13 December 2018
EMA/901707/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tobramycin PARI

International non-proprietary name: tobramycin

Procedure No. EMEA/H/C/005086/0000

Note

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

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Table of contents

List of abbreviations

CEP	Certificate of Suitability of the EP
DDR	Drug Delivery Rate
EDQM	European Directorate for the Quality of Medicines
GC	Gas Chromatography
HPLC	High performance liquid chromatography
MMAD	Mass-related median aerodynamic diameter
NMR	Nuclear Magnetic Resonance
Ph. Eur.	European Pharmacopoeia
PP	Polypropylene
SmPC	Summary of Product Characteristics
UV	Ultraviolet

1. Background information on the procedure

1.1. Submission of the dossier

The applicant PARI Pharma GmbH submitted on 31 July 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Tobramycin PARI, through the centralised procedure under Article 3 (1) of Regulation (EC) No. 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 31 May 2018.

This application was submitted, in accordance with Article 82.1 of Regulation (EC) No 726/2004, as a multiple of Vantobra (authorised on 20 March 2015).

The applicant applied for the following indication:

"management of chronic pulmonary infection due to Pseudomonas aeruginosa in patients aged 6 years and older with cystic fibrosis (CF)."

The legal basis for this application refers to:

Hybrid application (Article 10(3) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data, two bioequivalence studies with the reference medicinal product TOBI and appropriate non-clinical and clinical data.

Reference product chosen:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: TOBI, 60 mg/ml, Nebuliser solution
- Marketing authorisation holder: Novartis Pharmaceuticals UK Ltd.
- Date of authorisation: 10-12-1999
- Marketing authorisation granted by:
  - Member State (EEA): United Kingdom
  - National procedure
  - Marketing authorisation number: PL 00101/0935

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: TOBI, 60 mg/ml, Nebuliser solution
- Marketing authorisation holder: Novartis Pharmaceuticals UK Ltd.
- Date of authorisation: 10-12-1999
- Marketing authorisation granted by:
  - Member State (EEA): United Kingdom
  - National procedure
  - Marketing authorisation number: PL 00101/0935

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: TOBI, 60 mg/ml, Nebuliser solution
- Marketing authorisation holder: Novartis Pharmaceuticals UK Ltd.
- Date of authorisation: 10-12-1999
- Marketing authorisation granted by:
  - Member State (EEA): United Kingdom

- National procedure
- Marketing authorisation number: PL 00101/0935
- Bioavailability study number: 2010-023235-41

Information on paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

- Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

- Derogation from market exclusivity

Pursuant to Article 8 of Regulation (EC) No. 141/2000, the applicant submitted a claim addressing the following derogation laid down in Article 8.3 of the same Regulation; the holder of the marketing authorisation for the original orphan medicinal product has given consent to the applicant.

Scientific advice

The applicant received Scientific Advice from the CHMP on 19 November 2009 and 24 June 2010. The Scientific Advice pertained to clinical aspects of the dossier.

New active Substance status

The applicant indicated the active substance tobramycin contained in the above medicinal product to be considered as a known active substance.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Kristina Dunder

The application was received by the EMA on	31 July 2018
The procedure started on	20 August 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	24 September 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	24 September 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	18 October 2018
The applicant submitted the responses to the CHMP consolidated List of Questions on	12 November 2018
The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	29 November 2018

The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Tobramycin PARI on	13 December 2018

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

This hybrid marketing authorisation application for Tobramycin PARI 170mg / 1.7ml is a duplicate of the 2015 approved hybrid marketing authorisation application by the same MAH (PARI Pharma GmbH) for VANTOBRA 170mg / 1.7ml, with reference to the same originator product, TOBI (Novartis Pharmaceuticals Ltd, UK).

2.1.2. Disease or condition

Cystic fibrosis (CF, also known as mucoviscidosis) is a hereditary, autosomal recessive chronic disease that affects a variety of organ systems (Döring *et al*. 2007; Hagerman *et al.* 2007). Chronic airway disease is a prominent complication of the disease and is present in more than 98% of CF patients. Pulmonary features noted in CF patients include chronic cough highlighted by periodic episodes of increased sputum volume and purulence.

The currently accepted paradigm in the lung pathophysiology of CF is based on the hypothesis that reduced mucociliary clearance - as a consequence of a defective chloride channel - facilitates bacterial lung infection with opportunistic pathogens (Döring *et al.* 2007; Hagerman *et al.* 2007; Weiner *et al*. 2008). These infections become chronic due to a phenotypic switch from non-mucoid to mucoid variants which are resistant to antibiotics and the innate host response.

CF occurs predominantly in Caucasian populations, with approximately 1 in 1,500-3,200 individuals affected in the US, but it has been estimated that 1 out of 20–25 individuals carry the CF transmembrane regulator gene. About 50,000 CF patients are registered in Europe and North America (Hagerman et al. 2007).

Morbidity and mortality in patients with CF are primarily attributable to progressive obstructive pulmonary disease (lung function declines by ≈2% per year) in conjunction with chronic *Pseudomonas aeruginosa* (PA) endobronchial infection and an intense neutrophilic inflammatory response. The prevalence of PA infection increases with age, with positive respiratory tract cultures reported for 30-40% of children 2-10 years of age, and 60–80% of adolescents and adults with CF (Gibson *et al*. 2003).

Improvements in clinical care have resulted in a distinct increase in the life expectancy of people with CF over the last 40 years (Döring *et al*. 2007; Weiner *et al*. 2008). In several European countries, the median survival is now between 30 and 40 years. The aggressive treatment of lung disease and improvements in nutrition are the major factors in this context. However, eradication of PA (Ramsey *et al*. 1999) is rare and about 95% of CF patients still die from respiratory failure (Döring *et al.* 2007).

Tobramycin is the most frequently used antibiotic for the treatment of pulmonary infections caused by PA in patients suffering from CF. The value of intravenous (i.v.) tobramycin application for pulmonary exacerbations in CF is well established. Significant questions remain, however, as to optimum combinations, duration of treatment and frequency of administration (Döring *et al*. 2007). In addition, the low penetration of tobramycin into sputum after parenteral administration necessitates high doses of the

drug to achieve concentrations sufficient to inhibit PA, and thus leads to increased risk of systemic adverse events, such as ototoxicity and nephrotoxicity (Moss 2001).

About the product

This marketing authorisation application concerns a tobramycin formulation for inhalation developed by PARI Pharma GmbH, Tobramycin PARI 170 mg/1.7 ml nebuliser solution administered via a delivery system (Tolero), based on a vibrating membrane technology (eFlow).

Type of Application and aspects on development

The submitted dossier is identical with the dossier submitted for Vantobra with the following exceptions: Module 1 has been updated according to the requirements of the duplicate application. There are some editorial changes in module 2 and 3. Throughout the dossier, pouch has been replaced by the standard term sachet. The latest version of the CEP for the drug substance has been provided, i.e. R1-CEP 1997-046 Rev 04. This is the current version according to the EDQM webpage. More recent stability data has been provided for the drug product that supports the already approved shelf-life of 3 years. Furthermore the Risk Management Plan has been updated.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a sterile nebuliser solution containing 170 mg of tobramycin as active substance.

Other ingredients are: sodium chloride, calcium chloride, magnesium sulphate, water for injection, sulphuric acid (for pH adjustment) and sodium hydroxide (for pH adjustment).

The product is available in single-dose polyethylene (PE) ampoules that are packed in sealed aluminium foil sachets (8 ampoules per sachet). The ampoules are supplied with a single patient use, reusable, drug specific, electronic Tolero nebuliser handset which has a CE mark.

2.2.2. Active substance

The chemical name of tobramycin is 4-O-(3-Amino-3-deoxy-α-D-glucopyranosyl)-2-deoxy-6-O-(2,6-diamino-2,3,6-trideoxy- α -D-ribo-hexopyranosyl)-L-streptamine and has the following structure:

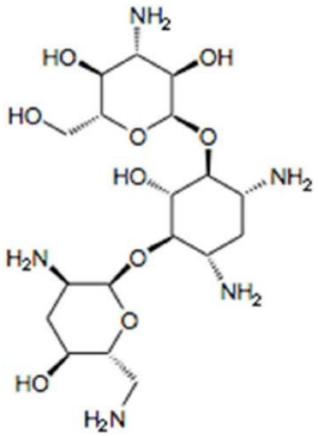


Figure 1: active substance structure

The active substance is a white or almost white hygroscopic powder freely soluble in water, very slightly soluble in ethanol (96%).

As there is a monograph of tobramycin in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for tobramycin which has been provided within the current Marketing Authorisation Application.

Manufacture

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) before issuing the Certificate of Suitability. Satisfactory quality of the active substance is ensured through the CEP.

Specification

The active substance specification includes tests for: appearance (Ph.Eur.), identity (Ph.Eur.), pH (Ph.Eur.), specific optical rotation (Ph. Eur.), assay (Ph. Eur, HPLC-UV), related substances (HPLC-UV), residual solvents (GC), water (Ph.Eur.) and sulphated ash (Ph.Eur.).

The active substance will be tested and assessed by the finished product manufacturer applying the methods and specifications laid down in the Ph.Eur. monograph and the CEP, except for assay and related substances. The applicant has developed two in-house methods to test these parameters in both the active substance and the finished product. Both methods have been adequately described and cross-validated against the Ph.Eur. methods. Batch analysis data on seven commercial scale and one pilot scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

The CEP of the active substance manufacturer includes a suitably validated re-test period in a defined container closure system, supported by the available stability data.

2.2.3. Finished medicinal product

Pharmaceutical development

Tobramycin PARI nebuliser solution is a clear, sterile, preservative- and stabiliser-free solution for nebulisation with a drug specific electronic nebuliser. It contains Tobramycin, Ph.Eur. in a concentration of 100 mg/ml and is supplied in single dose low density polyethylene ampoules.The nebuliser solution contains an overage to ensure that the target volume is dispensed.

The product has been developed in accordance with the requirements of the Guideline on the pharmaceutical quality of inhalation and nasal products (EMEA/CHMP/QWP/49313/2005 Corr.).

The aim of the pharmaceutical development was to prepare a tobramycin nebuliser solution with reduced inhalation time in comparison to TOBI, the reference product. The development focused on the reduction of the volume to be administered by increasing tobramycin concentration in the solution and the use of a different device for nebulisation. The results of this study showed that tobramycin concentrations up to 100 mg/ml gave appropriate lung deposition. Therefore this concentration was selected for further development.

A nominal dose of 150 mg in 1.5 ml of the 100mg/ml formulation was used during initial development, but based on the pharmacokinetic studies, the nominal dose was increased to 170 mg in 1.7 ml in order to maintain the therapeutic equivalence.

Subsequent studies were aimed at improving the formulation characteristics. Since aqueous solutions of tobramycin at 100 mg/ml have a pH around 10.5, pH adjustment was required to obtain physiological pH values in the solution for inhalation. The excipients chosen for pH adjustment were sulphuric acid 96% and sodium hydroxide. Moreover, in order to ensure an adequate osmolality range for a nebuliser solution and isotonicity, sodium chloride, calcium chloride and magnesium sulphate were added as tonicity agents.

The compatibility of tobramycin sulphate with the excipients used in the final formulation and other potential excipients investigated during pharmaceutical development was adequately demonstrated.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The primary packaging consists on single-dose polyethylene ampoules. The material complies with Ph.Eur. requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Nebuliser development

Tobramycin PARI was developed to be delivered with a drug-specific, single patient use, reusable electronic nebuliser called Tolero. The Tolero device is CE marked and is composed of three main components: a Controller (eBase controller or eFlowrapid control unit), a connection cord and a drug specific nebuliser handset (aerosol head) as illustrated below:

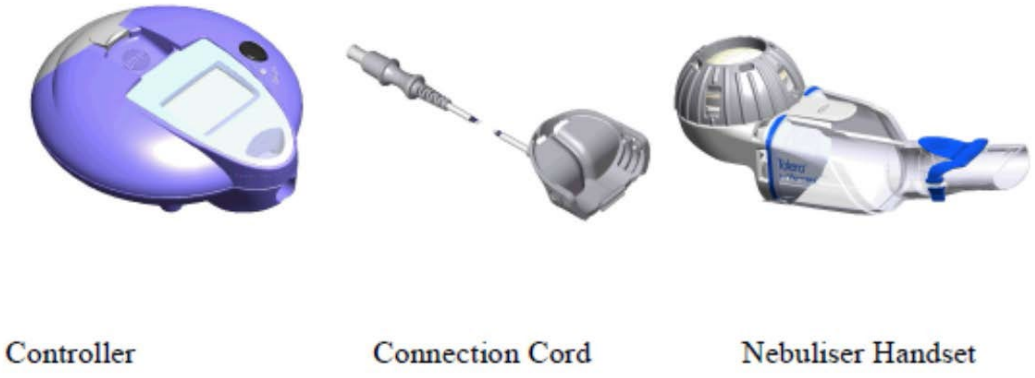


Figure 2

Appropriate studies have been performed to evaluate the compatibility of the device materials with the medicinal product.

In addition, the product has been adequately characterised and compared with TOBI/PARI LCPlus (nebuliser used to administer the reference product, TOBI) using the tests described in Ph. Eur. 2.9.44.monograph. Active substance delivery rate, total active substance delivered, and aerodynamic assessment of nebulised aerosols were evaluated. Tobramycin PARI nebulised with the Tolero handset was shown to have a similar delivered dose (DD), a similar mean mass-related median aerodynamic diameter (MMAD), a higher mean respirable dose and a shorter nebulisation time than the reference product.

Due to the different principles of aerosol generation between the two devices PARI LC Plus and eFlow, there were statistically significant differences between the two devices in Drug Delivery Rate (DDR), with the Tobramycin PARI/eFlow system significantly higher than for the jet nebulizer system TOBI/PARI LC Plus, both for adults and children. As a consequence the nebulisation times are much shorter for the eFlow device (3.4 minutes for the new devices and 4.5 minutes for the returned study devices compared to 14.6minutes for PARI LC Plus).

No statistically significant differences were seen between unused and used eFlow devices for any of the parameters tested. Breath simulation experiments also confirmed that the drug delivery rate of Tobramycin PARI is independent of the breathing pattern applied (adult or child).

Since there were differences in the concentration and delivery rate of both products, therapeutic equivalence between Tobramycin PARI and the reference product could not be established based on in-vitro data. Nevertheless, these results are supportive of the clinical efficacy studies presented.

A simulated user test was conducted to investigate the effect of operating eFlow/Tolero with Tobramycin PARI 170mg over 56 treatments (corresponding to 28 days twice daily use). The results from this study showed that Tolero nebuliser handset when nebulizing Tobramycin PARI delivers tobramycin in a consistent manner during a treatment cycle of 28 days.

Tilting of the handset and its effects on the delivered dose and nebulisation time was also evaluated. No significant effects were observed when tilting the device 15° in different directions. However, tilting 45°resulted in significant differences in delivered dose. Although 45° tilting is considered extreme since the instructions indicate to keep it horizontally, a warning has been included in the proposed SmPC (section 6.6).

Adventitious agents

No excipients derived from animal or human origin have been used.

Manufacture of the product

The manufacturing process consists of: preparation of tobramycin bulk solution, pH adjustment, double sterile filtration, aseptic filling using a blow/fill/seal technology and packaging. Sterile filtration was chosen as the sterilisation method due to the degradation of tobramycin at high temperatures.

The process is considered to be a non-standard manufacturing process and has been validated on three full scale batches of tobramycin 150 mg/1.5 ml solution at the proposed manufacturing site. This is acceptable since the process is identical and only the fill volume differs with respect to the product intended for commercialization (Tobramycin PARI 170 mg/1.7 ml). It has been demonstrated that the manufacturing process is capable of producing the finished product of the intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form as described in the Ph. Eur. and EMA/CHMP/QWP/49313/2005 Corr. It includes description, appearance (clarity, color and visible particles) (Ph. Eur.), sub-visible particles (Ph. Eur.), uniformity of dosage units (Ph. Eur.), pH (Ph. Eur.), osmolality (Ph.Eur.), sterility (Ph.Eur), bacterial endotoxins (Ph. Eur.), identity (HPLC-UV), assay (HPLC-UV) and related substances (HPLC-UV).

Batch analysis results are provided for four pilot scale batches used in clinical studies and three commercial scale validation batches confirming the consistency of the manufacturing process and its

ability to manufacture to the intended product specification. The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data of three validation and three production scale batches of tobramycin 150 mg/1.5 ml solution stored for 36 months under long term conditions (5 ºC) and accelerated conditions (25 ºC / 60% RH) according to ICH guidelines; and for up to 6 months under 40 ºC / 75% RH were provided. The batches are identical to those proposed for marketing, except of the fill volume.

In addition, supportive data from a clinical pilot scale batch of Tobramycin PARI (tobramycin 170 mg/ 1.7 ml) stored under long term conditions (5 ºC) and accelerated conditions (25 ºC / 60% RH) for 48 months, and at 30 ºC / 65% RH and 40 ºC / 75% RH) for 12 months was presented.

Samples were tested for appearance (clarity, colour and visible particles), uniformity of dosage units, pH, osmolality, sterility, assay and related substances. The clinical batch was also tested for mass per dosage unit (for information only).

The analytical procedures used are stability indicating.

The stability results of the three validation batches as well as of the three commercial batches demonstrate that all tested parameters are within the acceptance criteria and provide evidence that the finished product is stable for the claimed shelf-life of 36 months when stored at 5°C.

During six months at 25 °C/60 % RH all parameters were also within the defined specification. After six months at 25 °C/60 % RH a change of colour was observed but no correlation with the purity profile of the finished product could be established.

The stability results of the three validation batches as well as of the three commercial batches demonstrate that all tested parameters are within the acceptance criteria and provide evidence that the drug product is stable for the claimed shelf-life of 36 months when stored at 5°C.

Even up to six months when stored at 25 °C/60 % RH all parameters meet the defined specification. After six months at 25 °C/60 % RH a change of colour is observed but no correlation with the purity profile of the drug product could be established.

In addition, one clinical batch exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. A second photostability study was performed on samples from a clinical batch which had been stored at 5°C for a period of 32 months to assess the photostability nearly at the end of shelf-life. The shelf-life specification parameters assay, related substances, clarity and colour of the solution, visible particles, and uniformity of dosage units, pH-value, osmolality and also absorbance at 410nm were tested.

A third photo stability study using samples of one of the commercial batches was also conducted. This study was designed to assess the photo stability at start of shelf life. The shelf-life specification parameters; assay, related substances, clarity and colour of the solution, visible particles, pH-value and osmolality were tested.

The results from these studies confirmed that Tobramycin PARI 170 mg is photostable under the tested conditions as required in ICH Q1B and thus not sensitive to light.

An in-use stability study was conducted using one clinical batch which had been stored at 5°C for a period of 32 months (nearly end of shelf-life) and one commercial batch from the start of shelf-life. This study was designed to evaluate the stability of Tobramycin PARI after opening the aluminium foil sachet. The ampoules were removed from the sachets and stored for 4 weeks in a stability cabinet at 25°C/60% RH

(and at 25°C/60% RH the commercial batch only) or in the laboratory at ambient temperature and humidity.

Samples were tested for appearance (clarity, colour and visible particles), uniformity of dosage units, acceptance value, pH, osmolality, related substances, sterility and assay. The clinical batch was also tested for absorbance at 410 nm, surface tension and dynamic viscosity.

The results from these studies confirmed the in-use stability of the product for 4 weeks at ambient conditions and under controlled conditions (25°C/60% RH and 25°C/40% RH).

Based on available stability data, the proposed shelf-life of 3 years stored in a refrigerator (2 °C – 8°C), and in use shelf-life after opening the sachet of 4 weeks when stored below 25 °C as stated in the SmPC are acceptable. The contents of a single-dose ampoule should be used immediately after opening.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Overall information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.5. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of the active substance tobramycin are well known. As tobramycin is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Since this MAA is a hybrid application, and TOBI is an approved reference product for Tobramycin PARI, an overview based on limited literature data is acceptable.

2.3.2. Ecotoxicity/environmental risk assessment

Table 1: Summary of main study results

Substance (INN/Invented Name):tobramycin			
CAS-number (if available): 32986-56-4			
PBT screening		Result	**Conclusion**
Bioaccumulation potential - log K_{ow}	Clarke's Analysis of Drugs and Poisons	-5.8	Potential PBT (**N**)
Bioaccumulation potential - log K_{ow}	Shake flask method (OECD 107)- Report No. 12012.001	-3.11 to minus -1.85 (pH 11 and at pH 7)	Potential PBT (**N**)
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**

PEC $_{surfacewater}$, refined (literature)	0.0067	µg/L	> 0.01 threshold (**N**)

PEC surfacewater value of tobramcin was below the action limit of 0.01µg/L and tobramycin is not a PBT substance as experimentally determined log Kow does not exceed 4.5. Therefore, Tobramycin PARI is not expected to pose a risk to the environment.

2.3.3. Discussion on non-clinical aspects

No new non-clinical studies have been performed with Tobramycin PARI. In accordance with Article 10 of Directive 2001/83/EC, in a generic or hybrid application the nonclinical data can be bridged from the reference medicinal product. This is the approach adopted by the Applicant, who refers to the overview generated with the previously approved product TOBI, as well as to the fact that tobramycin has been widely used and is a well-known substance in the clinic for the last decades and its human safety profile is well established. This justification for the lack of new non-clinical studies is considered acceptable.

2.3.4. Conclusion on the non-clinical aspects

There are no objections to approval of Tobramycin PARI from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

- Tabular overview of clinical studies

Type of Study	**Study Identifier**	**Objective(s) of Study**	**Study Design and Type of Control**	**Test Product(s); Dosage Regime; Route of Administration**	**No. of Subjects**	**Duration of Treatment**
Lung deposition	G007.03	γ-Scintigraphy study	Phase Ib, randomised, open, controlled, cross-over,	Tobramycin PARI*/eFlow vs. TOBI***/PARI LC PLUS	17 patients (≥ 18 years)	2 single inhalation courses
Pharmaco-kinetics and safety	G007.05	Pharmaco-kinetics and safety	Phase Ib, randomized, open labeled, multi center, active controlled, parallel	Tobramycin PARI*/eFlow vs. TOBI***/PARI LC PLUS	86 patients (≥ 8 years)	28 day BID treatment
Bioequivalence, therapeutic equivalence	12012.101	Therapeutic equivalence of TOBRAMYCIN PARI)/ eFlow and TOBI / PARI LC PLUS	Phase Ib, comparative, randomised, two period, multi center, cross-over	TOBRAMYCIN PARI**/ eFlow and TOBI*** /PARI LC PLUS	58 patients (≥ 4 years)	28 day BID treatment
Bioequivalence	12012.102	Therapeutic equivalence of TOBRAMYCIN PARI)/ eFlow and TOBI / PARI LC PLUS	Phase I, comparative, single center, open, randomized, single-dose, cross-over	TOBRAMYCIN PARI**/ eFlow and TOBI*** /PARI LC PLUS	72 healthy volunteers (≥ 18 years)	1 single inhalation

2.4.2. Pharmacokinetics

The pharmacokinetic properties of tobramycin have been evaluated over time in children, adult and elderly subjects with CF. Data available in published literature are briefly summarised below:

Absorption

Tobramycin is not absorbed from the gastrointestinal tract following oral administration and hence the systemic exposure after inhalation is expected to result primarily from the pulmonary absorbed portion of the dose. Following tobramycin inhalation, serum concentrations are expected to be low; values around 1 µg/ml are reported in the literature. Concentrations in sputum are approximately 1000 times higher compared to serum concentrations. Binding of tobramycin to plasma proteins is less than 10%.

Distribution

Tobramycin is distributed in the extracellular fluid. The apparent volume of distribution is 0.3 L/kg body weight.

Elimination

Tobramycin is not metabolised and is primarily eliminated unchanged in the urine via glomerular filtration. The elimination half-life is approximately 2-3 h.

Pharmacokinetic studies

Four clinical/pharmacokinetic studies have been conducted:

- Study G007.03: a single-dose lung deposition study of Tobramycin 100 PARI/eFlow versus TOBI/PARI LC PLUS in adult and adolescent CF patients
- Study G007.05: a 28-day pharmacokinetic and safety study of Tobramycin 100 PARI/eFlow versus TOBI/PARI LC PLUS in CF patients
- Study 12012.101: a 14-week, 2-period, multi-centre, crossover bioequivalence as well as efficacy and safety study of TOBRAMYCIN PARI/Tolero (eFlow) versus TOBI/PARI LC PLUS
- Study 12012.102: a single-dose, 2-period, crossover bioequivalence study in healthy volunteers of TOBRAMYCIN PARI/Tolero (eFlow) versus TOBI/PARI LC PLUS

Studies G007.03 and G007.05 are mainly explorative as a dose lower than the proposed to be marketed dose was administered to the enrolled patients.

In the pivotal bioequivalence studies 12012.101 and 12012.102 the final TOBRAMYCIN PARI dose of 170 mg/1.7 ml dose was administered and compared to inhalation of TOBI 300 mg. The primary objective of these studies was to evaluate bioequivalence between TOBRAMYCIN PARI and TOBI. In addition, efficacy and safety of TOBRAMYCIN PARI and TOBI were evaluated.

Study G007.03

In this lung deposition study a lower dose of 150 mg/1.5 ml of the test product was administered.

Methods

This was a randomised, open-label, 2-way cross-over trial in which the lung deposition of Tobramycin PARI 150 mg/1.5 ml delivered by the eFlow electronic nebuliser and TOBI 300 mg/5 ml using the PARI LC PLUS jet nebuliser, was compared after a single-dose administration.

A total of 17 male patients with cystic fibrosis were enrolled: 9 subject aged 10-17 and 8 subjects >17 years. Subjects received inhaled tobramycin spiked with the radiolabel ^{99m}Tc-DTPA

(diethylenetriamine-pentaacetic acid). Tobramycin lung deposition was measured using gamma camera imaging.

The primary efficacy variable was the difference between the estimated lung deposition of Tobramycin PARI 150 mg delivered with the eFlow device run to dryness compared to TOBI delivered with the PARI LC PLUS device until sputtering, or 10 minutes (whichever occurred first).

Given that similar particle size distribution of tobramycin and ^{99m}Tc-DTPA after nebulisation into a particle sizing device (Next Generation Pharmaceutical Impactor) was obtained, it was assumed that the deposition of the radiolabel would be an accurate representation of the deposition of tobramycin.

The lungs were imaged at 5 minute intervals for 20 minutes following the deposition; it was possible to calculate the clearance rate of the radiolabel and then mathematically adjust the image to reflect what had been deposited during the entire period of nebulisation.

Results

The results are presented in the below table:

Table 2: Lung deposition (mg) of Tobramycin based on ^{99}Tc-DTPA counts (Study G007.03).

	Treatment		Between-treatment Difference
	B: 150mg T100 /eFlow N = 16	A: 300mg TOBI/LC PLUS N = 16	B – A N = 16
Mean	46.0	45.4	0.6
SD	10.8	11.5	9.7
Median	46.3	42.2	0.9
95% CI[a]	(40.3, 51.7)	(39.3, 51.6)	(-4.6, 5.7)
p-value			0.82

[a]t-distribution confidence intervals computed directly for this table (Mean±2.131×SD/4)
Source: Table 14.2.1

The mean lung deposition was similar between treatments and the p-value indicates no evidence of treatment difference. Similar results were obtained when the primary results were stratified by age group, except that the confidence intervals were wider due to smaller sample sizes. The lung deposition relative to the total drug amount was higher for Tobramycin PARI 150 mg (31%) compared to TOBI (17%). The extra-thoracic deposition in the mediastinum and stomach was not significantly different for the different formulations.

Study G007.05

In this explorative comparative bioavailability study the same lower dose of 150 mg/1.5 ml of the test product was administered-as in the lung deposition study G007.03.

Methods

This was a randomised, open-label, multicentre, active controlled, parallel safety and bioavailability study of Tobramycin PARI 150 mg (150 mg/1.5 ml) nebulised with eFlow versus TOBI (300 mg/5 ml) nebulised with PARI LC PLUS in cystic fibrosis patients with *Pseudomonas aeruginosa* lung infections.

A total of 78 patients, 21 aged 8-17 years and 18 adults per treatment group were randomised for either treatment A (Tobramycin PARI 150 mg/eFlow) or treatment B (TOBI 300 mg/PARI LC PLUS). The dose of the reference product (300 mg tobramycin bid) was in accordance with the SmPC for TOBI. The dose of

the test product (150 mg bid) was chosen as it had proven an equivalent *in vitro* aerosol characterisation of the respirable dose and delivered dose as the reference. After a 7-day wash-out phase, in which no tobramycin was allowed, the patients were treated with their assigned medication and devices for 28 consecutive days. Blood and sputum samples were taken at days 1, 7 and 28. Pre-dose blood samples were taken at day 1 and 28. At day 7 blood samples were taken pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6 and 8 hours post-dose. Sputum samples were taken 10 minutes after inhalation at days 1, 7 and 28. Concentrations of tobramycin in plasma and sputum were analysed using an LC-MS/MS assay.

The primary efficacy variable was Cmax on day 7. Secondary efficacy variables were AUC at day 7, sputum levels at days 1, 7 and 28 and plasma trough levels at days 1, 7 and 28.

Results - plasma

Plasma tobramycin C_{max} on day 7 and plasma tobramycin AUC on day 7 are shown in the following tables:

Table 3: Plasma tobramycin Cmax on Day 7 (Study G007.05).

	C_{max} (mg/L)	
	Tobramycin PARI 150 mg/eFlow®	**TOBI®/PARI LC PLUS®**
All ages	1.29 (1.05; 1.53)	1.65 (1.41; 1.89)
Adults (≥18 a)	1.21 (0.87; 1.55)	1.81 (1.47; 2.15)
Children (8-17 a)	1.36 (1.01; 1.70)	1.52 (1.17; 1.87)

Mean (90% CI); PP population (n=38, adults=17/group; children=21/group)

Table 4: Plasma tobramycin AUC on Day 7 (Study G007.05).

	AUC (h x mg/L)	
	Tobramycin PARI 150 mg/eFlow®	**TOBI®/PARI LC PLUS**
All ages	6.89 (5.84; 7.94)	8.64 (7.60; 9.67)
Adults (≥ 18 a)	6.89 (5.33; 8.45)	9.69 (8.13; 11.25)
Children (8-17a)	6.89 (5.44; 8.33)	7.79 (6.38; 9.20)

Mean (90% CI); PP population (n=38, adults=17/group; children=21/group)

Results - sputum

Sputum tobramycin levels on day 7 are shown below:

Table 5: Sputum tobramycin levels on Day 7 (PP population Study G007.05).

Sputum [mg/g]	Tobramycin PARI 150 mg/eFlow®	TOBI®/PARI LC PLUS
All ages	2.59 (1.97; 3.21)	2.27 (1.66; 2.89)
Adults (≥18 a)	2.69 (1.83; 3.55)	2.65 (1.76; 3.54)
Children (8-17 a)	2.50 (1.58; 3.43)	1.99 (1.11; 2.87)

Mean (90% CI); PP population (n=38, adults=17/group; children=21/group)

After the administration of Tobramycin PARI 150 mg, tobramycin plasma exposure did not exceed the exposure obtained after administration of TOBI 300 mg. Tobramycin sputum concentrations were similar between formulations. The fact that the plasma sampling period was rather short (8h) and that the sputum evaluation were based on one sample per subject and period (10 min post inhalation) only is acceptable for this supportive study.

Study 12012.101

This was a comparative, randomised, two period, multi-centre, cross-over, 14-week bioequivalence study of TOBRAMYCIN PARI (170 mg/1.7 ml) delivered by the eFlow electronic nebulizer versus TOBI (300 mg/5 ml) using the PARI LC PLUS jet nebulizer in cystic fibrosis patients with bronchopulmonary chronic *Pseudomonas aeruginosa* infection.

The primary objective was to determine bioequivalence of TOBRAMYCIN PARI and TOBI in children and adolescents/adults using eFlow or PARI LC PLUS devices, respectively. In addition, efficacy and safety of the two different medicinal products were evaluated as secondary objectives.

Methods

The clinical part of the study was conducted at four EU study centres. The bioanalytical part collected plasma and sputum samples. No issues regarding GCP have been identified.

Study design

This was a multicentre open label, randomised, 2-period, 2-sequence, crossover study following administration of Tobramycin with two different inhalation systems and different doses in 58 patients treated either with TOBRAMYCIN PARI (170 mg/1.7 ml) / eFlow or TOBI (300 mg/5 ml) / PARI LC PLUS. Tobramycin was administered twice daily (in the morning and in the evening), until dryness of the nebuliser. Each treatment period was 4 weeks, separated by a washout-phase of 4 weeks between periods 1 and 2.

At the end of each treatment cycle, blood- and sputum-samples were collected and analysed for tobramycin using a validated LC/MS/MS method. Blood-samples were collected pre-dose (30 - 15 min prior to inhalation), and at 30 min, 1, 1.5, 2, 4, 6, 8 and 12 h after end of inhalation. Sputum samples were collected pre-dose (30 - 15 min prior to inhalation), and at 10 min, 30 min, 1.5, 2 and 8 h after end of inhalation.

Populations studied

A total of 58 cystic fibrosis patients with bronchopulmonary chronic *Pseudomonas aeruginosa* infection (25 male and 33 female) were enrolled. Of the 58 enrolled patients, 28 were aged 7-13 years and 30

patients 13-36 years. All subjects were Caucasian. Fifty-four patients received both study treatments. Three patients stopped the treatment during the wash-out phase and one patient was withdrawn from the study participation 3 days after the start of TOBI treatment. The reasons were impairment or worsening of the disease in one case and in three cases because of (serious) adverse events. Five additional patients were excluded from the PK-analysis due to insufficient PK-sampling.

Hence, 49 subjects were included in the pharmacokinetic analysis.

Pharmacokinetic Variables

Pharmacokinetic variables were calculated using conventional non-compartmental methods. The primary endpoint was plasma AUC_{0-12h}. Secondary PK-endpoints included C_{max}, C_0 in plasma and sputum and T_{max}.

Statistical methods

The statistical analysis was performed on log-transformed plasma AUC_{0-12h} and C_{max} using ANOVA. Consistent with the two one-sided tests for bioequivalence, 90%-confidence intervals for the difference between drug formulation least-squares means (LSM) were calculated for the log-transformed parameters plasma AUC_{0-12h} and plasma C_{max}.

The acceptance range for the 90% confidence interval for the ratio of the back-transformed LSMEANS of tobramycin was determined as 80% to 125% for the parameters plasma AUC_{0-12h} and 70% to 133% for plasma C_{max}. The parameter plasma tmax was evaluated descriptively.

Results

Plasma concentration versus time profiles (AUC_{0-12h}), maximum concentration (C_{max}), time to maximum concentration (t_{max}) and trough levels (C_0) of the test treatment TOBRAMYCIN PARI in comparison to TOBI were determined at the end of each treatment phase. The results are presented below:

Table 6: Plasma pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) after a 4-week treatment of TOBRAMYCIN PARI/eFlow or TOBI/PARI LC PLUS, n=49 (Study 12012.01).

Treatment	AUC_{0-12h} ng*h/ml	C_{max} ng/ml	C_0 ng/ml	t_{max} h
Test	**5778.8 ± 3569.15**	**1271.2 ± 805.48**	**151.7 ± 153.64**	**1.0 0.5-2.0**
Reference	**5809.7 ± 3097.98**	**1333.7 ± 757.45**	**148.0 ± 123.26**	**1.0 0.5-1.6**
***Ratio (90% CI) All**	**85.03 (68.32-105.83)**	**83.05 (66.30-104.03)**	**-**	**-**
***Ratio (90% CI) 7-13 years**	**89.51 (66.09-121.22)**	**93.00 (67.58-127.99)**	**-**	**-**
***Ratio (90% CI) >13 years**	**81.78 (58.84-113.68)**	**75.89 (54.37-105.93)**	**-**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

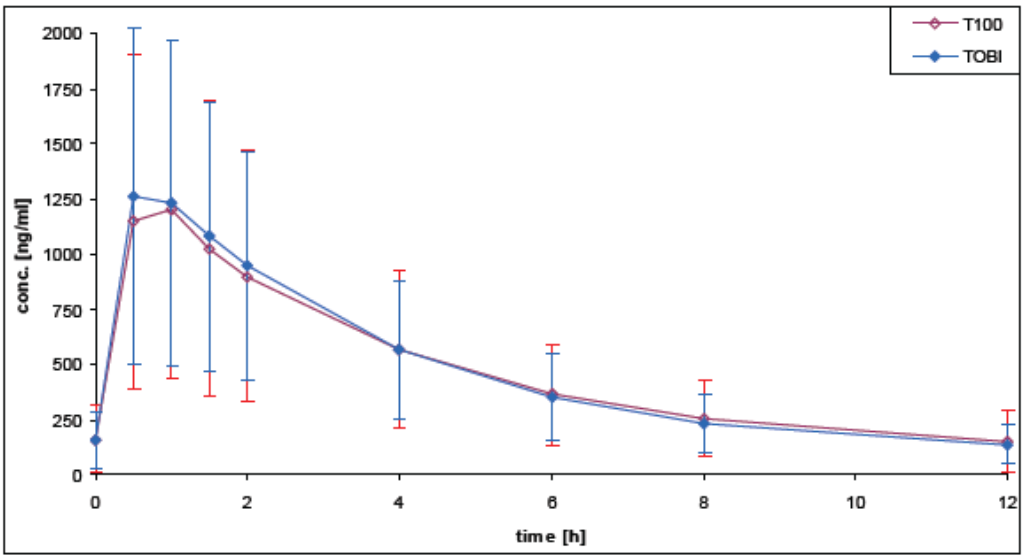


Figure 3: Plasma tobramycin concentration versus time profile (arithmetic mean ± SD; all groups) (Study 12012.01).

After a 28-days treatment period, the systemic exposure and peak concentrations of TOBRAMYCIN PARI was about 15% and 17% lower compared to TOBI (total data for both age groups) and the 90% CI was outside the conventional bioequivalence limits of 80.00-125.00. In the age group 7-13 years, the upper limit of the 90% CI for Cmax was also slightly above the conventional acceptance limit of 1.25, but below the prospectively defined widened limit of 1.33. Median tmax was comparable between the test and the reference formulation. A high variability in AUC and Cmax for both products was observed. When data was distinguishing between children (7-13 years) and adolescents (>13 years) a slightly lower AUC and Cmax in the older age group compared to the younger was observed.

Sputum concentrations versus time profiles (AUC_{0-8}), maximum concentrations (C_{max}), time to maximum concentration (t_{max}) and trough levels (C_0) of the test treatment TOBRAMYCIN PARI in comparison to TOBI were determined at the end of each treatment phase. The results are presented below:

Table 7: Sputum pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for tobramycin after a 4-week treatment of TOBRAMYCIN PARI/eFlow or TOBI/PARI LC PLUS, n=49 (Study 12012.01).

Treatment	AUC_{0-8h} ng*h/g	C_{max} ng/g	t_{max} h
Test	**1179692 ± 1154142**	**1950741 ± 2186547**	**0.17 0.17-8.00**
Reference	**869077 ± 801424**	**1416501 ± 1505653**	**0.17 0.00-8.00**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum plasma concentration			

Variability in sputum concentrations was high. A formal bioequivalence evaluation was not performed, but mean tobramycin exposure in sputum was approximately 35% higher for TOBRAMYCIN PARI compared to TOBI.

During the CHMP discussion of these results, it was acknowledged that, although the findings on lung function and *P. aeruginosa* suppression seemed suggestive of efficacy and did not indicate relevant differences in efficacy between TOBRAMYCIN PARI and the reference product, it was not possible to conclude whether the difference in pharmacokinetic parameters affected the efficacy of TOBRAMYCIN

PARI, because of the high variability of the results. A potential under-dosing could not be ruled out entirely, based only on the results of this study. To further support the efficacy and safety of TOBRAMYCIN PARI, the applicant also conducted a bioequivalence study in healthy volunteers (study 12012.102).

Study 12012.102

This was an open-label, single-dose, randomized, two-way crossover study to investigate the bioequivalence and compare the safety profiles following inhalation of TOBRAMYCIN PARI 170 mg/1.7 mL nebulizer solution to TOBI 300 mg/5 mL nebulizer solution. Plasma concentrations of tobramycin was analysed using a validated LC/MS/MS method.

Objectives:

The objectives of this study were to investigate the bioequivalence (in terms of relative systemic bioavailability based on pharmacokinetic plasma profiles) of TOBRAMYCIN PARI 170 mg/1.7 mL nebulizer solution as compared to TOBI300 mg/5 mL nebulizer solution in healthy subjects and to assess and compare the local and systemic safety and tolerability of the test and reference treatment.

Methods:

Bioequivalence in healthy subjects was planned to be investigated by analysing plasma concentrations of tobramycin following inhalation of TOBRAMYCIN PARI 170 mg/1.7 mL nebulizer solution and TOBI 300 mg/5 mL nebulizer solution in two treatment periods in randomized order.

Safety and tolerability were to be assessed on the basis of the following variables: adverse events, pregnancy test, vital signs, safety laboratory, drug and alcohol screening, serology, ECG, physical examination, local tolerability, and overall tolerability.

Study population:

72 healthy subjects were randomized; 69 completed the trial.

Results:

Plasma concentration versus time profiles (AUC_{0-12h}), maximum concentration (C_{max}) and time to maximum concentration (t_{max}) of the test treatment TOBRAMYCIN PARI in comparison to TOBI were determined in each period. The results are presented below:

Table 8: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for tobramycin, n=69 (Study 12012.102).

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**8237 ± 2739**	**1085 ± 407**	**4.00 1.50-8.00**
Reference	**6550 ± 1937**	**885 ± 322**	**4.00 1.00-6.02**
***Ratio (90% CI)**	**123.52 (114.64-133.08)**	**121.16 (111.32-131.87)**	**-**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum plasma concentration			

**calculated based on ln-transformed data*

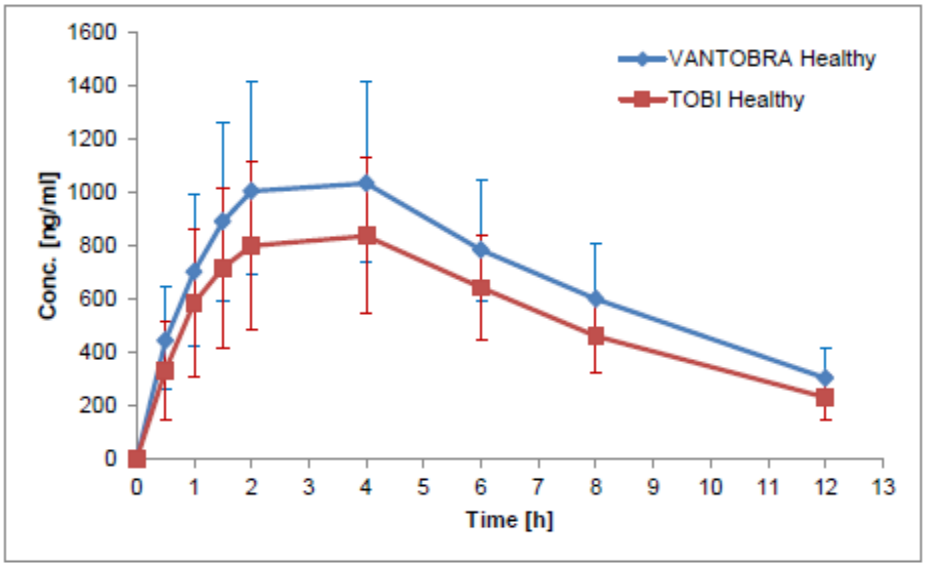


Figure 4: Mean concentration-time curves for TOBRAMYCIN PARI and TOBI in healthy volunteers, n=69 (Study 12012.12).

After single-dose administration in healthy volunteers the systemic exposure and peak concentrations of TOBRAMYCIN PARI was about 24% and 21% higher compared to TOBI and the 90% CI was outside the conventional bioequivalence limits of 80.00-125.00.

2.4.3. Pharmacodynamics

Mechanism of action

The mode of action of tobramycin is virtually the same as that of other aminoglycosides such as gentamicin. It is first actively transported across the bacterial cell membrane by an oxygen-dependent system. Hence, aminoglycosides are inactive under anaerobic conditions. Aminoglycosides primarily affect bacterial protein synthesis and result in rapid concentration-dependent killing. The molecule binds irreversibly to the A site of the 30S subunit of the bacterial ribosome where it blocks protein synthesis by inhibiting the movement of peptidyl-tRNA associated with translocation as well as increasing the frequency of misreading of the genetic code as a result of incorrect codon-anticodon interaction. The cell membrane permeability is affected, resulting in the disruption of the cell wall, and ultimately in cell death. The effect of tobramycin is bactericidal at concentrations equal to or slightly greater than inhibitory concentrations.

Primary and Secondary pharmacology

Tobramycin has a broad antibacterial spectrum including many Gram-positive species and most aerobic and facultative Gram-negative bacilli including Pseudomonas spp. The antibacterial effect of aminoglycosides correlates best with peak serum concentrations in relation to MIC (Cmax / MIC).

There is an extensive clinical experience of both intravenously administered tobramycin as well as inhaled tobramycin to patients with cystic fibrosis (CF). Local concentrations in the lungs after inhalation of tobramycin is considerably higher compared to concentrations obtained after systemic administration, leading to that conventional susceptibility breakpoints are not applicable. However, sputum from patients with CF exhibits an inhibitory action on the local biological activity of inhaled aminoglycosides. This necessitates sputum concentrations of tobramycin after inhalation to be about ten-fold above the minimum inhibitory concentration (MIC) or higher for *P. aeruginosa* suppression. The unique

characteristics of chronic *P. aeruginosa* lung 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. Tobramycin, like other aminoglycosides, is associated with renal toxicity and ototoxicity. In general, toxicity is seen at higher systemic tobramycin levels than are achievable by inhalation at the recommended clinical dose.

2.4.4. Clinical efficacy

As this is a hybrid application, the clinical efficacy data derive from the pivotal clinical study (phase 1b) performed with tobramycin 170mg in 1.7ml/eFlow (here referred to as Tobramycin PARI) in comparison to TOBI/PARI LC PLUS (here referred to as TOBI) and relevant available bibliographical data from studies performed with the reference medicinal product TOBI.

Study 12012.101

A comparative, randomized, two period, multi-centre, cross-over 14 week bioequivalence study of Tobramycin PARI versus TOBI in cystic fibrosis patients with bronchopulmonary chronic *Pseudomonas aeruginosa* infection.

Methods

Open, randomized, cross-over, multiple dose bioequivalence study (treatment phase 1: 4 weeks; wash-out phase between treatments: 4 weeks; treatment phase 2: 4 weeks).

Study Participants

58 patients were randomized:

- Patients analysed for safety: N = 58
- Patients analysed for clinical efficacy: N = 54
- Patients analysed for pharmacokinetics: N = 49

Treatments

Tobramycin PARI: One blow-fill-seal vial contained 1.7 ml preservative-free nebuliser solution with 170 mg tobramycin (aminoglycoside); nebuliser: eFlow

TOBI: One ampoule contained 5 ml preservative-free nebuliser solution with 300 mg tobramycin (aminoglycoside); nebuliser: PARI LC PLUS, with PARI Boy SX compressor.

Tobramycin was administered twice daily, in the morning and in the evening, until dryness of the nebuliser. Each treatment period was 4 weeks separated by a washout-phase of 4 weeks between periods 1 and 2. At the end of each treatment cycle, blood- and sputum-samples were collected. Blood-samples were collected pre-dose (30 - 15 min prior to inhalation), and at 30 min, 1, 1.5, 2, 4, 6, 8 and 12 h after end of inhalation. Sputum samples were collected pre-dose (30 - 15 min prior to inhalation), and at 10 min, 30 min, 1.5, 2 and 8 h after end of inhalation.

Objectives

The primary objective of this study was to determine bioequivalence of Tobramycin PARI/eFlow and TOBI/PARI LC PLUS in children and adolescents/adults (aged 7 to 13 and >13 years). In addition, the study collected some efficacy and safety data of the two medicinal products.

Outcomes/endpoints

-Primary endpoint (PK/bioequivalence)

- Plasma $AUC_{0\text{-}12h}$ area under the plasma concentration-time curve of tobramycin from the first time point [t=0] to the time point of the last measured concentration [$t_{(last)}$]

-Secondary endpoints

Efficacy:

- C_{max} and trough levels of tobramycin in plasma and sputum
- Change of Colony Forming Units (CFU) of *P. aeruginosa* (mean number of *P. aeruginosa* colony forming units (CFU) in sputum at Visit 3 compared to Visit 2 and Visit 5 compared to Visit 4, stratified into overall density and planktonic or mucoid for all age groups)
- Changes in lung function (FEV_1, FVC, $FEF_{25\text{-}75}$, PEF) at every study visit for all age groups

Safety:

- Proportion of treated lung exacerbations until end of treatment
- Audiology: voice alterations and signs of tinnitus
- Change in vital signs; number of bronchospasms
- Proportion of patients reporting ARs, by severity and by action taken
- Proportion of patients reporting SARs/SUSARs
- Proportion of patients with clinically significant laboratory value abnormalities related to the study drug
- Discontinuations due to ARs
- Bronchospasms after the end of inhalation
- Proportion of resistant *P. aeruginosa* strains with a minimal inhibitory concentration of > 4 µg/ml

others:

- Treatment compliance
- Inhalation time
- CFQ-R

Randomisation

Randomization to the treatment arms was performed centrally in a 1:1-ratio; stratification according to age (4-13 years or > 13 years) was performed in a 1:1-ratio.

Blinding (masking)

Not applicable. This was an open-label study.

Statistical methods

Clinical efficacy and safety variables were calculated using descriptive statistics and presented in tables and graphs.

Results

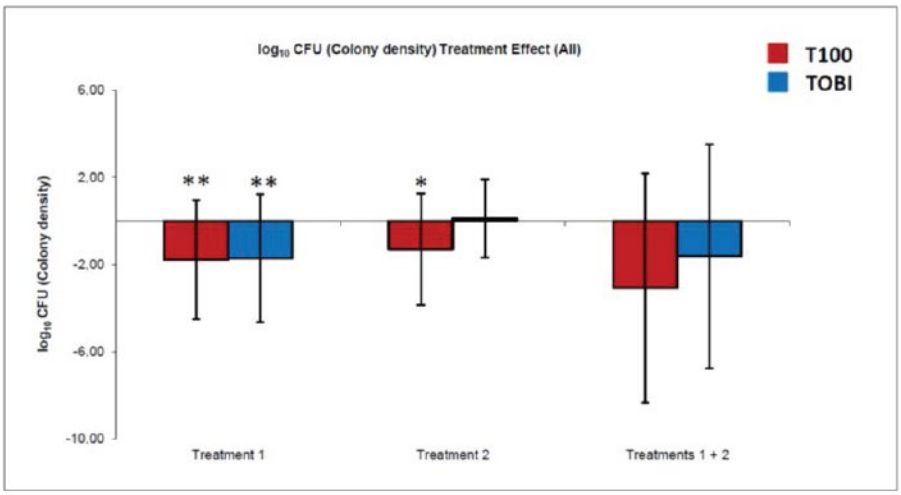
Baseline data

Table 9

	All	4 – 13 a	> 13 a
N	58	28	30
Sex			
Male [n (%)]	25 (43)	15 (54)	10 (33)
Female [n (%)]	33 (57)	13 (46)	20 (67)
Age (a)			
Mean ± SD	15.4 ± 6.81	10.0 ± 1.84	20.6 ± 5.52
Range	7 – 36	7 – 13	13 – 36
Weight (kg)			
Mean ± SD	43.3 ± 13.9	32.1 ± 9.5	53.7 ± 7.8
Range	15.0 – 72.0	15.0 – 52.0	38.7 – 72.0
Height (cm)			
Mean ± SD	152.6 ± 16.4	139.6 ± 13.5	164.6 ± 7.0
Range	113 - 182	113 - 164	151 - 182

Outcomes and estimation

The main efficacy results of this BE study are presented below:



*: p < 0.05; **: p < 0.01; ***: p < 0.001

Figure 5: Colony Forming Units (CFU): Overall reduction of PA (All); normalized on Visit 2 as Baseline

Note: in this figure, Tobramycin PARI is labelled T100.

Treatment with tobramycin resulted in an overall reduction in CFU density of *P. aeruginosa*, irrespective of the specific medicinal product/nebulizer used. In general, the treatment effect was more pronounced in the first than in the second treatment period. During the first treatment phase a similar log10 CFU reduction was achieved with Tobramycin PARI and TOBI (-1.77 ± 2.74 vs. -1.70 ± 2.93, $p < 0.005$), in the second treatment phase the reduction was -1. 30 ± 2.55 and 0.12 ± 1.78, respectively. The calculation over the complete treatment period revealed an overall reduction of PA CFU density of -3.07 ± 5.26 and -1.62 ± 5.14 for Tobramycin PARI and TOBI, respectively.

The changes in the different lung function parameters under investigation were consistently indicative for an improvement under both therapies.

The treatment effects of FEV_1 % predicted were very similar for both groups, Tobramycin PARI and TOBI, in the first treatment period. However, a positive treatment effect was also observed for Tobramycin PARI in the second treatment phase. During the first treatment phase a similar percentual increase in FEV_1 was achieved with Tobramycin PARI and TOBI (8.20 ± 9.49 vs. 24.80 ± 9.58), in the second treatment phase the change was 2.40 ± 10.64 and -0.44 ± 8.10, respectively. The calculation over the complete treatment period revealed an overall increase in FEV_1 of 10.59 ± 20.81 and 4.48 ± 18.24 for Tobramycin PARI and TOBI, respectively.

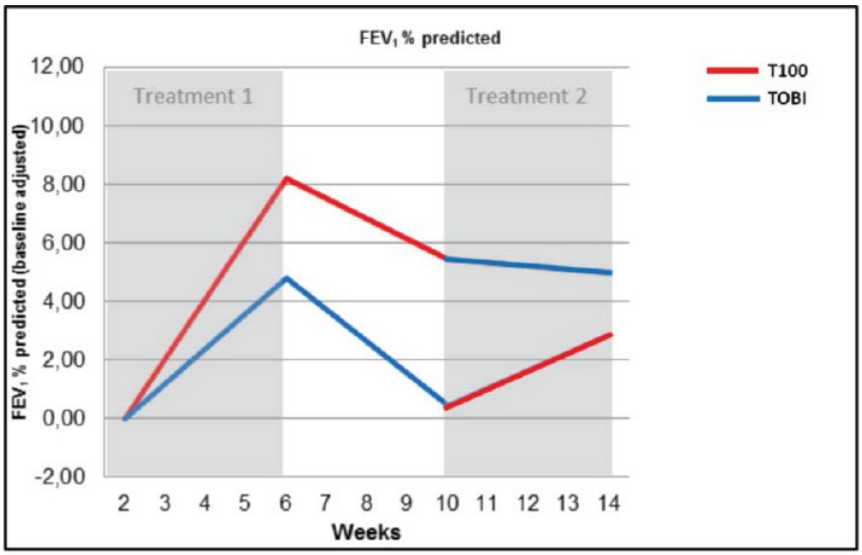
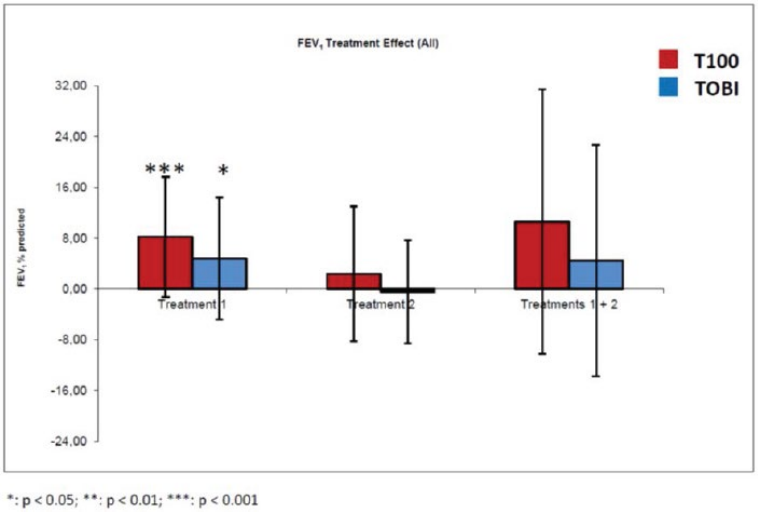


Figure 6: Time course of FEV1 % predicted (All), normalized to Visit 2 as Baseline

Note: in this figure, Tobramycin PARI is labelled T100.



*: p < 0.05; **: p < 0.01; ***: p < 0.001

Figure 7: Absolute changes in FEV1 % predicted (All), normalized to Visit 2 as Baseline

Note: in this figure, Tobramycin PARI is labelled T100.

Data for the different age categories indicate that the youngest patients (6-13 years) benefitted from both treatment regimens, irrespective of treatment cycle, while in adolescents and adults there was no improvement from TOBI when given in the second treatment cycle.

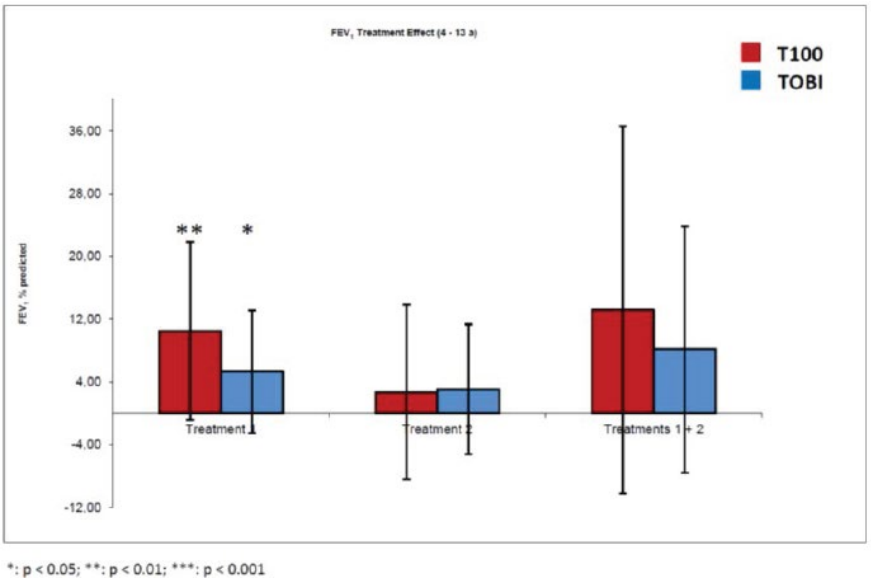


Figure 8: Absolute changes in FEV1 % predicted (6 – 13 a), normalized to Visit 2 as Baseline

Note: in this figure, Tobramycin PARI is labelled T100.

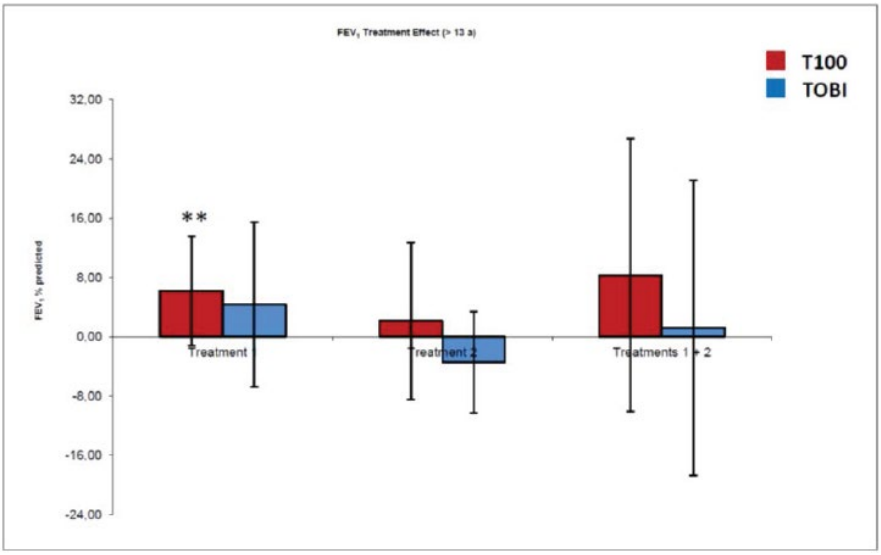


Figure 9: Absolute changes in FEV1 % predicted (>13 a), normalized to Visit 2 as Baseline

Note: in this figure, Tobramycin PARI is labelled T100.

The treatment effects of FEV_{25-75} (predicted) were very similar for both groups, Tobramycin PARI and TOBI, in the first treatment period. However, a positive treatment effect was also observed for Tobramycin PARI in the second treatment phase. During the first treatment phase a similar percentual increase in FEV_{25-75} was achieved with Tobramycin PARI and TOBI (9.15 ± 13.76 vs. 10.28 ± 14.32), in the second treatment phase the change was 2.35 ± 16.08 and -1.54 ± 15.20, respectively. The calculation over the complete treatment period revealed an overall increase in FEV_{25-75} of 11.50 ± 30.43 and 9.01 ± 31.29 for Tobramycin PARI and TOBI, respectively.

The treatment effects on the forced vital capacity (FVC) were comparable between Tobramycin PARI and TOBI. However, a positive treatment effect was also recognized in patients who received Tobramycin PARI in the second treatment phase, whereas in patients who received TOBI during the second treatment period the positive effect could not be preserved. During the first treatment phase a similar percentual increase in FVC was achieved with Tobramycin PARI and TOBI (6.53 ± 9.78 vs. 4.74 ± 11.45), in the second treatment phase the change was 0.03 ± 9.56 and -0.07 ± 6.99, respectively. The calculation over the complete treatment period revealed an overall increase in FVC of 6.56 ± 20.25 and 4.75 ± 19.40 for Tobramycin PARI and TOBI, respectively.

The treatment effects of PEF are not statistically different between the both groups Tobramycin PARI and TOBI. However, a positive treatment effect is seen in patients who received Tobramycin PARI in the second treatment phase. During the first treatment phase a similar percentual increase in PEF was achieved with Tobramycin PARI and TOBI (3.92 ± 16.60 vs. 5.44 ± 13.41), in the second treatment phase the change was 3.00 ± 12.30 and -0.95 ± 11.23, respectively. The calculation over the complete treatment period revealed an overall increase in PEF of 6.92 ± 28.96 and 4.65 ± 25.19 for Tobramycin PARI and TOBI, respectively.

2.4.5. Clinical safety

Patient Exposure

- **Exposure in healthy volunteers**

Study 12012.102 was an open-label, single-dose, randomized, two-way crossover study to investigate the bioequivalence and compare the safety profiles following inhalation of Tobramycin PARI 170 mg/1.7 mL nebulizer solution to TOBI 300 mg/5 mL nebulizer solution in 72 (69 completed) healthy subjects.

All patients who terminated the study according to protocol received a total of about 470 mg tobramycin. Three subjects, who terminated the study early, received about 300 mg tobramycin.

- **Patient exposure**

A total of 153 patients were included in the safety database from three phase 1 study populations: Study G007.03 (17 patients), Study G007.05 *Safety and bioavailability study* (78 patients) and a phase 1b study, 12012.101, *Bioequivalence as well as safety assessment of Tobramycin PARI /eFlow versus TOBI PARI LC/PLUS* (58 patients). Study 12012.101 was considered pivotal. In this study, the dose that is currently applied for, 170 mg/1.7 ml, was used. The other two studies (G007.03 and G007.05) investigated lower doses.

Study G007.03

Three of the 17 subjects (17.6%) experienced a total of 5 AEs, all of which occurred after the nebulisation of Tobramycin PARI (125 mg or 150 mg). AEs were labelled most commonly as ´mild´ (4/5 AEs 80%) and had resolved by the end of the study. According to the investigator´s assessment the causal drug-reaction relationship was ´highly probable´ for 1 AE (cough) and ´unlikely´ for 3 AEs (abdominal pain, nausea, cough).

Four other subjects experienced cough of low intensity, which was not deemed as an AE after nebulisation of Tobramycin PARI 150 mg. Bronchospasm, voice alteration, tinnitus or dyspnoea were not reported.

One serious AE of moderate intensity (allergic bronchopulmonary aspergillosis) was reported, judged 'definitely not related' to study treatment by the investigator.

Study G007.05

Of the 246 AEs reported, 179 AEs (72.8%) were considered unrelated to the study medication, whereas 67 (27.2%) were considered related and thus qualified as ADRs. In the reference group (TOBI/PARI LC PLUS), 41 of the 143 AEs (28.7%) were considered therapy-related, in the Tobramycin PARI 150 mg/eFlow group these were 26 of the 103 AEs (25.2%).

Of the 246 AEs in randomised patients, 147 (59.8%) events were of mild and 75 (30.5%) of moderate severity; 24 (9.8%) were severe. Severe AEs were more frequent in the TOBI/PARI LC PLUS group (17/143 AEs, i.e. 11.9%) compared to the Tobramycin PARI 150 mg/eFlow group (7/103 AEs, i.e. 6.8%). There were no SAEs reported in this study. Two patients treated with TOBI experienced seven respiratory AEs which were considered significant.

Study 12012.101

In this study 1.7 ml of the 100 mg/ml solution was used, i.e. 170 mg which is the dose proposed for approval of market authorisation (Tobramycin PARI). Thus the total dose is considerably lower (170 mg) compared to the reference product TOBI (300 mg). However, according to *in vitro* data, the delivered dose and the respirable doses seems to be quite similar between the two products.

Adverse events

Healthy subjects

Safety assessment amongst Tobramycin PARI and TOBI using eFlow and PARI LC PLUS devices, respectively, was considered as secondary endpoint in the bioequivalence study in healthy volunteers (12012.102).

In total, 70 adverse events (AEs) were reported in 49 out of 72 patients (68.1%). Reported AEs were generally mild in intensity and distributed into the System Organ Class (SOC) "respiratory, thoracic and mediastinal disorders" and "nervous system disorders". The most frequent AEs for Tobramycin PARI were reported from the SOC respiratory, thoracic and mediastinal disorders (25 events in 22 subjects), the most frequently reported preferred term was "cough", reported from 17 subjects. The most frequent AEs for TOBI were reported from the SOC nervous system disorders with preferred term "headache" (11 events in 10 subjects). All other SOC were reported with a frequency of five or less events with a similar rate between the treatment groups.

Of the 70 AEs, 16 (22.9%) were rated as not related and 54 (77.1%) were rated as related with tobramycin inhalation. The distribution of related events over the treatment groups was 64.8% (Tobramycin PARI) and 35.2% (TOBI). Reported AEs were generally mild in intensity. Events were categorized as mild in 92.7% and 65.5%, moderate in 7.3% and 27.6%, and severe in 0% and 6.9% for Tobramycin PARI and TOBI, respectively.

CF Patients

As expected from active ingredient properties AEs were mainly represented by respiratory, thoracic and mediastinal disorders. Overall, 76 adverse events were reported in 29 patients (50 % of all patients) of the safety population under investigation (n = 58). 29 patients experienced no AEs. Three AEs were severe in intensity, and all others were classified to be mild to moderate. 32 adverse events (approx. 42% of all AEs) were considered to be related to the study drug, i.e. they were defined as ADRs. All of them were classified as mild to moderate in intensity.

There were no clinically relevant pre- vs. end-of-study changes in vital signs. Neither were there any pre- vs. end-of-study changes in physical examination observed.

Bronchospasms as defined in the protocol occurred only in 2 patients under TOBI (3.4% of the patients) and were considered by the investigator as an ADR.

Audiology testing revealed two cases of tinnitus in patients under Tobramycin PARI treatment (3.4% of all patients). Both cases were mild in severity and transient as resolving shortly after inhalation. One patient in the Tobramycin PARI group showed pathological signs in pure tone audiometry measured by bone connectivity (highest value for left ear at 2 KHz was 35 dB).

Pulmonary exacerbation was observed in one patient (1109) only during the wash-out phase after TOBI treatment. This patient required treatment with antibiotics which were prohibited as per study protocol and thus was withdrawn from further study participation.

Investigations on the occurrence of resistant *P. aeruginosa* revealed only inconclusive results as cultures of sputum samples showed no growth of the pathogen in approx. half of the assays.

Analysis of the CFQ-R revealed only inconclusive results. Neither relevant differences nor even trends were found between the treatment groups or age strata.

The time per inhalation was markedly reduced in the drug/device combination of Tobramycin PARI / eFlow (mean: 4.4 min) as compared to the combination TOBI / PARI LC PLUS (mean: 24.3 min).

Compliance to therapy of the patients was generally high in both groups with 99% for Tobramycin PARI patients (as recorded by an electronic Monitoring System of the device) and 99% for TOBI patients (as recorded in patient diaries).

Serious adverse event/deaths/other significant events

In study 12012.102 in healthy volunteers, no death occurred during the study. One serious adverse event (SAE) occurred in the current study (ankle fracture), considered as not related to study drug.

In total, five SAEs due to hospitalization occurred in 4 CF patients during the washout period; however, none of them was considered drug-related. No fatality was observed.

Laboratory findings

Six events were described as clinically relevant increases in laboratory values (4 in one patient, who discontinued TOBI-treatment and increase of LDH in another two patients, one patient in the Tobramycin PARI, one patient in the TOBI group, both continued the treatment). All of those abnormal parameters were recorded as AEs, i.e. none of these were drug related. All other changes of laboratory values outside of the normal range were assessed by the investigators as "not clinically significant".

Safety in special populations

The study was performed in patients aged 7-36 years of age, mean age 15 years. This represents the target population. In study 12012.101 the number of AEs in the age stratum 6-13 years was twice as frequent as in the stratum group >13 years (40 vs. 19 events), but the system organ class (SOC) pattern was similar between the age strata.

Discontinuation due to adverse events

In study 12012.102 in healthy volunteers, two subjects of the total of 72 subjects in the safety population terminated the study early because of a SAE (ankle fracture and common cold). Among studies in CF patients, in no case study medication had to be discontinued temporarily or permanently due to an ADR.

There were 5 serious adverse events (SAEs) recorded in 4 patients; the reason for seriousness was hospitalisation in all cases. None of the SAEs was drug-related.

Post marketing experience

No new safety concerns have arisen in the post-marketing period since VANTOBRA, for which this marketing authorisation application is a duplicate, was authorised in 2015, according to the most recent PSUR (EMEA/H/C/PSUSA/00010370/201803). The number of patients exposed to VANTOBRA is estimated by the MAH at 227 person-years up to 18-March 2018 (note that VANTOBRA has been introduced after different intervals and with different market shares in 6 countries; Germany, Austria, Italy, United Kingdom, the Netherlands and Greece).

Since VANTOBRA was authorised, published data identified by routine EMA signal detection activities have identified possible antagonism arising with combinations of oral azithromycin and inhaled tobramycin (Nick *et al.*, 2014; Nichols 2015; Nichols *et al.* 2017;). While some *in vitro* data offer a potential theoretical / mechanistic support for this potential interaction, the published clinical data carry several limitations that hinder conclusive interpretation, and PRAC ultimately determined that there is not sufficient evidence of an interaction at this time (PRAC 2017, EMEA/H/C/0002155/SDA/032). A planned, prospective clinical trial will test the impact of adding azithromycin to inhaled tobramycin in CF patients with chronic *P. aeruginosa* infection (ClinicalTrials.gov NCT02677701; expected completion 2019), which will further inform the need to update the product information and/or risk management measures for relevant products, including Tobramycin PARI.

2.4.6. Discussion on clinical aspects

Pharmacokinetics

The main objective was to analyse the bioequivalence between TOBRAMYCIN PARI and TOBI in order to bridge to the efficacy and safety data obtained with TOBI. In the pivotal bioequivalence study (Study 12012.101), the administration of TOBRAMYCIN PARI and TOBI was compared in CF patients. The results showed slightly lower systemic exposure (15% lower) with TOBRAMYCIN PARI compared to TOBI. In order to further support the efficacy profile evaluation of TOBRAMYCIN PARI, an additional bioequivalence study in healthy subjects (Study 12012.102) was conducted. In this study the systemic exposure of TOBRAMYCIN PARI was, on the contrary, slightly higher compared to TOBI.

Discussion of the design of the studies

Study 12012.101 was conducted in CF patients and had a multiple-dose cross-over design where plasma and sputum samples were analysed on day 28 in each period. For immediate release products it is usually recommended to evaluate bioequivalence after single-dose administration since a multiple-dose study is less sensitive to detect differences in Cmax due to accumulation. Given the relatively short half-life of tobramycin (2-3 h), the risk of accumulation is however minor and the choice of sampling at day 28 is acceptable. Almost half of the subjects (46%) reached tmax at the first sampling point (30 min), indicating that a more frequent early sampling would have been recommendable. Hence there are uncertainties in the estimation of Cmax. Inhalation of a larger volume for a longer time period, as for TOBI, might lead to larger volumes of sputum. The total amount of tobramycin in sputum could therefore have been additionally measured. Sputum samples are hence a mixture of sputum ranging from the upper respiratory tract to deeper parts of the lungs. It is therefore difficult to draw firm conclusions about the clinical relevance of the possibly higher tobramycin concentration found in sputum after administration of TOBRAMYCIN PARI.

Study 12012.102 was a well-designed single-dose study in healthy volunteers.

In both studies, TOBI (300 mg/5 ml) was used as comparator. The bioanalytical methods for determination of tobramycin in plasma and sputum were adequately validated.

Discussion of the results

The absorption of tobramycin was faster in patients compared to healthy volunteers with a median t_{max} of 1 h and 4 h, respectively. The overall systemic exposure also appeared to be lower in patients (between-study comparison). In CF patients the systemic exposure was slightly lower with TOBRAMYCIN PARI while in healthy subjects the systemic exposure was slightly higher with TOBRAMYCIN PARI compared to TOBI.

According to the guideline on the requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD) in adults and for use in the treatment of asthma in children and adolescents (CPMP/EWP/4151/00 Rev. 1), pharmacokinetic data could be used as a surrogate of pulmonary deposition, and hence efficacy, for an orally inhaled product used in the treatment of asthma and COPD, under the condition that gastro-intestinal absorption is negligible or blocked by charcoal. Since tobramycin is not absorbed from the gastrointestinal tract following oral administration the systemic exposure after inhalation is expected to result primarily from the pulmonary absorbed portion of the dose. However, given the disease-associated effects on the airways including presence of mucous in patients with CF the situation is more complex. In CF patients, the relationship between plasma exposure and pulmonary deposition is therefore not obvious and the use of PK-data as a surrogate of efficacy may be questioned in this patient population. However, the results from the pharmacokinetic study in healthy volunteers provide useful complementary information about the in vivo performance of TOBRAMYCIN PARI, avoiding the bias in CF patients, which have a heterogeneous and variable obstruction.

In patients the exposure was approximately 15% lower after administration of TOBRAMYCIN PARI compared to TOBI while in healthy subjects the exposure was approximately 24% higher with TOBRAMYCIN PARI than with TOBI.

The lower systemic exposure in CF patients did however raise questions pertaining to the fact that less tobramycin could have reached the lungs and that TOBRAMYCIN PARI might have been less efficacious compared to TOBI. However, in healthy subjects the airways are not affected by mucous etc. and the systemic exposure is therefore expected to better reflect pulmonary deposition. The higher systemic exposure obtained with TOBRAMYCIN PARI compared to TOBI in healthy volunteers does therefore indicate that the amount of tobramycin deposited in the lung was not lower, but actually slightly higher with TOBRAMYCIN PARI in comparison to TOBI. A higher pulmonary deposition is relevant from an efficacy point of view and the efficacy of TOBRAMYCIN PARI is thus expected to be comparable with that of TOBI. Although the evaluation of sputum concentration had some limitations, the higher sputum concentrations obtained with TOBRAMYCIN PARI compared to TOBI is indicative of a somewhat higher lung deposition.

It is concluded that the overall results of the in vitro characterisation and the pharmacokinetic studies show that despite the fact that TOBRAMYCIN PARI was not completely equivalent to TOBI, the *in vivo* differences were rather small and are not expected to impact on the efficacy or safety of TOBRAMYCIN PARI. Furthermore, the clinical efficacy data in CF patients, although limited, did not indicate clear differences between the two medicinal products.

Pharmacodynamics

The mechanism of action and mechanisms of resistance of tobramycin are well known and there is an extensive clinical experience of both intravenously administered tobramycin as well as inhaled tobramycin to patients with CF.

Local concentrations in the lungs after inhalation of tobramycin is considerably higher compared to concentrations obtained after systemic administration, leading to fact that conventional susceptibility

breakpoints are not applicable. However, sputum from patients with CF exhibits an inhibitory action on the local biological activity of inhaled aminoglycosides. This necessitates sputum concentrations of tobramycin after inhalation to be about ten-fold above the minimum inhibitory concentration (MIC) or higher for *P. aeruginosa* suppression. The unique characteristics of chronic *P. aeruginosa* lung 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 thorough data on susceptibility to tobramycin of the *P. aeruginosa* strains isolated during the study period was submitted. The limited information regarding susceptibility to tobramycin is acceptable for this hybrid application. The pharmacodynamic properties of tobramycin are well known and no further studies are needed.

Clinical efficacy

The main differences between the two medicinal products are the concentration and total amount of inhaled tobramycin, related to different inhalation device systems. Efficacy data were primarily derived from the comparative, randomized, open-label, two bioequivalence study 12012.101, in which clinical efficacy was collected as a secondary endpoint.

Design and conduct of clinical studies

The pivotal study was designed in accordance with protocol assistance from the CHMP to analyse the bioequivalence between Tobramycin PARI and TOBI. Of note, the study was not designed or powered for efficacy endpoints, which were secondary endpoints.

The open-label design was deemed acceptable, because the differences in nebulisers used for both treatments complicated a double-blind design.

The included participants (not treatment-naïve) can largely be regarded representative for the target population.

The youngest patient included was 7 years old. TOBI is the current "gold standard" in the inhalational therapy for management of pulmonary infections in CF and, therefore, an adequate comparator. The measured secondary efficacy endpoints (clinical: lung function parameters FEV_1 %, FVC, FEV_{25-75}, PEF; microbiological: *P. aeruginosa* suppression) were considered relevant and in accordance with recommendations in the CHMP CF guideline (CHMP/EWP/9147/2008). According to the report of a recent workshop on endpoints for cystic fibrosis clinical trials (EMA/69571/2012) lung function parameters, in particular FEV1, are recommended as the core outcome parameters. Microbiology outcome should focus on CFU/g in respiratory samples and should be regarded as supportive, but it is stressed that microbiological impact generally does not predict the clinical response or magnitude of response.

Efficacy data and additional analyses

No large drop-out rates were observed and compliance was high for both treatments. No large differences were observed at baseline for both groups. Overall, the observed treatment effects of Tobramycin PARI were supportive of efficacy. For both products a significant improvement of lung function relative to baseline was observed. This effect was, furthermore, consistent over the various parameters, as well as with the observed decrease in *P. aeruginosa* CFU. Although there was a large variability in the data as apparent from the large standard deviations (also due to the small numbers), the improvement seemed slightly more pronounced for Tobramycin PARI treatment. Despite the fact that the treatment effect diminished during the treatment phase 2, the treatment effect with Tobramycin PARI still seemed beneficial, while a reduction in lung function was observed with TOBI, in particular in participants >13 years. Because of the small sample size, the relevance of these findings cannot be fully concluded upon. It may be speculated that the lack of efficacy in adolescents and adult patients receiving TOBI in the

second cycle, may be due to compliance issues, considering the longer administration time compared to the previous treatment in this subgroup with Tobramycin PARI. Although compliance was recorded as high in both groups, the figures reported for TOBI may not be fully reliable, considering that they were only reported in patients' diaries. The available data indicate that the clinical efficacy of Tobramycin PARI is comparable with that of TOBI, notwithstanding that some differences between Tobramycin PARI and TOBI with regard to effect on lung function and *P. aeruginosa* suppression could still exist, provided results from the Patient Reported Outcome (PRO) records did not provide divergent results.

Clinical safety

Safety data were available from all four conducted clinical studies. However, study 12012.102 was performed in healthy subjects and only study 12012.101 provided safety data obtained from patients exposed to the proposed dose.

Overall, study 12012.102 did not detect any events justifying safety concerns in healthy volunteers. No signs of local intolerability (paradoxical bronchospasm) were recorded after administration of both tobramycin products.

The results from study 12012.101 showed that the systemic exposure of tobramycin is lower after administration of Tobramycin PARI/eFlow compared TOBI/PARI LC PLUS. Thus, the systemic safety of Tobramycin PARI is not expected to be different or worse than for TOBI and is therefore reassuring.

The most frequent observed drug-related AEs were in the respiratory, thoracic and mediastinal system organ classes, with cough being most frequently reported. No unexpected safety issues, including laboratory findings, were identified in the safety population in the different studies. The observed safety profile was largely similar for both treatment groups, although a slightly higher frequency of drug-related AEs were observed for Tobramycin PARI compared to TOBI, but because of the small size of the safety population, this cannot be fully concluded upon.

Special attention was aimed at the audiometry assessment, but no evidence was found indicating that patients treated with Tobramycin PARI were at higher risk for alterations due to higher local drug concentrations that derive from higher strength of the tobramycin concentration in Tobramycin PARI or the enhanced drug delivery rate using the Tolero device. No safety signals could be observed which where indicative for effects resulting from faster drug delivery.

Inhaled tobramycin is widely used in CF patients and has a well-known safety profile and quality and PK assessment did not indicate any relevant findings that might affect safety. However, the small safety population due to small sample sizes of the various studies and differences in the doses of the investigational product patients were exposed to complicate interpretation and determination of the relevance of the observed AEs. Since the safety profile of nebulised tobramycin for inhalation is well-known, the first PSUR for Tobramycin PARI should be submitted in accordance to the frequency listed in the EURD list for tobramycin nebuliser solution.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

2.4.7. Conclusions on clinical aspects

The pharmacodynamic properties of tobramycin are well known and no further studies are needed.

The target site for inhaled tobramycin is the lungs where the active substance exerts its effect. Systemic absorption is not desirable, low systemic exposure reduces the potential for systemic toxicity. Given that the oral bioavailability of tobramycin is negligible, the systemic exposure will primarily result from pulmonary absorbed tobramycin.

The pharmacokinetics of TOBRAMYCIN PARI/eFlow has been evaluated in four comparative studies with TOBI/PARI LC PLUS as reference. In the first two studies a lower dose than the proposed to be marketed dose was given and these are only considered as explorative.

The overall results of the *in vitro* characterisation and the pharmacokinetic studies show that TOBRAMYCIN PARI is not behaving exactly in the same way as TOBI. However, the *in vivo* differences were rather small and are not expected to have an impact either on efficacy or on safety.

Pharmacokinetic data provided showed a slightly higher lung deposition of Tobramycin PARI compared to TOBI. A higher pulmonary deposition is expected to be beneficial from an efficacy point of view and Tobramycin PARI is thus expected to be at least as efficacious as TOBI. In the pivotal study in patients (12012.101) the observed treatment effects were overall favourable without clear differences between the products. For both products, a significant improvement of the lung function relative to baseline was observed for the first treatment phase. This effect was consistent over the various parameters (FEV_1 %, FVC, FEV_{25-75}, PEF), as well as with the observed decrease in *P. aeruginosa* CFU. The treatment effect of Tobramycin PARI was beneficial in terms of the lung function, in particular during the second treatment period.

Studies 101 and 102 constitute a relevant bridge for safety and efficacy between Tobramycin PARI and TOBI in patients 6 years and older with chronic *Pseudomonas aeruginosa* lung infection and cystic fibrosis. The safety findings of the submitted studies support this conclusion. Available data generated from the submitted studies indicate a similar safety profile as for the reference product in the general CF population. AE reported are mainly associated with drug administration, primarily respiratory, thoracic and mediastinal disorders.

2.5. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Nephrotoxicity Ototoxicity
Missing information	Use during pregnancy or lactation

Pharmacovigilance plan

No additional pharmacovigilance activities are planned.

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important potential risks		
Nephrotoxicity	- SmPC section 4.4 - SmPC section 4.5 - SmPC section 4.6 - SmPC section 4.8 - SmPC section 4.9 - SmPC section 5.3	Routine PV activities
Ototoxicity	- SmPC section 4.4 - SmPC section 4.5 - SmPC section 4.6 - SmPC section 4.8 - SmPC section 4.9 - SmPC section 5.3	Routine PV activities
Missing information		
Use during pregnancy or lactation	SmPC section 4.6	Routine PV activities; Follow-up questionnaires

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.3 is acceptable.

2.6. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal. The EURD list entry on tobramycin (nebuliser solution) (centrally authorised product only) - 1 year cycle will be followed by analogy.

2.7. Product information

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Vantobra 170 mg nebuliser solution. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a hybrid version of tobramycin nebuliser solution (170 mg /1.7 mL). The reference product TOBI is indicated for suppressive therapy of chronic pulmonary infection due to Pseudomonas aeruginosa in adults and children aged 6 years and older with cystic fibrosis.

Nonclinical studies have not been provided for this application and the literature review is considered sufficient. Pharmacodynamic, pharmacokinetic and toxicological properties of the active substance tobramycin are well known.

The submitted clinical package composed of PK, efficacy and safety data generated by the performed studies comparing Tobramycin PARI with the reference product TOBI as well as literature references, is considered to constitute a relevant bridge between Tobramycin PARI and the reference product TOBI, for which preclinical and clinical trial data are available. Efficacy and safety data for TOBI can therefore be extrapolated to Tobramycin PARI.

With its well-established anti-pseudomonal activity, inhaled tobramycin is a well-known, widely used antibiotic for the treatment of pulmonary infections caused by *P. aeruginosa* in patients suffering from CF.

The changes in the strength of the formulation proposed for Tobramycin PARI and the new nebuliser used (Tolero/eFlow) have resulted in a substantial decrease in inhalation time compared to the use of TOBI (approximately 4–5 minutes vs. 14 – 18 min, respectively) through reduction of the volume of tobramycin solution that needs to be nebulised and by more rapid and efficient nebulisation using a new technology with a perforated vibrating membrane. This is considered to have an important impact on patient care.

In the pivotal bioequivalence study (Study 12012.101), the administration of TOBRAMYCIN PARI and TOBI was compared in CF patients. The bioequivalence study forms the basis together with an open, randomized, cross-over, multiple dose bioequivalence study with healthy volunteers (study -201). The study designs were considered adequate to evaluate the bioequivalence of this formulation and were in line with the respective European requirements.

Although the test formulation of Tobramycin PARI did not meet the protocol-defined criteria for bioequivalence when compared with Tobi, the study results demonstrate only small *in vivo* differences

In vitro, Tobramycin PARI has shown to have a narrower size distribution of droplets compared to the broader distribution for TOBI/PARI LC PLUS and a slightly lower mean mass-related medial aerodynamic diameter, MMAD (3.8 and 4.5 µm, respectively) in drug mass distribution measurements with impactor stages.

The different particles size distribution is reflected in the conducted pharmacokinetic studies. In healthy subjects a slightly higher systemic exposure was observed with Tobramycin PARI compared to TOBI which is an indication of a higher lung deposition of tobramycin with Tobramycin PARI in comparison to TOBI. A higher lung deposition is considered relevant from an efficacy point of view and the efficacy profile of Tobramycin PARI is deemed to be comparable to that of TOBI.

The overall results of the in vitro characterisation and the pharmacokinetic studies show that despite the fact that Tobramycin PARI was not completely equivalent to TOBI, the *in vivo* differences were rather small and are not expected to impact on the efficacy or safety of Tobramycin PARI.

Although in the pivotal BE study conducted in CF patients the evaluation of efficacy was a secondary objective, the observed treatment effects were overall beneficial, without clear differences between Tobramycin PARI and TOBI. For both products, a significant improvement of lung function relative to baseline was observed for the first treatment phase. This effect was consistent over the various parameters (FEV1 %, FVC, FEV25-75, PEF), as well as with the observed decrease in *P. aeruginosa* CFU. Generally, Tobramycin PARI was shown to be beneficial, in particular during the second treatment period.

Long-term use of inhaled antibiotics in the management of chronic *P. aeruginosa* pulmonary infections in CF patients is associated with selection of resistant *P. aeruginosa* strains. The submitted deposition data did not fully elucidate how Tobramycin PARI was distributed in the lungs. An uneven distribution may carry the risk that not everywhere in the lungs sufficient anti-Pseudomonal activity can be acquired, potentially inducing resistance. Requirement to monitor for resistance is mentioned in the SmPC (section 4.4.)

Available data generated from the submitted studies indicate a similar safety profile as for the reference product in the general CF population. AE reported are mainly associated with drug administration, primarily respiratory, thoracic and mediastinal disorders.

Special attention was aimed at audiometry assessment, but no evidence was found indicating that patients treated with Tobramycin PARI were at higher risk for alterations due to higher local drug concentrations that derive from higher strength of the tobramycin concentration in Tobramycin PARI or the enhanced drug delivery rate using the eFlow device. No safety signals could be observed which were indicative for effects resulting from faster drug delivery. Potential for ototoxicity and nephrotoxicity are identified as important potential risks and subject to routine pharmacovigilance measures.

Benefit-risk assessment and discussion

Tobramycin nebulisation is presently the current "gold standard" in the management of chronic bronchopulmonary infections caused by *P. aeruginosa* in CF patients. The long inhalation time associated with nebulisation is a burden for patients, in particular since they require long-term treatment. Therefore, a shortened inhalation time for the tobramycin nebulisation (as is the case for Tobramycin PARI), making it comparable to the time needed for dry powder inhalation is beneficial to patients. It may improve the user convenience and its therapy adherence and thus clinical efficacy.

Inhaled tobramycin is a widely used medicinal product with a well characterised safety profile and the quality and PK data generated did not indicate any relevant findings that might affect safety.

Conclusions

The overall B/R of Tobramycin PARI is positive in the proposed indication.

Similarity assessment

Reference is made to Appendix 1 of this report, outlining the similarity assessment in greater detail.

The existence of orphan market exclusivity for TOBI Podhaler would normally prevent the granting of a Marketing Authorisation for Tobramycin PARI in the therapeutic indication of "management of chronic pulmonary infection due to *Pseudomonas aeruginosa* in patients aged 6 years and older with cystic fibrosis (CF)".

The applicant relies on one of the derogations foreseen in Article 8(3) of Regulation (EC) No 141/2000 in order to be authorised. Pursuant to Article 8 of Regulation (EC) No. 141/2000, the applicant submitted a claim addressing the following derogation laid down in Article 8.3 of the same Regulation; the holder of the marketing authorisation for the original orphan medicinal product has given consent to the applicant. Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for TOBI Podhaler in the treatment of *Pseudomonas aeruginosa* lung infection in cystic fibrosis, does not preclude the granting of the marketing authorisation of Tobramycin PARI.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Tobramycin PARI is favourable in the following indication:

Tobramycin PARI is indicated for the management of chronic pulmonary infection due to Pseudomonas aeruginosa in patients aged 6 years and older with cystic fibrosis (CF).
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

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

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

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

Not applicable.