22 January 2015
EMA/86872/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

VANTOBRA

International non-proprietary name: tobramycin

Procedure No. EMEA/H/C/002633/0000

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

List of abbreviations

ACT	Anatomical, chemical, therapeutical (WHO code for medicinal products)
AE(s)	Adverse event(s)
AR	Adverse reaction
AUC	Area under the curve
BE	Bioequivalence
BID/b.i.d.	bis in die=twice a day
CEP	Certificate of Suitability
CF	Cystic fibrosis
CFTR	Cystic fibrosis transmembrane conductance regulator
CI	Confidence interval
C_0	Trough level
C_{max}	Maximal tobramycin concentration
C_{min}	Minimal (trough plasma) concentration
CRO	Contract research organization
CV	Coefficient of variation [in %]
DD	Delivered dose
DDR	Drug delivery rate
EDQM	European Directorate for the Quality of Medicines
e.g.	Exempli gratia (for example)
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FEV_1	Forced expiratory volume in one second
$FEV_{25/75}$	Forced expiratory flow at the midportion (25-75%) of vital capacity
FVC	Forced vital capacity
GCP	Good Clinical Practice
GSD	Geometric standard deviation
HPLC	High-performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (USA, Europe, Japan)
i.e.	id est (that is)
IMP(D)	Investigational Medicinal Product (Dossier)
ITT	Intent-to-Treat
IV	Intravenous
LC	Liquid chromatography
LD50	Lethal dose for 50% of the population
LDH	Lactose dehydrogenase
LDL	Low density lipoprotein
LLoQ	Lower limit of quantitation
MAA	Marketing authorization application
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MIC	Minimal inhibitory concentration
mL	Milliliter
MMAD	Mass median aerodynamic diameter
MS	Mass spectrometry
N/n	Number/frequency
n.a. or N/A	Not applicable
PA	*Pseudomonas aeruginosa*
PBT	Persistence, bioaccumulation and toxicity
PEC	Predicted environmental concentration
PEF	Peak expiratory flow
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PP	Per protocol
PP	Polypropylene
PT	Preferred term
RD	Respirable dose
RF	Respirable fraction
SAE	Serious adverse event
SAR(s)	Serious adverse reaction(s)

SmPC	Summary of product characteristics
SOC	System Organ Class
SUSAR(s)	Suspected unexpected serious adverse reaction(s)
$T_{1/2}$	Half-life
T_{max}	Time until Cmax is reached
TOBI	TOBI(Novartis), Tobramycin 300 mg/5 ml nebuliser solution

1. Background information on the procedure

1.1. Submission of the dossier

The applicant PARI Pharma GmbH submitted on 26 July 2012 an application for a Marketing Authorisation to the European Medicines Agency (EMA) for VANTOBRA, through the centralised procedure, falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 September 2011.

The applicant initially applied for the following indication:

- VANTOBRA is indicated for the long-term treatment of chronic pulmonary infection due to *Pseudomonas aeruginosa* in patients aged 6 years and older with cystic fibrosis. Consideration should be given to official guidance on the appropriate use of antibacterial agents.

On 23 August 2013, at the time of submission of the responses to the D120 List of Questions, the Applicant changed the indication applied for to:

- VANTOBRA is indicated for the long-term treatment of chronic pulmonary infection due to *Pseudomonas aeruginosa* in patients aged 6 years and older with cystic fibrosis (CF) who do not tolerate or are physically unable to manage tobramycin dry powder inhalation. Consideration should be given to official guidance on the appropriate use of antibacterial agents.

On 28 March 2014 this proposed indication was further changed by the Applicant to:

- VANTOBRA is indicated for the long-term treatment of chronic pulmonary infection due to *Pseudomonas aeruginosa* in patients aged 6 years and older with cystic fibrosis (CF) who cannot use tobramycin dry powder inhalation due to intolerance. Consideration should be given to official guidance on the appropriate use of antibacterial agents.

On 15 April 2014 the proposed indication was further changed by the Applicant to:

- VANTOBRA is indicated for the suppressive therapy of chronic pulmonary infection due to Pseudomonas aeruginosa in patients aged 6 years and older with cystic fibrosis (CF) who cannot use tobramycin dry powder inhalation due to intolerance. Consideration should be given to official guidance on the appropriate use of antibacterial agents.

On 24 April 2014, the final proposed indication was agreed with the CHMP:

- VANTOBRA is indicated for the management of chronic pulmonary infection due to Pseudomonas aeruginosa in patients aged 6 years and older with cystic fibrosis (CF) who cannot use tobramycin dry powder inhalation due to intolerance. Consideration should be given to official guidance on the appropriate use of antibacterial agents.

During the decision-making phase, the European Commission raised concerns with regard to the interpretation of the orphan legislation provisions on similarity.

On 25 September 2014, the CHMP agreed to re-assess the Similarity Assessment Report for VANTOBRA vis-à-vis authorised orphan medicinal products.

On 20 November 2014, the CHMP adopted a similarity assessment based on the indication last applied by the applicant on 24 April 2014.

- VANTOBRA is indicated for the management of chronic pulmonary infection due to Pseudomonas aeruginosa in patients aged 6 years and older with cystic fibrosis (CF) who cannot use tobramycin

dry powder inhalation due to intolerance. Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Since the proposed mode of action, molecular structure and therapeutic indication were the same as those for the approved orphan medicinal product TOBI Podhaler, the CHMP concluded that VANTOBRA was similar to TOBI Podhaler and that the applicant would have to rely on at least one of the derogations foreseen in Article 8(3) of Regulation (EC) No 141/2000 in order to be authorised.

On 28 November 2014, the Applicant changed the proposed indication to:

- VANTOBRA 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 legal basis for this application refers to:

Article 10(3) of Directive 2001/83/EC, as amended – relating to applications for hybrid medicinal products.

The application submitted is composed of administrative information, complete quality data, some non-clinical tests (*in vitro* aerosol characterisation), clinical studies (2 bioequivalence studies with the reference medicinal product TOBI, one in healthy volunteers and one in cystic fibrosis patients), additional supportive clinical data (pulmonary deposition study, safety and efficacy data generated in the BE study in patients and a series of narratives from patients who were switched from tobramycin dry powder inhalation to tobramycin solution for inhalation due to intolerance), and supportive bibliographic literature.

Information on Paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant submitted a critical report addressing the possible similarity with authorised orphan medicinal products. An updated report was submitted to reflect the applicant's new proposed indication for VANTOBRA during the procedure.

Derogation from market exclusivity

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant submitted a claim addressing the following derogation laid down in Article 8(3) of Regulation (EC) No141/2000: the applicant can establish in the application that the medicinal product, although similar to the orphan medicinal product already authorised, is safer, more effective or otherwise clinically superior. An updated report was submitted to reflect the applicant's revised claims, in line with the final proposed indication for VANTOBRA.

Protocol Assistance

The applicant received Protocol Assistance from the CHMP on 3 December 2009 and 24 June 2010. The Protocol Assistance pertained to the clinical aspects of the dossier.

Licensing status

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

1.2. Manufacturers

Manufacturer responsible for batch release

PARI Pharma GmbH
Lochhamer Schlag 21
82166 Graefelfing
Germany

1.3. Steps taken for the assessment of the product

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

Rapporteur: Kristina Dunder Co-Rapporteur: Pieter de Graeff

CHMP Peer reviewer: Karsten Bruins Slot

- The application was received by the EMA on 20 July 2012.
- The procedure started on 24 October 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 January 2013. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 11 January 2013.
- VANTOBRA PRAC RMP Advice and assessment overview was adopted by PRAC on 7 Feburary 2013.
- During the meeting on 21 February 2013, the CHMP agreed on the consolidated List of Questions and derogation assessment report to be sent to the applicant. The consolidated List of Questions and derogation assessment report were sent to the applicant on 22 February 2013.
- The applicant's requests for clock stop extension were received 19 March 2013 and 17 May 2013; both were agreed by CHMP on 21 March 2013 and 30 May 2013.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 23 August 2013.

  The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the consolidated List of Questions to all CHMP members on 24 September 2013.
- PRAC Rapporteur's Risk Management Plan Assessment Report was endorsed by PRAC on 10 October 2013.
- During the CHMP meeting on 24 October 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 17 February

2014 and requested an oral explanation before the CHMP in March 2014.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 28 February 2014.
- PRAC Rapporteur's Risk Management Plan (RMP) Assessment Report was endorsed by PRAC on 6 March 2014.
- During the CHMP meeting on 20 March 2014, no oral explanation took place in front of the CHMP and a second list of outstanding agreed upon by the CHMP.
- The Rapporteurs circulated the Assessment Report on similarity to all CHMP members on 21 March 2014.
- The applicant submitted the responses to the CHMP Second List of Outstanding Issues on 31 March 2014.
- List of questions on similarity was adopted by CHMP via written procedure on 2 April 2014.
- The applicant submitted the responses to the CHMP List of questions on similarity on 8 April 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the second List of Outstanding Issues and the list of questions on similarity to all CHMP members respectively on 9 April 2014 and 11 April 2014.
- During the CHMP meeting on 25 April 2014 the CHMP agreed on a third list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP third List of Outstanding Issues on 5 May 2014 and a request for oral explanation.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the third List of Outstanding Issues to all CHMP members on 8 May 2014.
- During the CHMP meeting on 21 May 2014, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- The CHMP adopted a report on similarity of VANTOBRA with authorised orphan medicinal products via written procedure on 2 June 2014.
- On 2 June 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion via written procedure for granting a Marketing Authorisation to VANTOBRA.
- The CHMP re-adopted a report on similarity of VANTOBRA with authorised orphan medicinal products on 26 June 2014.
- On 26 June 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, re-adopted a positive opinion for granting a Marketing Authorisation to VANTOBRA.
- During the decision-making phase, the European Commission raised concerns with regard to the interpretation of the orphan legislation provisions on similarity.
- On 25 September 2014, the CHMP agreed to re-assess the similarity assessment report for VANTOBRA vis-à-vis authorised orphan medicinal products.
- The Rapporteurs circulated the assessment report on similarity to all CHMP members on 10 October 2014.

- On 17 October 2014, the applicant submitted a request for oral explanation.
- A List of questions on similarity was adopted by CHMP on 23 October 2014.
- The applicant submitted the responses to the CHMP List of questions on similarity on 31 October 2014.
- The Rapporteurs circulated an updated Assessment Report on similairty to all CHMP members on 07 November 2014.
- On 18 November 2014, the Applicant attended an Oral Explanation at the CHMP.
- During the CHMP meeting on 17- 20 November 2014, a new Assessment Report on Similarity was adopted in which VANTOBRA and TOBI Podhaler were considered to be similar due to overlap of their target populations and thus similarity of the indications.
- On 28 November 2014, the applicant submitted a report claiming that VANTOBRA is clinically superior to the authorised orphan medicinal product TOBI Podhaler, pursuant to Article 8(3) of Regulation (EC) No141/2000.
- The Rapporteurs circulated the Assessment Report on the derogation claim to all CHMP members 08 December 2014.
- On 17 December 2014, the Applicant attended an Oral Explanation at the CHMP.
- During the meeting on 19-22 January 2015, 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 VANTOBRA.
- The CHMP adopted a report on similarity of Vantobra with authorised orphan medicinal products on 22 January 2015.
- The CHMP adopted a report on derogations applicable to similar orphan products for Vantobra on 22 January 2015.

2. Scientific discussion

2.1. Introduction

Cystic fibrosis (CF) is a hereditary, autosomal recessive chronic condition in which the chronic airway disease is a prominent complication present in more than 98% of patients. Its clinical features, which include chronic cough, are complemented by periodic episodes of exacerbations, characterised by increased sputum volume and purulence.

Tobramycin, an aminoglycoside antibacterial agent, is the most frequently used antibiotic for the treatment of chronic pulmonary infections caused by Pseudomonas aeruginosa (PA) in patients suffering from CF.

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

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.

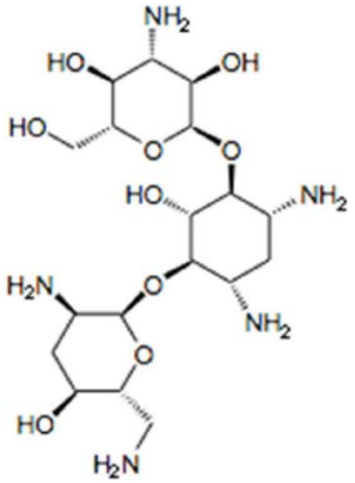
Other ingredients are: sodium chloride, calcium chloride, magnesium sulphate, water for injection, sulphuric acid (for pH adjustment) and sodium hydroxide (for pH adjustment)

The product is available in single-dose polypropylene (PP) ampoules that are packed in sealed aluminium foil pouches (2 ampoules per pouch). 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.



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 (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

Finished product development

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 show 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 polypropylene 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

VANTOBRA 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.

Controller Connection Cord Nebuliser Handset

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 LC Plus (nebuliser used to administer the reference product, TOBI) using the tests described in Ph. Eur. 2.9.44. monograph. Namely, active substance delivery rate, total active substance delivered, and aerodynamic assessment of nebulised aerosols were evaluated. VANTOBRA 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 VANTOBRA/ eFlow system significantly higher than for the jet nebuliser 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 14.6 minutes 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 VANTOBRA 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 VANTOBRA 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 use test was conducted to investigate the effect of operating eFlow/Tolero with VANTOBRA 170mg over 56 treatments (corresponding to 28 days twice daily use). The results from this study showed that Tolero nebuliser handset when nebulising VANTOBRA 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 commercialisation (VANTOBRA 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 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 pilot scale batch of VANTOBRA (tobramycin 170 mg/ 1.7 ml) stored under long term conditions (5 ºC) and accelerated conditions (25 ºC / 60% RH, 30 ºC / 65% RH and 40 ºC / 75% RH) for 33 , 12 and 6 months, respectively, was presented.

Samples were tested for appearance (clarity, colour and visible particles), uniformity of dosage units, pH, osmolality, sterility, assay, related substances, calcium chloride, magnesium sulfate, discoloration, density, surface tension, dynamic viscosity, refractive index, weight loss and dispensing volume.

The analytical procedures used are stability indicating.

The stability results of the three production scale batches over 36 months, showed that all tested parameters were within the acceptance criteria when the drug product was stored at 5°C.

During six months at 25 °C/60 % RH all parameters were also within the defined specification. However, after 6 months the color changed due to the effect of the temperature, but this is known and no correlation with purity profile was found.

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 results from these studies confirmed that VANTOBRA 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 to simulate possible short-time storage of the ampoules outside the pouch as used by the patient and confirmed that the product is stable for at least 4 weeks of storage without pouch in a stability cabinet (25°C/60%RH, darkness) or at ambient temperatures.

Based on available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological 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.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Tobramycin, the active substance of VANTOBRA 170 mg nebuliser solution, belongs to the pharmacotherapeutic group of aminoglycoside antibacterials (ATC Code: J01GB01), originally obtained from cultures of *Streptomyces tenebrarius*.

Tobramycin, the active substance of VANTOBRA, is a water-soluble aminoglycoside antibiotic, which acts primarily by disrupting protein synthesis leading to altered cell membrane permeability, progressive disruption of the cell envelope and eventual cell death.

Tobramycin inhibits protein synthesis of numerous Gram-negative (including *Escherichia coli*, the species *Proteus*, *Enterobacter*, *Klebsiella*, *Acinetobacter*, *Pseudomonas*, *Serratia*, *Providencia)* and Gram-positive (*Staphylococcus aureus)* bacteria. It is bactericidal at concentrations equal to or slightly greater than inhibitory concentrations.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The clinical trial data and the post-marketing experience available for the approved reference product TOBI were considered sufficient by the CHMP for establishing primary pharmacodynamic properties of VANTOBRA and no further studies were deemed necessary. In addition, recent European data collected by EARS-Net showed that the resistance against tobramycin does not appear to be increasing in Europe.

Cross-resistance to other aminoglycosides is nevertheless possible, dependent on the mechanism of resistance that is involved.

Secondary pharmacodynamic studies

No new studies were submitted. This was considered acceptable by the CHMP, in view of the existing evidence provided for the approved reference product.

Safety pharmacology programme

The lack of safety pharmacology studies was justified by the fact that there is no mention of any particular adverse effects having been identified in the reference medicinal product, TOBI SmPC, and this was considered sufficient by the CHMP. No further studies were deemed necessary.

Pharmacodynamic drug interactions

As known for tobramycin containing medicinal products, concurrent and/or sequential use of tobramycin with other medicinal products with neurotoxic or ototoxic potential should be avoided. Some diuretics can enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue. Tobramycin should not be administered concomitantly with ethacrynic acid, furosemide, urea, or intravenous mannitol.

2.3.3. Pharmacokinetics

The already publicly available information on the PK of tobramycin is summarized below and was considered sufficient by the CHMP, no further studies were deemed necessary:

Absorption

The oral bioavailability of tobramycin is very low. Following administration by inhalation in humans, the median serum concentration of tobramycin 1 hour after inhalation of a single 300 mg dose of TOBI is 1 µg/ml. This is in contrast to the situation in rats, where considerably higher serum concentrations (20-45 µg/ml) were achieved when a concentration of 60 mg/ml tobramycin was administered by inhalation for 180 minutes per day in a 6-month study. The terminal plasma half-life is comparable between humans, rabbits and dogs (2.6, 1.23, and 0.9 hours respectively).

Distribution

Tobramycin has no plasma protein binding. VANTOBRA is expected to have no or little plasma protein binding after absorption. The distribution of VANTOBRA after absorption is likely to be the same as for tobramycin administered subcutaneously, i.e. widespread distribution into tissues with highest concentrations in the kidney. In addition, high local concentrations in the lung are expected following inhalation of tobramycin. The high concentrations in the kidney are linked to nephrotoxicity (see also the toxicology section of this CHMP AR).

Tobramycin has been shown to cross the placenta and concentrate in the kidney and urine of the foetus. No information was available regarding exposure via mother milk. The Applicant stated that systemic tobramycin was excreted in the breast milk. According to the TOBI SmPC, the amount of tobramycin

excreted in breast milk after administration by inhalation is unknown, but is estimated to be very low in view of the low systemic exposure. CHMP considered this to be a reasonable assumption.

Metabolism

Tobramycin is not metabolized in the human body; thus no studies on the metabolism of VANTOBRA were considered necessary by the CHMP.

Excretion

Tobramycin is eliminated primarily unchanged in the urine of humans, through glomerular filtration. There is no information regarding excretion of tobramycin in laboratory animals; however, since tobramycin has been shown to concentrate in the kidney of rats it seems likely that urinary excretion is also the major excretory pathway in rodents. After inhalatory administration, the excretion of VANTOBRA is expected to follow the same mechanisms as systemically administered tobramycin.

2.3.4. Toxicology

Single dose toxicity

The publicly available tests description on the acute toxicity studies of the reference medicinal product were considered adequate and sufficient by the CHMP. These studies were conducted in rats and mice in support of another tobramycin product, using the intravenous and subcutaneous routes of administration. No information as to direct cause of death is available, however, clinical signs of tobramycin toxicity included clonic convulsions, decreased and labored respiration, hypoactivity, ataxia and prostration. LD50 values for mice were 53-107 mg/kg with intravenous (i.v.) and 416-484 mg/kg with subcutaneous (s.c.) administration. In rats, the LD50 values were 131-134 mg/kg with i.v. and 928-1020 mg/kg with s.c. administration. CHMP agreed that no further studies should be required.

Repeat dose toxicity

Three inhalation studies in rats (one of these also included guinea pigs) were performed with the reference product TOBI.

Table 1. Repeat-dose toxicity studies with TOBI

Study ID / Duration	Species / Sex / Number / Group	Dose / Route	NOEL / NOAEL (mg / kg / day)	Major findings
N00I328A GLP? 14 days	Sprague Dawley rat/?/?/group	0, 60 mg/ml (21.6 mg/kg), 100 mg/ml (36 mg/kg) inhalation for 6 h/day[1]	None	**Mortality:** none **Clinical**: none **Pathology**: **≥ 21.6 mg / kg**: *upper respiratory tract* (necrosis of olfactory epithelium; inflammatory cell infiltration in nasal turbinates, larynx and trachea; hyperplasia of laryngeal, bronchial and tracheal epithelium). *Lung* (bronchiolar hyperplasia, alveolar histiocytosis).
SC950011 GLP? 14 days	Sprague Dawley rat + Guinea Pig/?/?/group	0, 60 mg/ml 30 min/day (1.8 mg/kg), 60 mg/ml 60 min/day (3.6 mg/kg), 60 mg/ml 120 min/day (7.2 mg/kg)[2]	NOEL: none **NOAEL**: 7.2 mg/kg (rat)	**Rats:** non-dose dependent ↑ lung weight, no microscopic lesions in lungs or other organs **Guinea pigs**: non-dose dependent ↑ kidney weightt, no microscopic lesions in kidneys, lungs or cochleae. **HD**: ulceration of larynx or tracheal mucosa (interpreted as non-specific lesions due to aerosol administration)
N001328B GLP 6 months + 4 weeks recovery	Sprague Dawley rat/M+F/15+15/ group (5/sex/group for recovery and TK)	0, 60 mg/ml 20 min/day (1.24 mg/kg), 60 mg/ml 60 min/day (3.72 mg/kg), 60 mg/ml 180 min/day (11.16 mg/kg)/Nose-only inhalation[3]	NOEL: none **NOAEL**$_{resp}$: 1.24 mg/kg **NOAEL**$_{renal}$: 3.72 mg/kg	**Mortality**: none **Clinical**: none **Body weight**:↓ HD **Hematology**: none **Clin. Chem**:all dose levels (M) ↓ tot protein + globulin **Organ weight**: all dose levels ↑ lung weight HD (M) ↑ kidney weight **Pathology**: *upper respiratory tract* (degeneration olfactory epithelium nose, squamous epithelial hyperplasia larynx) all dose levels; *lung* (bronchiolar hyperplasia, chronic interstit. inflam.) MD + HD; lung (alveolar histiocytosis) all dose levels; *kidney* (increased incidence of chronic progressive nephropathy) HD **After recovery**: most effects still present, although trend toward lower incidence at LD and MD.

[1] Estimated deposited doses were calculated using the equation applied by the CDER reviewer (CDER 1997a).

[2]The doses in mg/kg have been calculated for rats only.

[3]In the non-clinical overview, the mean lung deposited doses are stated as 4.9, 14.3 and 57.5 mg/kg, respectively. However, the CDER reviewer re-calculated these values, adjusting the figures to 1.24, 3.72, and 11.16 mg/kg (CDER 1997a)

Two of these studies were of 14 days and one of 6 months duration, with a 4 week recovery period. Target organs for toxicity were the kidney and respiratory tract.
Kidney effects, in the form of an increased incidence of chronic progressive nephropathy (a spontaneous age-related condition in Sprague-Dawley rats) were only observed in the 6-month study. Treatment with TOBI is considered to have shortened the time to appearance of this condition, thus indicating some systemic toxicity. Nephrotoxicity is a well-known adverse effect of parenteral aminoglycoside therapy both in animals and humans. Renal lesions result from accumulation and retention of aminoglycoside in the proximal tubular cells, causing a defect in renal concentrating ability, mild proteinuria, and appearance of hyaline and granular casts. The impairment in renal function is usually reversible, as the proximal tubular cells have the capacity to regenerate.

With regard to the administration by inhalation, systemically absorbed tobramycin is assumed to behave the same way as any other tobramycin product. Accordingly, any systemic effects will depend on exposure. Whether VANTOBRA will cause any increased risk for nephrotoxicity as compared with TOBI depends on systemic exposure, which was evaluated clinically in one of the conducted BE studies and was deemed unproblematic. In addition, in the VANTOBRA SmPC, the risk for nephrotoxicity is appropriately highlighted under 4.4 “Special warnings and precautions for use”.

Local degenerative and inflammatory changes in the upper respiratory tract and lungs were seen in the preclinical inhalation studies with TOBI. Such changes are commonly seen in inhalation toxicity studies and are likely to result from high local concentrations of the drug in lung tissue following extended inhalation in animals. Although complete reversibility was not demonstrated for respiratory effects in the 6-month inhalation study in rats, given enough time these types of lesions are judged to be fully reversible. In addition, lesions in the nose are not considered relevant for humans, since inhalation occurs by mouth. CHMP therefore did not consider necessary to include any information about preclinical respiratory adverse effects in the SmPC for VANTOBRA.

In addition to nephrotoxicity, ototoxicity is a well-known adverse effect of aminoglycosides. Although this effect was mentioned by the applicant in the provided non-clinical overview, no preclinical data were presented or discussed; nevertheless in the clinical overview, a brief mention of a published study in cats where tobramycin at doses of 40-80 mg/kg/day produced degeneration of cochlear hair cells and supporting sensory structures was made. In the SmPC for TOBI, ototoxicity is described and highlighted in 4.4 “Special warnings and precautions for use”. This was considered to be sufficient by the CHMP, which agreed that no further data were deemed necessary.

Genotoxicity

A complete package of genotoxicity studies, including tests for gene mutations and chromosomal aberrations *in vitro* and chromosomal aberrations *in vivo*, has been performed with the reference product TOBI.

Table 2. Genotoxicity studies performed with TOBI

Type of test / study ID / GLP	Test system	Concentrations / Concentration range / Metabolising system	Results Positive / negative / equivocal
Gene mutations in bacteria 17452-0-409R GLP	S. typhimurium, TA 1535, 1537, 98, 100 E. Coli WP2uvrA	5-667 µg/plate (± S9) 0.01-25 (± S9)	Negative
Gene mutations in mammalian cells 17452-0-431R GLP	Mouse lymphoma L5178Y cells	500-5000 µg/mL (± S9)	Negative
Chromosomal aberrations in mammalian cells 17452-0-437Z GLP	V79 Chinese hamster cells	500-5000 µg/mL (± S9)	Negative
Chromosomal aberrations in vivo 17452-0-455CO GLP	Mouse, micronuclei in bone marrow	90, 180, 360 mg/kg	Negative

The results of these studies were negative. It should be noted that there is no information available concerning the exposure in the *in vivo* mouse micronucleus study. The CHMP concluded based on these test results, that tobramycin does not have any genotoxic potential and no further studies were deemed necessary.

Carcinogenicity

The Applicant refers to a 2-year rat carcinogenicity study with the aerosolised TOBI inhalation solution formulation, where no evidence of a carcinogenic potential was seen. No short or medium-term studies have been submitted. This was considered acceptable by the CHMP and no further studies were deemed necessary.

Reproduction Toxicity

The Applicant refers to studies conducted in the 1970s, in support of another tobramycin product. These studies were later submitted in the application of the reference product TOBI.

Table 3. Reproductive and developmental toxicity studies on tobramycin

Study type / Study ID / GLP	Species	Route & dose	Dosing period	Major findings	NOAEL (mg / kg)
Male/Female fertility/ /non-GLP	Sprague Dawley rat	s.c. bolus 0, 50, 100	M: from 98 days pre-mating F: 14 days pre-mating to lactation	No treatment-related findings	100
Embryo-foetal development/ /non-GLP	Sprague Dawley rat	s.c. bolus 0, 50, 100	GD 6-15	No treatment-related findings on reproduction 100: nephrosis	$NOAEL_{repro:}$ 100
Embryo-foetal development/ /non-GLP	Rabbit	s.c. bolus 20, 40, 60, 120	14 days GD 6-18	≥ 40: Maternal toxicity, ↓ live fetuses	20
Peri & postnatal development/ /non-GLP	Sprague Dawley rat	s.c. bolus 0, 50, 100	GD 14–LD 20	**F0** No effects on parturition **F1** No treatment-related findings	$NOAEL_{repro}$: 100

GD = gestation day; LD = lactation day

The applicant considered that the same studies could be used in support of VANTOBRA. This approach was accepted by the CHMP. It was noted that the reproductive toxicity studies referred to in the application were conducted before the adoption of GLP standards for toxicity studies, but it was acknowledged that the guidelines in place at the time were followed. This was considered acceptable by the CHMP and no further studies were deemed necessary.

Tobramycin did not impair fertility in male or female rats at s.c. doses up to 100 mg/kg/day, nor were these doses associated with any increased pre- or post-implantation loss. In rats and rabbits, s.c. doses of tobramycin up to 100 mg/kg (rats) or 20 mg/kg (rabbits) given during organogenesis were not associated with visceral or skeletal malformations in the offspring. Doses $\geq$40 mg/kg were toxic to the rabbit dams, leading to abortion or death in many animals and precluding the evaluation of teratogenicity. In rats, the 100 mg/kg dose was not associated with clinical signs of toxicity, but microscopic changes (nephrosis) were observed in the kidneys of the dams. Tobramycin did not appear to affect late gestation or parturition in a peri/postnatal study in rats. Fetal body weights and survival were similar across the treatment groups and no external malformations were observed. Ototoxicity was not evaluated.

Although the exposure to tobramycin was not measured in the reproductive toxicology studies, the doses given were 10-100 times higher than those in the 6-month inhalation study. In view of this, and taking into consideration the much lower systemic bioavailability after administration by inhalation, the risk for adverse effects on fertility, and for teratogenic effects, with VANTOBRA is regarded as low. On the other hand, since tobramycin has been shown to cross the placenta in humans and concentrate in the kidney and urine of the fetus, a risk for nephrotoxicity in the fetus cannot be excluded. This risk has been appropriately described and highlighted in section 4.6 of the VANTOBRA SmPC.

Toxicokinetic data

The Applicant presents limited toxicokinetic data in the three inhalation toxicity studies with TOBI. Mean serum levels of tobramycin immediately after exposure on Day 1 are shown in the following table:

Table 4. Mean serum level on Day 1 in inhalation rat toxicity studies with TOBI

Study ID	Daily Dose (mg/kg)	Serum level (µg/ml)	Comments
N00I328A (rat)	21.6	14.6	Only respiratory findings
	36	22.5	
SC950011 (rat)	1.8	7.2	
	3.6	11.4	
	7.2	15.8	NOAEL
N001328B (rat)	1.24	3.7	$NOAEL_{resp}$
	3.72	9.6	$NOAEL_{renal}$
	11.16	20.0	

In the 6-month rat study, serum levels in the high dose group immediately after dosing were 20 µg/ml on average. The comparison with the average serum level of 1 µg/ml observed in humans one hour after inhalation of 170 mg VANTOBRA, suggests that rats get considerably higher systemic exposure to tobramycin than humans following inhalatory administration. There was no accumulation in serum in the 6-month study. In terms of safety margin, the renal NOAEL in the 6-month study is 9-fold above the average human serum level (1 µg/ml).

Local Tolerance

The local tolerance of inhaled tobramycin was evaluated in the repeated dose toxicity studies. As discussed above, the findings in the respiratory tract are considered typical of non-specific inflammatory responses to extended inhalation of the drug in animals and thus CHMP agreed that the risk for local respiratory adverse effects in humans is low and no further studies were deemed necessary.

Other toxicity studies

No other antigenicity, immunotoxicity, dependence or metabolites studies were submitted by the applicant. CHMP agreed that no further data were deemed necessary.

Juvenile toxicity studies

No studies on juvenile animals were submitted for the present application. The applicant justified this by referring to already existing clinical experience with tobramycin in children. This approach was considered acceptable by CHMP and no further studies were deemed necessary.

Impurities

The levels of organic impurities contained in VANTOBRA nebuliser solution were below the qualification thresholds given in the ICH Q3A (R2) and ICH Q3B (R2) guidelines. Accordingly, the CHMP agreed that no toxicological qualification was needed.

2.3.5. Ecotoxicity/environmental risk assessment

Table 5.

Substance (INN/Invented Name):tobramycin (VANTOBRA)			
CAS-number (if available): 32986-56-4			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD 107 (non-GLP)	log K_{ow} = -3.11 to -1.85	Potential PBT (**N**)
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, refined (literature)	0.0067	µg/L	> 0.01 threshold (**N**)

VANTOBRA PECsurfacewater value is below the action limit of 0.01 µg/L. Log Dow is <4.5 at both pH 7 and pH 11. Tobramycin is positively charged at multiple sites at lower and neutral pH and becomes fully neutral only at very high pH values (around pH 11).

Tobramycin was therefore considered not persistent, bioaccumulative and toxic (PBT), nor very persistent and bioaccumulative (vPvB). CHMP agreed to this conclusion.

2.3.6. Discussion on non-clinical aspects

The non-clinical pharmacology and toxicology data can be bridged from that of the reference medicinal product. This is the approach adopted by the applicant, who refers to toxicity data generated with the approved reference product TOBI, as well as to the fact that tobramycin has been widely used in the clinic for the last decades and its human safety profile is well known. Therefore this justification for non performing new studies was considered acceptable by the CHMP.

The non-clinical data package provided on VANTOBRA was considered sufficient by the CHMP. The main toxic side effects, i.e. nephrotoxicity and ototoxicity, including risks for the foetus, are appropriately described and highlighted in the VANTOBRA SmPC.

2.3.7. Conclusion on the non-clinical aspects

The pharmacological and toxicological profiles of tobramycin are well known. The non-clinical toxicity studies conducted with the approved tobramycin reference product are considered adequate and sufficient by the CHMP and no further studies are needed.

2.4. Clinical aspects

2.4.1. Introduction

GCP

According to the Applicant, the clinical trials G007.05, 12012.101 and 12012.102 were conducted in accordance with the appropriate protocols and in compliance with Good Clinical Practice (GCP) issued by the International Conference on Harmonisation (ICH).

- 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 VANTOBRA)/ eFlow and TOBI / PARI LC PLUS	Phase Ib, comparative, randomised, two period, multi center, cross-over	VANTOBRA**/ eFlow and TOBI*** /PARI LC PLUS	58 patients (≥ 4 years)	28 day BID treatment
Bioequivalence	12012.102	Therapeutic equivalence of VANTOBRA)/ eFlow and TOBI / PARI LC PLUS	Phase I, comparative, single center, open, randomized, single-dose, cross-over	VANTOBRA**/ 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. They are 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 VANTOBRA/Tolero (eFlow) versus TOBI/PARI LC PLUS
- Study 12012.102: a single-dose, 2-period, crossover bioequivalence study in healthy volunteers of VANTOBRA/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 VANTOBRA 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 VANTOBRA and TOBI. In addition, efficacy and safety of VANTOBRA 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 6. Lung deposition (mg) of Tobramycin based on ^{99m}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] 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 7. 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 (8-17a)	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 8. 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 9. 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)

CHMP agreed that 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 was considered acceptable by the CHMP for this supportive study.

Study 12012.101

This was a comparative, randomised, two period, multi-centre, cross over, 14-week bioequivalence study of VANTOBRA (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 VANTOBRA 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 VANTOBRA (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 of 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

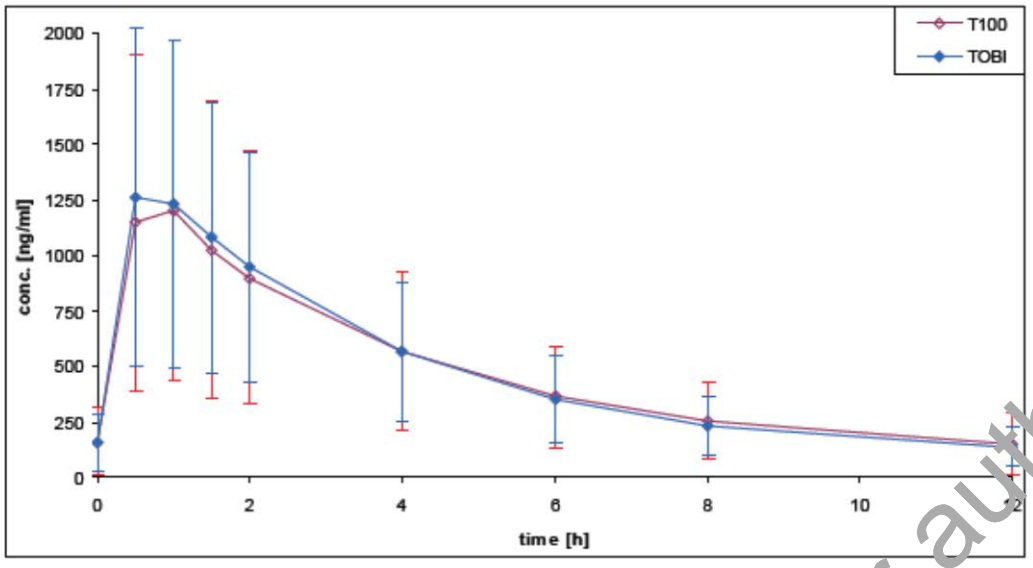
Plasma concentration versus time profiles (AUC_{0-12h}), maximum concentration (C_{max}), time to maximum concentration (t_{max}) and trough levels (C_0) of the test treatment VANTOBRA in comparison to TOBI were determined at the end of each treatment phase. The results are presented below:

Table 10. Plasma pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) after a 4-week treatment of VANTOBRA/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 VANTOBRA 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 VANTOBRA in comparison to TOBI were determined at the end of each treatment phase. The results are presented below:

Table 11. Sputum pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for tobramycin after a 4-week treatment of VANTOBRA/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 VANTOBRA 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 VANTOBRA and the reference product, it was not possible to conclude whether the difference in pharmacokinetic parameters affected the efficacy of VANTOBRA, 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 VANTOBRA, 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 VANTOBRA 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 VANTOBRA 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 VANTOBRA 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 VANTOBRA in comparison to TOBI were determined in each period. The results are presented below:

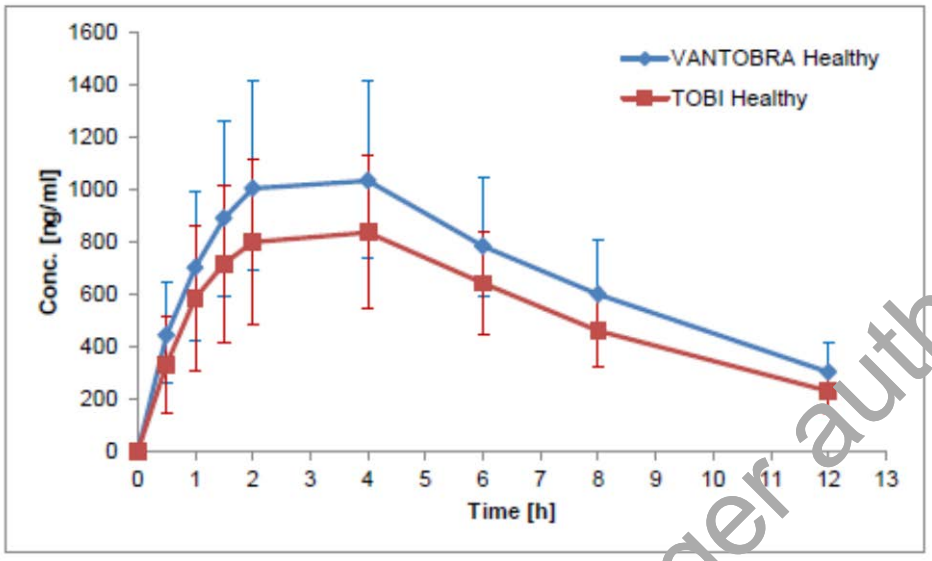
Table 12. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for tobramycin, n=69 (Study 12012.102).

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 VANTOBRA and TOBI in healthy volunteers, n=69 (Study 12012.12).

Figure Q3-1: Mean Concentration-Time-Curves (linear) for VANTOBRA and TOBI of study 12012.102 (N=69)



After single-dose administration in healthy volunteers the systemic exposure and peak concentrations of VANTOBRA 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. Discussion on clinical pharmacology

Pharmacokinetics

The main objective was to analyse the bioequivalence between VANTOBRA 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 VANTOBRA and TOBI was compared in CF patients. The results showed slightly lower systemic exposure (15% lower) with VANTOBRA compared to TOBI. In order to further support the efficacy profile evaluation of VANTOBRA, an additional bioequivalence study in healthy subjects (Study 12012.102) was conducted. In this study the systemic exposure of VANTOBRA 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 VANTOBRA.

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 VANTOBRA while in healthy subjects the systemic exposure was slightly higher with VANTOBRA 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 VANTOBRA, avoiding the bias in CF patients, which have a heterogenous and variable obstruction.

In patients the exposure was approximately 15% lower after administration of VANTOBRA compared to TOBI while in healthy subjects the exposure was approximately 24% higher with VANTOBRA 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 VANTOBRA 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 VANTOBRA 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 VANTOBRA in comparison to TOBI. A higher pulmonary deposition is relevant from an efficacy point of view and the efficacy of VANTOBRA 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 VANTOBRA compared to TOBI is indicative of a somewhat higher lung deposition.

CHMP concluded that the overall results of the in vitro characterisation and the pharmacokinetic studies showed that despite the fact that VANTOBRA was not completely equivalent to TOBI, the *in vivo* differences were rather small and were not expected to impact on the efficacy or safety of VANTOBRA. 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 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. 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. CHMP agreed that the pharmacodynamic properties of tobramycin were well known and that no further studies were needed.

2.4.5. Conclusions on clinical pharmacology

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 VANTOBRA/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 VANTOBRA 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. Furthermore the clinical efficacy data in CF patients (e.g. FEV1%) -although limited-did not indicate clear differences between the products.

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

2.5. Clinical efficacy

As this is a hybrid application, the clinical efficacy data derive from the pivotal clinical study (phase 1b) performed with VANTOBRA/eFlow (here referred to as VANTOBRA) 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.

2.5.1. Main studies

2.5.1.1. Study 12012.101

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

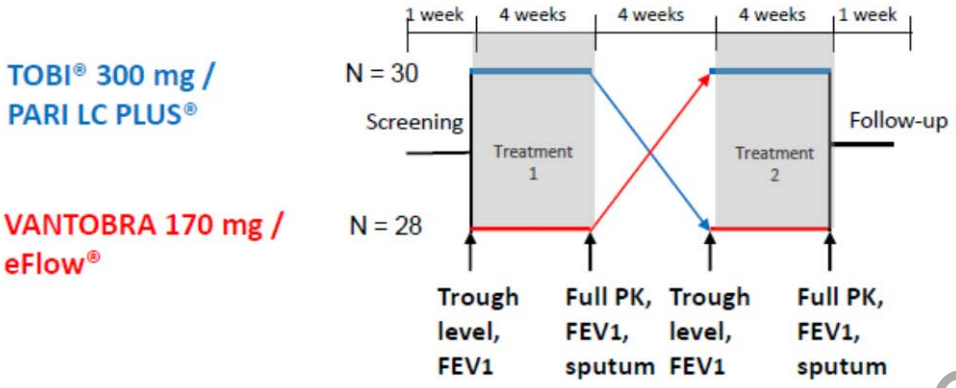
Methods

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 design

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.

Figure 5. Time course of study 12012.201



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

VANTOBRA: 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.

Objectives

The primary objective of this study was to determine bioequivalence of VANTOBRA/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_{0-12h} 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_{25-75}, 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

Sample size

The primary objective of this study was the assessment of bioequivalence. This study was therefore not powered for efficacy or safety. Clinical efficacy and safety variables were secondary endpoints and corresponding parameters were calculated using descriptive statistics.

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.

Baseline Demographic Data.

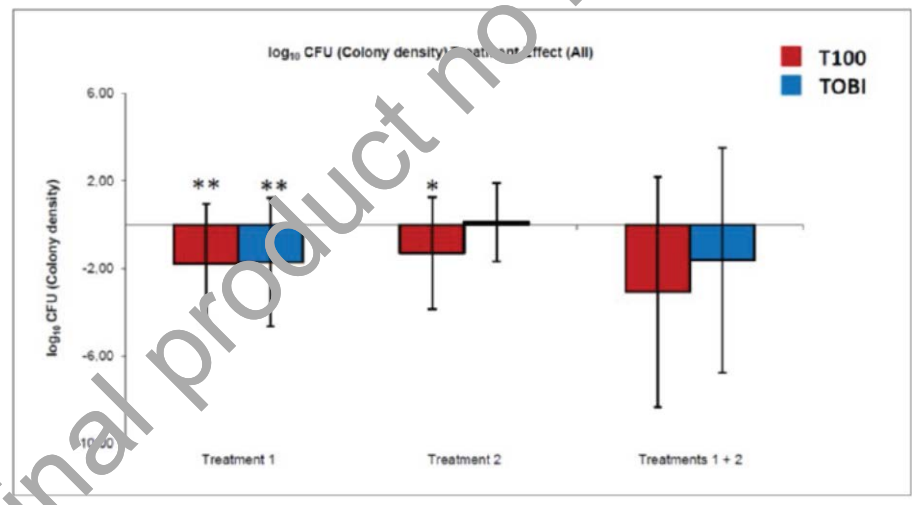
Table 13.

	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

Results

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

Figure 6. Colony Forming Units (CFU): Overall reduction of PA (All); normalized on Visit 2 as Baseline



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

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 VANTOBRA 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 VANTOBRA and TOBI, respectively.

The changes in the different lung function parameters under investigation were consistently indicative for an improvement under both therapies with a tendency of better improvement under VANTOBRA therapy.

The treatment effects of FEV_1 % predicted were very similar for both groups, VANTOBRA and TOBI, in the first treatment period. However, a positive treatment effect was also observed for VANTOBRA in the second treatment phase. During the first treatment phase a similar percentual increase in FEV_1 was achived with VANTOBRA 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 VANTOBRA and TOBI, respectively.

Figure 7. Time course of FEV1 % predicted (All), normalized to Visit 2 as Baseline

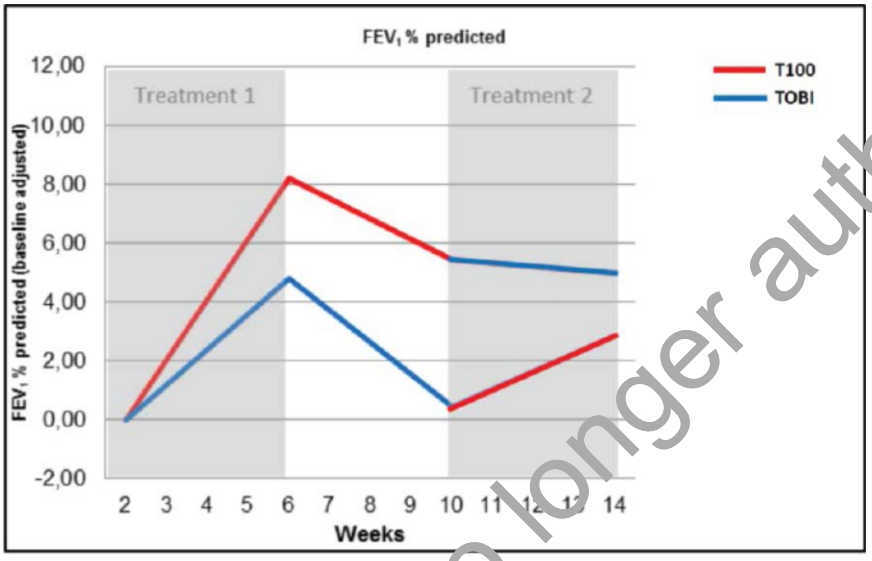
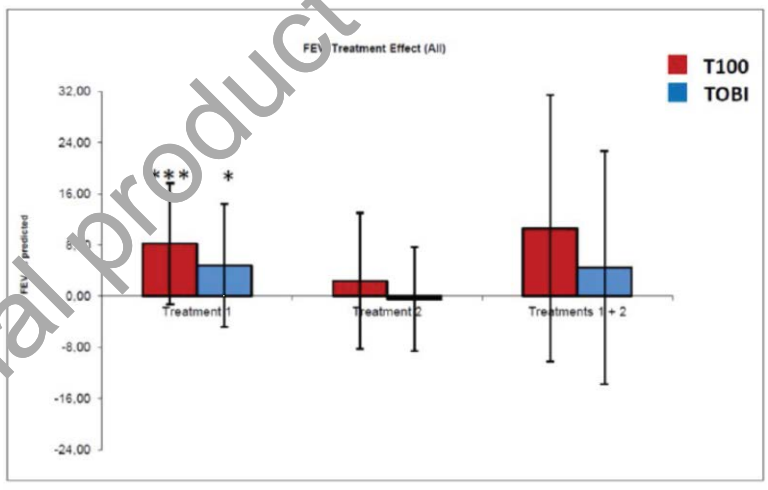


Figure 8. Absolute changes in FEV1 % predicted (All), normalized to Visit 2 as Baseline



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 9. Absolute changes in FEV1 % predicted (6 – 13 a), normalized to Visit 2 as Baseline

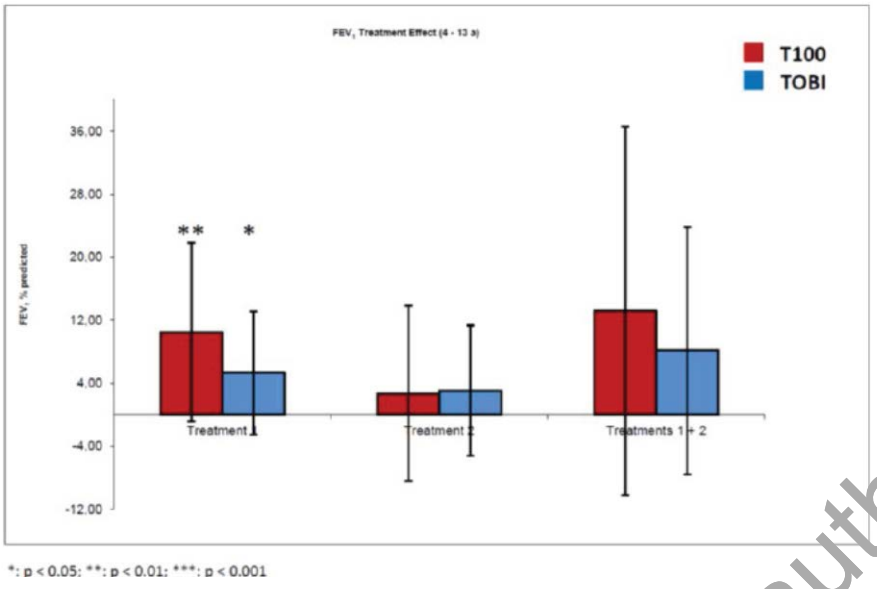
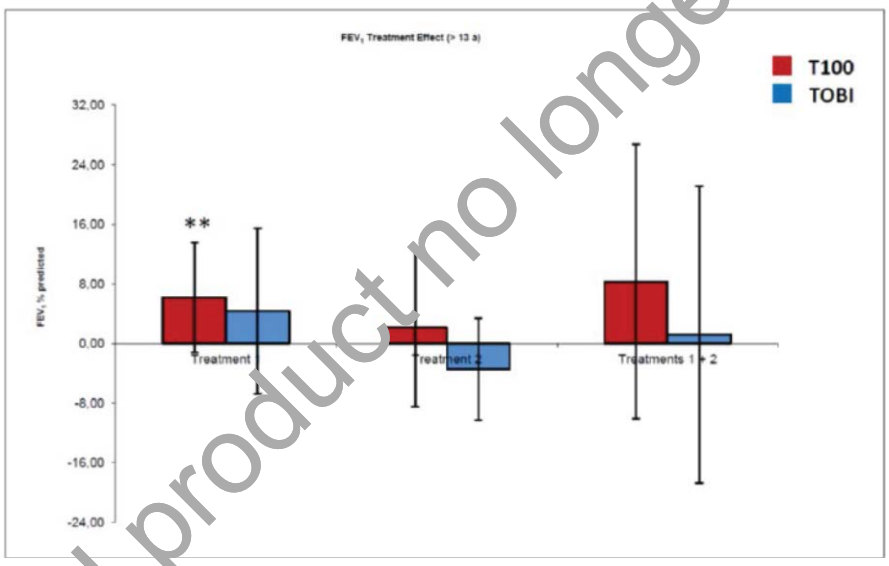


Figure 10. Absolute changes in FEV1 % predicted (>13 a), normalized to Visit 2 as Baseline



The treatment effects on FEV_{25-75} (predicted) were very similar for both groups, VANTOBRA and TOBI, in the first treatment period. However, a positive treatment effect was also observed for VANTOBRA in the second treatment phase. During the first treatment phase a similar percentual increase in FEV_{25-75} was achieved with VANTOBRA 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 VANTOBRA and TOBI, respectively.

The treatment effects on the forced vital capacity (FVC) were comparable between VANTOBRA and TOBI. However, a positive treatment effect was also recognized in patients who received T100 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 VANTOBRA 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 VANTOBRA

and TOBI, respectively.

The treatment effects of PEF are not statistically different between the both groups VANTOBRA and TOBI. However, a positive treatment effect is seen in patients who received VANTOBRA in the second traetment phase. During the first treatment phase a similar percentual increase in PEF was achieved with VANTOBRA 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 VANTOBRA and TOBI, respectively.

2.5.2. Discussion on 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 period bioequivalence study 12012.101, in which clinical efficacy data 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 VANTOBRA 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 for which the applicant received an orphan designation.

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 VANTOBRA 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 VANTOBRA treatment. Despite the fact that the treatment effect diminished during the treatment phase 2, the treatment effect with VANTOBRA 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 VANTOBRA. 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. CHMP acknowledged that the available data indicate that the clinical efficacy of VANTOBRA is comparable with that of TOBI, notwithstanding that some differences between VANTOBRA 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.

2.5.3. Conclusions on the clinical efficacy

Pharmacokinetic data provided showed a slightly higher lung deposition of VANTOBRA compared to TOBI. A higher pulmonary deposition is expected to be beneficial from an efficacy point of view and VANTOBRA 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 VANTOBRA was beneficial in terms of the lung function, in particular during the second treatment period.

Taking into account the results of both conducted BE studies 101 and 102, the CHMP concluded that they constitute a relevant bridge for safety and efficacy between VANTOBRA and TOBI in patients 6 years and older with chronic *P.aeruginosa* lung infection and cystic fibrosis.

2.6. Clinical safety

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 VANTOBRA 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 VANTOBRA/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 T100 (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 150 mg (T100). 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 (VANTOBRA). 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 VANTOBRA 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 VANTOBRA 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% (VANTOBRA) 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 VANTOBRA 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 VANTOBRA treatment (3.4% of all patients). Both cases were mild in severity and transient as resolving shortly after inhalation. One patient in the VANTOBRA 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 VANTOBRA / 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 VANTOBRA 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 VANTOBRA, 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.

2.6.1. Discussion on 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 VANTOBRA/eFlow compared TOBI/PARI LC PLUS. Thus, the systemic safety of VANTOBRA 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 VANTOBRA 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 VANTOBRA were at higher risk for alterations due to higher local drug concentrations that derive from higher strength of the tobramycin concentration in VANTOBRA 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. The CHMP agreed that since VANTOBRA was a hybrid of TOBI and since the safety profile of nebulised tobramycin for inhalation was well-known, the first PSUR for Vantobra should be submitted within 12 months after the marketing authorisation.

2.6.2. Conclusions on the clinical safety

Taking into account the results of both conducted BE studies 101 and 102, the CHMP concluded that they constitute a relevant bridge for safety and efficacy between VANTOBRA and TOBI in patients 6 years and older with chronic *P.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.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

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

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

The PRAC considered that the risk management plan version 4.0 is acceptable.

The CHMP endorsed this advice without changes. However, following the change in the indication, the applicant implemented the changes in the RMP as requested by CHMP, to reflect the new PI.

The CHMP endorsed the Risk Management Plan version 5.0 with the following content:

- **Safety concerns**

Summary of safety concerns	
Important identified risks	Cough Bronchospasm Haemoptysis
Important potential risks	**VAN TOBRA** Nephrotoxicity Ototoxicity Foetal harm Pathogen resistance: Decreased PA susceptibility to tobramycin Potential drug-drug interactions with diuretics and other drugs affecting renal clearance, nephrotoxicity, neurotoxic and ototoxic drugs (class effect of parenteral use of aminoglycosides) Off-label use in children < 6 years of age **Tolero nebuliser handset** Bacterial growth in the Tolero nebuliser handset
Missing information	Individuals after transplantation Pregnancy or lactation Disease severity different from clinical trial populations (e.g. patients with FEV1 < 25%)

Summary of safety concerns	
	Individuals treated with aminoglycosides before VANTOBRA treatment

- **Pharmacovigilance plans**

The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

- **Risk minimisation measures**

In addition to the risk minimisation measures listed below, the full prescribing and counselling information to help the patient is provided in the EU Patient Leaflet.

Summary Table of Risk Minimisation

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risk: Cough	- SmPC section 4.4 – Haemoptysis: Inhalation of nebulised tobramycin solutions may induce a cough reflex. - SmPC section 4.8 Undesirable effects: Summary of the safety profile: In controlled clinical trials with VANTOBRA the most frequent adverse reactions in cystic fibrosis patients with P. aeruginosa infection were cough and dysphonia. - SmPC section 4.8 Undesirable effects: Table 'Adverse reactions': Frequency of 'uncommon' (≥1/1,000 to <1/100) for cough	None proposed
Important identified risks: Bronchospasm	- SmPC section 4.4 - Special warnings and precautions for use: Bronchospasm: Bronchospasm can occur with inhalation of medicinal products and has been reported with the use of nebulized tobramycin. Bronchospasm should be treated as medically appropriate. The first dose of VANTOBRA should be used under supervision, after taking a bronchodilator if this is part of the current regimen for the patient. FEV1 should be measured before and after nebulization. If there is evidence of therapy-induced bronchospasm, the physician should carefully evaluate whether the benefits of continued use of VANTOBRA outweighs the risks to the patient. If an allergic response is suspected, VANTOBRA should be discontinued. - SmPC section 4.8 - Undesirable effects: Table 'Adverse reactions': Frequency of 'rare' (≥1/10,000 to <1/1,000) for bronchospasm	None proposed
Important identified risks: Haemoptysis	- SmPC section 4.4 - Special warnings and precautions for use: Haemoptysis: Inhalation of nebulised tobramycin solutions may induce a cough reflex. The treatment with VANTOBRA in patients with active, severe haemoptysis should be initiated only if the benefits of treatment are considered to outweigh the risks of inducing further haemorrhage. - SmPC section 4.8 - Undesirable effects: Table 'Adverse reactions': Frequency of 'rare' (≥1/10,000 to <1/1,000) for haemoptysis	None proposed
Important potential risk: Nephrotoxicity	- SmPC section 4.4 - Special warnings and precautions for use: Nephrotoxicity: Nephrotoxicity has been associated with parenteral aminoglycoside therapy. There was no evidence of nephrotoxicity during clinical trials with inhaled tobramycin and VANTOBRA. Caution should be exercised when prescribing VANTOBRA to patients with known or suspected renal dysfunction. According to current clinical practice baseline renal function should be assessed. Urea and creatinine levels should be reassessed after every 6 complete cycles of VANTOBRA therapy (180 days of nebulized aminoglycoside therapy). - SmPC section 4.4 - Special warnings and precautions for use: Monitoring of serum tobramycin concentrations: Patients with known or suspected auditory or renal dysfunction should be monitored for serum tobramycin concentrations. If oto- or nephrotoxicity occurs in a patient receiving VANTOBRA, tobramycin therapy should be discontinued until serum concentration falls below 2 µg/ml. Serum concentrations greater than 12 µg/ml are associated with tobramycin toxicity and treatment should be discontinued if concentrations exceed this level. The serum concentration of tobramycin should only be monitored using validated methods. Finger prick blood sampling is not recommended due to the risk of contamination of the sample. - SmPC section 4.4 - Special warnings and precautions for use: Other precautions: Patients receiving concomitant parenteral aminoglycoside therapy (or any medicine affecting renal excretion, such as diuretics) should be monitored as clinically appropriate taking into account the risk of cumulative toxicity. This includes monitoring of serum concentrations of tobramycin. - SmPC section 4.5 - Interaction with other medicinal products and other forms of interaction: […] Based on the interaction	None proposed

	profile for tobramycin following intravenous and aerosolised administration, concurrent and/or sequential use of VANTOBRA is not recommended with other medicinal products with nephrotoxic or ototoxic potential, such as: mphotericin B, cefalotin, ciclosporin, tacrolimus, polymyxins (risk of increased nephrotoxicity); platinum compounds (risk of increased nephrotoxicity and ototoxicity);. - SmPC section 4.6 - Fertility, pregnancy and lactation: Pregnancy: [...] However, aminoglycosides can cause foetal harm (e.g., congenital deafness and nephrotoxicity) when high systemic concentrations are achieved in a pregnant woman. Systemic exposure following inhalation of VANTOBRA is very low; however VANTOBRA should not be used during pregnancy unless clearly necessary, i.e. when the benefit to the mother outweigh the risks to the foetus. - SmPC section 4.6 - Fertility, pregnancy and lactation: Pregnancy: [...] However, aminoglycosides can cause foetal harm (e.g., congenital deafness and nephrotoxicity) when high systemic concentrations are achieved in a pregnant woman. Systemic exposure following inhalation of VANTOBRA is however low. If VANTOBRA is used during pregnancy, or if the patient becomes pregnant while taking VANTOBRA, she should be informed of the potential hazard to the foetus. - SmPC section 4.6 - Fertility, pregnancy and lactation: Breast feeding: [...] Because of the potential for ototoxicity and nephrotoxicity in infants, a decision should be made whether to terminate breast-feeding or discontinue treatment with VANTOBRA, taking into account the importance of the treatment to the mother. - SmPC section 4.8 - Undesirable effects: Summary of safety profile: [...] Parenteral aminoglycosides have been associated with hypersensitivity, ototoxicity and nephrotoxicity (see 4.4). - SmPC section 4.9 - Overdose: [...] In the event of inadvertent administration of VANTOBRA by the intravenous route, signs and symptoms of parenteral tobramycin overdose may occur that include dizziness, tinnitus, vertigo, loss of hearing acuity, respiratory distress and/or neuromuscular blockade and renal impairment. Acute toxicity should be treated with immediate withdrawal of VANTOBRA, and baseline tests of renal function should be undertaken. Assessment of tobramycin serum concentrations may be helpful in monitoring overdose. In the case of any overdose, the possibility of drug interactions with alterations in the elimination of VANTOBRA or other medicinal products should be considered. - SmPC section 5.3 - Preclinical safety data: Non-clinical data reveal that the main hazard for humans, based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development, consists of renal toxicity and ototoxicity. In repeated dose toxicity studies, target organs of toxicity are the kidneys and vestibular/cochlear functions. In general, toxicity is seen at higher systemic tobramycin levels than are achievable by inhalation of the recommended clinical dose.	

Important potential risk: Ototoxicity	- SmPC section 4.4 - Special warnings and precautions for use: Ototoxicity: Ototoxicity, manifested as both auditory toxicity (hearing loss) and vestibular toxicity, has been reported with parenteral aminoglycosides. Vestibular toxicity may be manifested by vertigo, ataxia or dizziness. Tinnitus may be a sentinel symptom of ototoxicity, and therefore the onset of this symptom warrants caution. Auditory toxicity, as measured by complaints of hearing loss or by audiometric evaluations, was observed with parenteral aminoglycosides and may be considered also for the inhalative route of administration. In open label studies and post-marketing experience, some patients with a history of prolonged previous or concomitant use of intravenous aminoglycosides have experienced hearing loss. Physicians should consider the potential for aminoglycosides to cause vestibular and cochlear toxicity and carry out appropriate assessments of auditory function during VANTOBRA therapy. In patients with a predisposing risk due to previous prolonged, systemic aminoglycoside therapy it may be necessary to consider audiological assessment before initiating VANTOBRA therapy. If a patient reports tinnitus or hearing loss during aminoglycoside therapy the physician should consider referring them for audiological assessment. - SmPC section 4.4 - Special warnings and precautions for use: Monitoring of serum tobramycin concentrations: Patients with known or suspected auditory or renal dysfunction should be monitored for serum tobramycin concentrations. If oto- or nephrotoxicity occurs in a patient receiving VANTOBRA, tobramycin therapy should be discontinued until serum concentration falls below 2 µg/ml. Serum concentrations greater than 12 µg/ml are associated with tobramycin toxicity and treatment should be discontinued if concentrations exceed this level. The serum concentration of tobramycin should only be monitored using validated methods. Finger prick blood sampling is not recommended due to the risk of contamination of the sample. - SmPC section 4.4 - Special warnings and precautions for use: Other precautions: Patients receiving concomitant parenteral aminoglycoside therapy (or any medicine affecting renal excretion, such as diuretics) should be monitored as clinically appropriate, taking into account the risk of cumulative toxicity. This includes monitoring of serum concentrations of tobramycin. - SmPC section 4.5 - Interaction with other medicinal products and other forms of interaction: […] Based on the interaction profile for tobramycin following intravenous and aerosolised administration, concurrent and/or sequential use of VANTOBRA is not recommended with other medicinal products with nephrotoxic or ototoxic potential, such as: amphotericin B, cefalotin, ciclosporin, tacrolimus, polymyxins (risk of increased nephrotoxicity); platinum compounds (risk of increased nephrotoxicity and ototoxicity).. - SmPC section 4.6 - Fertility, pregnancy and lactation: Pregnancy: […] However, aminoglycosides can cause foetal harm (e.g., congenital deafness and nephrotoxicity) when high systemic concentrations are achieved in a pregnant woman. Systemic exposure following inhalation of VANTOBRA is very low, however VANTOBRA should not be used during pregnancy unless clearly necessary, i.e. when the benefits to the mother outweigh the risks to the foetus or baby. - SmPC section 4.6 - Fertility, pregnancy and lactation: Breast feeding: […] Because of the potential for ototoxicity and nephrotoxicity in infants, a decision should be made whether to terminate breast-feeding or discontinue treatment with VANTOBRA, taking into account the importance of the treatment to the mother. - SmPC section 4.8 - Undesirable effects: Summary of safety profile: Clinical experience with tobramycin nebuliser solutions reports dysphonia and tinnitus in patients treated with tobramycin. The episodes of tinnitus are transient and	None proposed

	resolved without discontinuation of tobramycin therapy. Occasionally, patients with a history of prolonged previous or concomitant use of intravenous aminoglycosides may experience hearing loss. Parenteral aminoglycosides have been associated with hypersensitivity; ototoxicity and nephrotoxicity (see 4.4). - SmPC section 4.8 - Undesirable effects: Table 'Adverse reactions': Frequency of 'rare' (≥1/10,000 to <1/1,000) for hearing loss, 'rare' (≥1/10,000 to <1/1,000) for tinnitus, 'very rare' (<1/10,000) for ear pain and 'very rare' (<1/10,000) for ear disorder. - SmPC section 4.9 – Overdose: […] In the event of inadvertent administration of VANTOBRA by the intravenous route, signs and symptoms of parenteral tobramycin overdose may occur that include dizziness, tinnitus, vertigo, loss of hearing acuity, respiratory distress and/or neuromuscular blockade and renal impairment. Acute toxicity should be treated with immediate withdrawal of VANTOBRA, and baseline tests of renal function should be undertaken. Assessment of tobramycin serum concentrations may be helpful in monitoring overdose. In the case of any overdose, the possibility of drug interactions with alterations in the elimination of VANTOBRA or other medicinal products should be considered. - SmPC section 5.3 - Preclinical safety data: Non-clinical data reveal that the main hazard for humans, based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development, consists of renal toxicity and ototoxicity. In repeated dose toxicity studies, target organs of toxicity are the kidneys and vestibular/cochlear functions. In general, toxicity is seen at higher systemic tobramycin levels than are achievable by inhalation of the recommended clinical dose. No reproduction toxicology studies have been conducted with tobramycin administered by inhalation, but subcutaneous administration at doses of 100 mg/kg/day in rats and the maximum tolerated dose of 20 mg/kg/day in rabbits, during organogenesis, was not teratogenic. Teratogenicity could not be assessed at higher parenteral doses in rabbits as they induced maternal toxicity and abortion. Based on available data from animals a risk of toxicity (e.g. ototoxicity) at prenatal exposure levels cannot be excluded. Tobramycin did not impair fertility in male or female rats at subcutaneous doses up to 100 mg/kg/day.	

Important potential risk: Foetal harm	- SmPC section 4.6 - Fertility: No effect on male or female fertility was observed in animal studies after subcoutaneous administration. - SmPC section 4.6 -Pregnancy: There are limited data from the parenteral use of tobramycin in pregnant women. There are no adequate data from the use of tobramycin administered by inhalation in pregnant women. Animal studies do not indicate a teratogenic effect of tobramycin (see section 5.3). However, aminoglycosides can cause foetal harm (e.g., congenital deafness and nephrotoxicity) when high systemic concentrations are achieved in a pregnant woman. Systemic exposure following inhalation of VANTOBRA is very low, however VANTOBRA should not be used during pregnancy unless clearly necessary, i.e. when the benefits to the mother outweigh the risks to the foetus or baby. If VANTOBRA is used during pregnancy, or if the patient becomes pregnant while taking VANTOBRA, she should be informed of the potential hazard to the foetus. VANTOBRA should not be used during pregnancy unless the benefits to the mother outweigh the risks to the foetus or baby. - SmPC section 5.3 - Preclinical safety data: Non-clinical data reveal that the main hazard for humans, based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development, consists of renal toxicity and ototoxicity. In repeated dose toxicity studies, target organs of toxicity are the kidneys and vestibular/cochlear functions. In general, toxicity is seen at higher systemic tobramycin levels than are achievable by inhalation of the recommended clinical dose. No reproduction toxicology studies have been conducted with tobramycin administered by inhalation, but subcutaneous administration at doses of 100 mg/kg/day in rats and the maximum tolerated dose of 20 mg/kg/day in rabbits, during organogenesis, was not teratogenic. Teratogenicity could not be assessed at higher parenteral doses in rabbits as these induced maternal toxicity and abortion. Based on available data from animals a risk of toxicity (e.g. ototoxicity) at prenatal exposure levels cannot be excluded. Tobramycin did not impair fertility in male or female rats at subcutaneous doses up to 100 mg/kg/day.	None proposed
Important potential risk: Pathogen resistance: Decreased PA susceptibility to tobramycin	- SmPC section 4.4- Special warnings and precautions for use: Development of resistance: The development of antibiotic resistant P. aeruginosa and superinfection with other pathogens represent potential risks associated with antibiotic therapy. Development of resistance during inhaled tobramycin therapy could limit treatment options during acute exacerbations; this should be monitored. - SmPC section 5.1 - Pharmacodynamic properties: Mechanism of action Tobramycin is an aminoglycoside antibiotic produced by Streptomyces tenebrarius. It acts primarily by disrupting protein synthesis leading to altered cell membrane permeability, progressive disruption of the cell envelope and eventual cell death. It is bactericidal at concentrations equal to or slightly greater than inhibitory concentrations. Breakpoints: Established susceptibility break-points for parenteral administration of tobramycin are inappropriate in the aerosolised administration of the medicinal product. Sputum of cystic fibrosis patients exhibits an inhibitory action on the local biological activity of nebulised amino-glycosides. This necessitates sputum concentrations following treatment with aerosolised tobramycin to be ten to twentyfive-fold above the Minimum Inhibitory Concentration (MIC) for both P. aeruginosa growth suppression and control of bactericidal activity. In controlled clinical trials, 97% of patients receiving tobramycin nebuliser solution achieved sputum concentrations 10-fold of the highest P. aeruginosa MIC cultured from the patient and 95% of patients receiving tobramycin nebuliser solution achieved 25-fold of the highest MIC. Susceptibility: In the absence of conventional susceptibility	None proposed

	breakpoints for the nebulised route of administration, caution must be exercised in defining organisms as susceptible or insusceptible to nebulised tobramycin. In clinical studies with TOBI, most patients with P. aeruginosa isolates with tobramycin MICs < 128 µg/ml at baseline showed improved lung function following treatment with TOBI. Patients with a P. aeruginosa isolate with MIC 128 µg/ml at baseline are less likely to show a clinical response. However, seven of 13 patients (54%) in the placebo-controlled trials who acquired isolates with MICs of 128 µg/ml while using TOBI had improvement in pulmonary function.	
Important potential risk: Potential drug-drug interactions with diuretics and other drugs affecting renal clearance, nephrotoxicity, neurotoxic and ototoxic drugs (class effects of parenteral use of aminoglycosides)	- SmPC section 4.4 - Special warnings and precautions for use: […] In open label studies and post-marketing experience, some patients with a history of prolonged previous or concomitant use of intravenous aminoglycosides have experienced hearing loss. Physicians should consider the potential for aminoglycosides to cause vestibular and cochlear toxicity and carry out appropriate assessments of auditory function during VANTOBRA therapy. In patients with a predisposing risk due to previous prolonged, systemic aminoglycoside therapy it may be necessary to consider audiological assessment before initiating VANTOBRA therapy. If a patient reports tinnitus or hearing loss during aminoglycoside therapy the physician should consider referring them for audiological assessment. - SmPC section 4.4 - Special warnings and precautions for use: Other precautions: Patients receiving concomitant parenteral aminoglycoside therapy (or any medicine affecting renal excretion, such as diuretics) should be monitored as clinically appropriate taking into account the risk of cumulative toxicity. This includes monitoring of serum concentrations of tobramycin. - SmPC section 4.5 - Interaction with other medicinal products and other forms of interaction: No interaction studies have been performed. Based on the interaction profile for tobramycin following intravenous and aerosolised administration, concurrent and/or sequential use of VANTOBRA is not recommended with other medicinal products with nephrotoxic or ototoxic potential, such as: amphotericin B, cefalotin, ciclosporin, tacrolimus, polymyxins (risk of increased nephrotoxicity); platinum compounds (risk of increased nephrotoxicity and ototoxicity). Concurrent use of VANTOBRA with diuretic compounds (such as ethacrynic acid, furosemide, urea or mannitol) is not recommended. Such compounds can enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue (see section 4.4). Other medicinal products that have been reported to increase the potential toxicity of parenterally administered aminoglycosides include: anticholinesterases, botulinum toxin (neuromuscular effects). In clinical studies patients using inhaled tobramycin continued to take dornase alfa, bronchodilators, inhaled corticosteroids and macrolides. No evidence of drug interactions with these medicines was identified. - SmPC section 4.8 - Undesirable effects: Summary of the safety profile: […] Occasionally, patients with a history of prolonged previous or concomitant use of intravenous aminoglycosides may experience hearing loss. Parenteral aminoglycosides have been associated with hypersensitivity, ototoxicity and nephrotoxicity (see 4.4). - SmPC section 4.9 - Overdose: […] In the case of any overdose, the possibility of drug interactions with alterations in the elimination of VANTOBRA or other medicinal products should be considered.	None proposed
Important potential risk: Off-label use in children < 6 years of age	- SmPC section 4.1 - Therapeutic indications: VANTOBRA is indicated for the management of chronic pulmonary infection due to Pseudomonas aeruginosa in patients aged 6 years and older with cystic fibrosis (CF)..	None proposed

	- SmPC section 4.2 - Posology and method of administration: Paediatric population: There is no relevant use of VANTOBRA in children below 6 years of age.	

Important potential risk: Bacterial growth in the Tolero® nebuliser handset	- IFU Tolero® nebuliser handset introduction: Please read these instructions carefully to learn how to use your Tolero® nebuliser handset. Please make sure you also read the instructions for use of the eFlow® rapid nebuliser system before first use. They include important additional information about use of the Tolero® nebuliser handset in particular in relation to connection, operation and hygiene. - IFU Tolero® nebuliser handset section 4 – Hygienic reprocessing: The nebuliser handset (incl. aerosol head) must be cleaned immediately after each use and disinfected at least once a day (see instructions for use of the eFlow® rapid nebuliser system). - IFU eFlow® rapid nebuliser system section 1: Life cycle: The nebuliser handset is designed for multiple uses. The individual components of the eFlow®rapid nebuliser handset are subject to changing stresses during treatment and during preparation for hygienic reprocessing. The frequency and duration of use are decisive factors. The distinction must also be made between use at home (without a change of patients) and use in a clinic or a doctor's practice (change of patients is possible). When the life cycle has expired, it is recommended that the components be replaced to ensure proper functioning. - IFU eFlow® rapid nebuliser system section 5: Hygienic reprocessing pages 51 - 56: please refer to Annex 2 of this RMP, IFU of eFlow® rapid nebuliser is included therein.	None proposed
Missing information: Individuals after transplantation	Individuals after transplantation are not included in the current SmPC of VANTOBRA.	None proposed
Missing information: Pregnancy or lactation	- SmPC section 4.6 – Fertility, pregnancy and lactation: Pregnancy: There are limited data from the parenteral use of tobramycin in pregnant women. There are no adequate data from the use of tobramycin administered by inhalation in pregnant women. Animal studies do not indicate a teratogenic effect of tobramycin (see section 5.3). However, aminoglycosides can cause foetal harm (e.g., congenital deafness and nephrotoxicity) when high systemic concentrations are achieved in a pregnant woman. Systemic exposure following inhalation of VANTOBRA is very low, however VANTOBRA should not be used during pregnancy unless clearly necessary, i.e. when the benefits to the mother outweigh the risks to the foetus or baby. If VANTOBRA is used during pregnancy, or if the patient becomes pregnant while taking VANTOBRA, she should be informed of the potential hazard to the foetus. VANTOBRA should not be used during pregnancy unless the benefits to the mother outweigh the risks to the foetus or baby. - SmPC section 4.6 – Fertility, pregnancy and lactation: Breast-feeding: Tobramycin is excreted in human breast milk after systemic administration. The amount of tobramycin excreted in human breast milk after administration by inhalation is not known, though it is estimated to be very low considering the low systemic exposure. Because of the potential for ototoxicity and nephrotoxicity in infants, a decision should be made whether to terminate breast-feeding or discontinue treatment with VANTOBRA, taking into account the importance of the treatment to the mother.	None proposed
Missing information: Disease severity different from clinical trial populations (e.g. patients with FEV1 < 25%	- SmPC section 5.1 – Pharmacodynamic properties: Clinical efficacy and safety: Data from controlled clinical studies over one treatment cycle have shown that the improvement in lung function was maintained above baseline during the 28-day off-treatment period. As a result of study 12012.101, lung function improvement FEV1 % predicted relative to baseline increased by 8.2 ± 9.4% under VANTOBRA and by 4.8 ± 9.6% under the reference therapy in the first treatment cycle showing non-inferior (p=0.0005) efficacy. CFU reduction as an indicator for suppression of P. aeruginosa was comparable for VANTOBRA and the reference product. - SmPC section 4.4 – Special warnings and precautions for use: Bronchospasm: The first dose of VANTOBRA should be used under supervision of a physician, after taking a	None proposed

	bronchodilator if this is part of the current regimen for the patient. FEV1 should be measured before and after nebulisation.	
Missing information: Individuals treated with aminoglycosides before VANTOBRA treatment	- SmPC section 4.4 – Special warnings and precautions for use: Ototoxicity: […] Auditory toxicity, as measured by complaints of hearing loss or by audiometric evaluations, was observed with parenteral aminoglycosides and may be considered also for the inhalative route of administration. In open label studies and post-marketing experience, some patients with a history of prolonged previous or concomitant use of intravenous aminoglycosides have experienced hearing loss. Physicians should consider the potential for aminoglycosides to cause vestibular and cochlear toxicity and carry out appropriate assessments of auditory function during VANTOBRA therapy. In patients with a predisposing risk due to previous prolonged, systemic aminoglycoside therapy it may be necessary to consider audiological assessment before initiating VANTOBRA therapy. If a patient reports tinnitus or hearing loss during aminoglycoside therapy the physician should consider referring them for audiological assessment. - SmPC section 4.4 – Special warnings and precautions for use: Other precautions: […]In patients with a predisposing risk due to previous prolonged, systemic aminoglycoside therapy it may be necessary to consider renal and audiological assessment before initiating VANTOBRA therapy.	None proposed

2.9. User consultation

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

3. Benefit-Risk Balance

Benefits

Beneficial effects

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 VANTOBRA 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 vitro, VANTOBRA 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 VANTOBRA compared to TOBI which is an indication of a higher lung deposition of tobramycin with VANTOBRA in comparison to TOBI. A higher lung

deposition is considered relevant from an efficacy point of view and the efficacy profile of VANTOBRA is deemed to be comparable to that of TOBI.

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 VANTOBRA 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 (FEV_1 %, FVC, FEV_{25-75}, PEF), as well as with the observed decrease in *P. aeruginosa* CFU. Generally, VANTOBRA was shown to be beneficial, in particular during the second treatment period.

Uncertainty in the knowledge about the beneficial effects

The use of systemic pharmacokinetic data as a surrogate for efficacy for an orally inhaled product in patients with cystic fibrosis presents some limitations, considering the local efficacy and the disease associated effect on the airways. However, the CHMP considered in this case of two similar formulations of the same active substance that this option was more sensitive to compare the two tobramycin nebulised solutions. Altogether the results from the two pharmacokinetic studies conducted in patients and in healthy volunteers provided useful information about the *in vivo* performance of VANTOBRA.

In CF patients the systemic exposure was slightly lower for VANTOBRA compared to TOBI. Based on these data only, it was not possible to determine whether the lower systemic exposure was attributable to product- and/or device-related differences or to patient-related differences. The study was performed in CF patients, with inherent difficulties to inhale and limited normalising distribution that may change over time, potentially affecting study outcome. A lower systemic exposure might reflect that less tobramycin have reached the lungs and therefore not been available for absorption. Another possibility is that more tobramycin actually remains at the target site of action, i.e. in sputum in the lungs. The higher systemic exposure obtained with VANTOBRA compared to TOBI in healthy volunteers did however indicate that the amount of tobramycin deposited in the lung was in fact slightly higher with VANTOBRA in comparison to TOBI, which is expected to be beneficial from an efficacy point of view.

Sputum concentrations were higher for VANTOBRA compared to TOBI, which could be an advantage. However, no definitive conclusions on the clinical relevance of the higher tobramycin concentration found in sputum after administration of VANTOBRA can be drawn.

In vitro data on aerosol characteristics of VANTOBRA nebulised with the Tolero nebuliser, compared with that of TOBI nebulised with PARI LC PLUS and TOBI Podhaler (DPI) in different impactor stages, possibly indicate a higher respirable dose and a lower throat deposition for VANTOBRA compared to TOBI and the DPI.

From the deposition data using labelled 99mTc it could not be definitively concluded that tobramycin from VANTOBRA was similarly distributed to the central, intermediate and peripheral lung regions compared to TOBI due to lack of data.

Risks

Unfavourable effects

The systemic exposure of tobramycin in CF patients was lower or in the same range after administration of VANTOBRA/eFlow compared TOBI/PARI LC PLUS. Thus, systemic safety is not expected to be worse than for TOBI in the intended patient population. In healthy volunteers the systemic exposure was on the other hand slightly higher after administration of VANTOBRA compared to TOBI. The systemic exposure was however still very low in comparison to IV administered tobramycin.

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 VANTOBRA were at higher risk for alterations due to higher local drug concentrations that derive from higher strength of the tobramycin concentration in VANTOBRA 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.

Uncertainty in the knowledge about the unfavourable effects

The Applicant has provided a discussion and references concerning the differences between TOBI and VANTOBRA (higher tobramycin concentration, shorter administration time and different device). The important factors that may have impact on tolerability of nebuliser solutions include the use of a preservative, pH, osmolality, and chloride content. None of these factors differ between VANTOBRA and other tobramycin nebuliser solutions. The tobramycin concentration is higher for VANTOBRA. However, there are references supporting that the concentration is not likely to have impact on tolerability. The delivery rate of VANTOBRA is rather similar to other products but the administration time is shorter. A study of TOBI administered by different devices (short and longer delivery time) did not show any differences with respect to bronchospasm.

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 VANTOBRA 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.

Benefit-risk balance

Importance of favourable and unfavourable effects

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 VANTOBRA), 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.

Benefit-risk balance and discussion

The applied VANTOBRA indication is: 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 reference product for this application is TOBI, with the following approved indication:
“Suppressive therapy of chronic pulmonary infection due to *Pseudomonas aeruginosa* in adults and children aged 6 years and older with cystic fibrosis.”

The submitted clinical package composed of PK, efficacy and safety data generated by the performed studies comparing VANTOBRA with the reference product TOBI as well as literature references, is considered to constitute a relevant bridge between VANTOBRA 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 VANTOBRA.
In line with prescription status for other centrally approved inhaled antibiotics for CF patients, the CHMP considers that the prescription status for VANTOBRA should be 'subject to medical prescription'.
TOBI Podhaler is also an approved, inhaled tobramycin product. This is a dry powder inhaler and is approved with a wording of the indication identical to TOBI.

TOBI Podhaler is an orphan medicinal product and received a positive opinion from CHMP (European Commission Decision: 20 July 2011) and significant benefit was established versus TOBI based on shorter inhalation time. At the time of approval, CHMP acknowledged that approximately 10 % of patients treated with TOBI Podhaler develop intolerance to the product. This is reflected in the SmPC for TOBI Podhaler, albeit not in the wording of the indication, as these patients cannot a priori be identified. CHMP concluded in its similarity assessment that VANTOBRA and TOBI Podhaler are similar.

The overall benefit-risk of VANTOBRA 170 mg nebuliser solution in the proposed indication is considered positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that VANTOBRA is not similar to Cayston but is similar to TOBI Podhaler within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. (See appendix1)

Derogation from market exclusivity

The CHMP considered by consensus that pursuant to Article 8(1) of Regulation (EC) No 141/2000 and Article 3(3) of Commission Regulation (EC) No 847/2000, the following derogation laid down in Article 8(3) of Regulation (EC) No 141/2000 apply:

- the applicant could establish in the application that VANTOBRA, although similar to TOBI Podhaler, is safer, more effective or otherwise clinically superior (as defined in Article 3(3)(d) of Commission Regulation (EC) No 847/2000) for the same therapeutic indication (see appendix 2).

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of VANTOBRA for the indication "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" is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 12 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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.

If the dates for submission of a PSUR and the update of an RMP coincide, they can be submitted at the same time.

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

Not applicable.