.* *Breastfeeding* *Tobramycin is excreted in human breast milk after systemic administration. The amount of tobramycin excreted in human breast milk after administration by inhalation is not known, though it is estimated to be very low considering the low systemic exposure. Because of the potential for ototoxicity and nephrotoxicity in infants, a decision should be made whether to terminate breast-feeding or discontinue treatment with TOBI Podhaler, taking into account the importance of the treatment to the mother*."
Patients with disease severity different from that studied in clinical trials	Routine pharmacovigilance	Should routine pharmacovigilance activities uncover additional data, this risk will be communicated through the IB, CDS, and EU-SmPC and additional risk minimization activities may be proposed if necessary.
Patients with co-morbidities (i.e., severe hepatic impairment)	Routine pharmacovigilance	This risk is adequately addressed and communicated in the SmPC Dosage and Administration (Section 4.2 of the SmPC) "*Patients with hepatic impairment* *No studies have been performed on patients with hepatic impairment. As tobramycin is not metabolised, an effect of hepatic impairment on the exposure to tobramycin is not expected."*
Effects of medications prior to treatment (e.g., steroids, other antibiotics)	Routine pharmacovigilance	Should routine pharmacovigilance activities uncover additional data, this risk will be communicated through the IB, CDS, and EU-SmPC and additional risk minimization activities may be proposed if necessary.
Demographics of risk for aminoglycoside-related deafness in both Caucasians and Non-Caucasians	Routine pharmacovigilance	Should routine pharmacovigilance activities uncover additional data, this risk will be communicated through the IB, CDS, and EU-SmPC and additional risk minimization activities may be proposed if necessary.
Handling of the T-326 Inhaler in young pediatric patients (6-	Routine pharmacovigilance Usability evaluation of the T-326 Inhaler in children	This risk is adequately addressed and communicated in the SmPC Dosage and administration (Section 4.2 of the

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
10 years)	(TBM100C_HANDP_T-326 USABILITY STUDY_01)	SmPC) "*Caregivers should provide assistance to children starting TOBI Podhaler treatment, particularly those aged 10 years or younger, and should continue to supervise them until they are able to use the Podhaler device properly without help.*" Should routine pharmacovigilance activities and/or the usability evaluation of the T-326 Inhaler in children (TBM100C_HANDP_T-326 USABILITY STUDY_01) uncover additional data, this risk will be communicated through the IB, CDS, and EU-SmPC and additional risk minimization activities may be proposed if necessary.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

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.*

2.8. Benefit-risk balance

Benefits

The objective of treatment by inhalation with TOBI Podhaler as recommended in cycles of 28 days on-treatment followed 28 days off-treatment in the management of CF patients with chronic PA infection of the lung is improvement of lung function. In this regard, the two pivotal studies in CF patients who were either naïve to inhalational tobramycin (C2301) or tobramycin experienced patients (C2302) showed positive results. In line with the CHMP CF-guideline, change in percent predicted FEV_1 from baseline was used as the primary end point and the need for additional anti-PA antibiotics to treat acute exacerbation of the lung disease, and change from baseline with regard to PA growth density as key secondary efficacy parameters.

TOBI Podhaler showed to be superior to placebo in the first treatment cycle in the placebo-controlled study C2301. This can be considered as proof of concept, as the lung function results after the 2^{nd} and 3^{rd} cycle of treatment were consistent with those of patients in TOBI Podhaler group after the 1^{st} cycle.

The second study C2302 showed that TOBI Podhaler was at least as efficacious as TOBI after 3 cycles of treatment in CF patients, although the effect in terms of relative change in percent predicted FEV_1 from baseline, was less evident in the group of adult patients > 20 years of age. The differential effect, together with the observed higher discontinuation rate due to AEs in the adult patients, is reflected in the SmPC. The results from the subgroup analyses suggest that both treatments are of value in an important proportion of patients across age categories and strata defined by baseline FEV1 % predicted and macrolide use.

As expected, TOBI Podhaler treatment decreased the sputum PA CFU density for specific biotypes during Cycle 1 markedly more compared to placebo. This decrease was also observed in study C2302, although the impact of TOBI on PA CFU density was less pronounced compared to TOBI Podhaler.

In addition, the PRO questionnaire favoured TOBI Podhaler above TOBI especially with regard to convenience (i.e. portability and duration of administration) to the patient. Remarkably, TIP administration time was approximately 70% shorter than that for TOBI at all weeks.

Long-term efficacy data like those documented for TOBI (12 cycles or more) are not available for TOBI Podhaler. The known efficacy profile for TOBI is supportive to some extent but not sufficient to address the long-term efficacy profile of the inhalation powder TOBI Podhaler due to the differences in the formulations and patient characteristics. The applicant has committed to collect long-term efficacy data from the ongoing Phase III study C2303 extensions and from the new open uncontrolled study C2401. Given that the sensitivity of the pivotal study C2302 to detect predictive factors may have been compromised by the small data base, impact of age and prior exposure to inhaled tobramycin, the applicant has been requested to also explore predictive factors of poor or good clinical response (efficacy/tolerance) to TOBI Podhaler in the long-term (see follow-up measures).

Risks

Cough, oropharyngeal pain, dysgeusia and dysphonia were the most frequently associated DR-AE with the use of TOBI Podhaler in both studies and were more frequently reported compared to TOBI in C2302. The difference is probably caused by TOBI Podhaler being a powder formulation and not due to the excipients (such as sulfuric acid which is present in a much lower quantities than in the TOBI dose). Discontinuations due to AEs in patients $\geq$ 20 years of age occurred at a higher rate in the TOBI Podhaler than in the TOBI group, which suggests that TIP is less tolerated than TOBI in an important proportion of the targeted adult patients. With regard to side effect ratings, in PRO report no difference between treatment groups were noted suggesting that in the patient's opinion the unwanted effects had a similar impact upon their lives.

No differences in serious adverse reactions between TOBI Podhaler and TOBI were shown.

Haemoptysis was reported as DR-AE in equal frequencies for TOBI Podhaler and TOBI. Of note, patients with haemoptysis more than 60 ml at any time within 30 days prior to study drug administration were excluded from the pivotal studies. Furthermore there is a possibility that the risk of increased rates of haemoptysis may be higher for patients using the inhalation powder TOBI Podhaler in real life because of the high rate of induced cough in such patients. Given the above concerns a relevant warning on haemoptysis has been included in section 4.4 of the SmPC

Notwithstanding differences observed in frequencies of specific adverse reactions, overall no new safety issues were observed in patients exposed to TIP compared to TOBI.

No new issues related to laboratory findings or drug-drug interactions were noted for TOBI Podhaler compared to TOBI.

In both studies there was a tendency toward increased MIC during treatment with TOBI Podhaler. Since there are no data beyond the presently documented 6 months (3 cycles), the applicant will monitor changes in the susceptibility/resistance to tobramycin within the Risk Management Plan activities.

Long-term data are not available to assess the long-term safety of TOBI Podhaler. Therefore, the applicant has committed to collect data on the long-term effect on lung function, safety and

development of resistance. Information will be obtained in the extensions of the ongoing study C2303 with additional cycles (6-12) and in the new study C2401.

Other safety concerns, such as medication errors, monitoring of outcome of use in children 6-13 years of age, due to potential mishandling issues, haemoptysis, hearing loss, nephrotoxicity and adverse events occurring from off-label use, will be closely monitored by the applicant and discussed in the PSURs (see follow-up measures).

Benefit-risk balance

The above mentioned clinical benefits of TOBI Podhaler together with improved convenience, portability and shorter duration of administration for the patient outweigh the potential increased risk of unfavourable effects such as cough, oropharyngeal pain, dysgeusia and dysphonia. This seems to be of a lower magnitude in adult patients previously exposed to inhaled tobramycin, when the effect in this subgroup, increased discontinuation rate and potential for a greater risk of haemoptysis are considered. However, notwithstanding all the highlighted uncertainties, it is considered that also in the adult population the benefit of TOBI Podhaler outweighs the risks which are essentially linked to tolerability aspects in a portion of the population to be treated.

Relevant information on efficacy and tolerability in different age groups has been included in the SmPC to allow health-care professionals to choose the appropriate inhalational tobramycin for their CF patients in this indication considering the tolerability of the available products and individual patient's characteristics. Long-term efficacy and safety for TOBI Podhaler are not currently available; such data are deemed necessary since data available for TOBI cannot be extrapolated entirely to TOBI Podhaler. The applicant has committed to generate long-term data from study C2303 extensions, and to perform a new study, C2401, which will include both paediatric and adult patients. Study C2401 will also explore the presence of any potential baseline or demographic factor that would predict patients' response to TOBI Podhaler (see follow-up measures).

2.8.1. Risk management plan

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- Pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.
- No additional risk minimisation activities were required beyond those included in the product information.

2.8.2. Similarity with authorised orphan medicinal products

The applicant included in module 1.7.1 an assessment based on comparing the product with authorised orphan medicinal products in the context of similarity as defined in Art. 3 of Commission Regulation (EC) No. 847/2000 based on the three criteria for assessing similarity: molecular structural features, mechanism of action, and therapeutic indication. The only approved product with an Orphan Designation for cystic fibrosis aimed at *P. aeruginosa* lung infection is Cayston (aztreonam lysine). Cayston is approved for use in adult cystic fibrosis patients.

The CHMP is of the opinion that TOBI Podhaler is not similar to Cayston within the meaning of the above mentioned Regulation.

2.8.3. Significance of paediatric studies

The CHMP is of the opinion that study C2302, which is contained in the agreed Paediatric Investigation Plan and has been completed after 26 January 2007, is considered as significant.

2.8.4. Conformity with agreed Paediatric Investigation Plan

The CHMP concluded that study C2302 is in conformity with the agreed Paediatric Investigation Plan.

2.9. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of TOBI Podhaler in the "treatment of suppressive therapy of chronic pulmonary infection due to *Pseudomonas aeruginosa* in adults and children aged 6 years and older with cystic fibrosis" was favourable and therefore recommended the granting of the marketing authorisation.

Furthermore, the CHMP takes note that the agreed Paediatric Investigation Plan is not fully completed yet as only some of the measures are completed. The CHMP reviewed the already available paediatric data of studies subject to this plan and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

In accordance with Article 45(3) of Regulation EC (No) 1901/2006, significant studies in the agreed paediatric investigation plan have been completed after the entry into force of that Regulation.

In addition, the CHMP, with reference to Article 8 of Regulation EC No 141/2000, considers TOBI Podhaler not to be similar (as defined in Article 3 of Commission Regulation EC No. 847/2000) to Cayston for the same therapeutic indication.