

**Public Assessment Report
for paediatric studies submitted in accordance
with Article 46 of Regulation (EC) No1901/2006, as
amended**

**Tobi Podhaler: Tobramycin inhalation powder
Tobi: Tobramycin nebuliser solution**

Tobramycin

UK/W/0089/pdWS/002

**Marketing Authorisation Holder:
Novartis Europharm Ltd.**

Rapporteur:	UK
Finalisation procedure (day 120):	20/12//2016

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Tobramycin inhalation powder Tobramycin nebuliser solution
INN (or common name) of the active substance(s):	Tobramycin
MAH:	Novartis Europharm Ltd.
Currently approved Indication(s)	TOBI is indicated in cystic fibrosis (CF) patients aged 6 years and older for long-term management of chronic pulmonary infection due to <i>Pseudomonas aeruginosa</i> . TOBI Podhaler is indicated for the suppressive therapy of chronic pulmonary infection due to <i>Pseudomonas aeruginosa</i> in adults and children aged 6 years and older with cystic fibrosis.
Pharmaco-therapeutic group (ATC Code):	Aminoglycoside Antibacterials J01GB01
Pharmaceutical form(s) and strength(s):	TOBI Nebulizer Solution 300mg/5ml TOBI Podhaler 28 mg inhalation powder, hard capsule

I. EXECUTIVE SUMMARY

No SmPC and PL changes proposed.

II. RECOMMENDATION

The rapporteur concludes that based on the data provided as part of this European work-sharing procedure under Article 46, the benefit: risk for either TOBI Podhaler or TOBI in paediatrics remains unchanged. Thus the results from this study do not warrant changes to the product information and no further regulatory action is required.

Summary of Outcome

- ☒ No change
- ☐ Change
- ☐ New study data: <section(s) xxxx, xxxx>
- ☐ Paediatric information clarified: < section(s) xxxx, xxxx >

III. INTRODUCTION

The MAH submitted a completed paediatric study for Tobramycin (TOBI), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric study does not influence the benefit risk for Tobi or Tobi Podhaler and that there is no consequential regulatory action.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the study

Tobramycin nebuliser solution (TOBI) and tobramycin inhalation powder (TOBI Podhaler) are composed of the active drug tobramycin, which is an aminoglycoside antibiotic produced by *Streptomyces tenebrarius*. It is active against Gram-negative bacteria and acts primarily by disrupting protein synthesis which leads to altered cell membrane permeability, progressive disruption of the cell envelope and eventual cell death. Both formulations are licensed for the long-term management of chronic pulmonary infection due to *Pseudomonas aeruginosa* in CF patients aged six years and older.

The recommended dosage for Tobramycin nebuliser solution in adults and children ≥ 6 years of age is one single-use ampoule (300 mg/5mL) administered twice daily for 28 days. It is administered using a nebulizer and the formulation is the same for both adults and children.

The recommended dosage for tobramycin inhalation powder in adults and children ≥ 6 years of age is the inhalation of 4x28 mg capsules (112 mg total) twice daily for 28 days. It is administered by the T-326 Inhaler using the same formulation in both age groups.

It should be noted that the doses used for both formulations are the same for all patients regardless of age or body weight.

Rapporteur comments:

This study was not a part of a PIP procedure and was designed to assess ease of use of the TOBI Podhaler against Tobramycin nebuliser solution and colistimethate sodium/colistin sulfate. In this procedure, the MAH proposes that the data are assessed to inform the benefit: risk profiles for both formulations of tobramycin used (TOBI and TOBI Podhaler) in this study.

IV.2 Clinical aspects

1. Introduction

The MAH submitted a final report for:

Study: an open-label, crossover, interventional Phase IV study to compare the ease of use of tobramycin inhalation powder with tobramycin inhalation solution and nebulized colistimethate for the treatment of pulmonary *Pseudomonas aeruginosa* in patients with cystic fibrosis.

2. Clinical study

- **Description**

This is an open-label, crossover, interventional Phase IV study to compare the ease of use of tobramycin inhalation powder with tobramycin inhalation solution and nebulized colistimethate for the treatment of pulmonary *Pseudomonas aeruginosa* in patients with cystic fibrosis.

- **Methods**

- Objective(s)

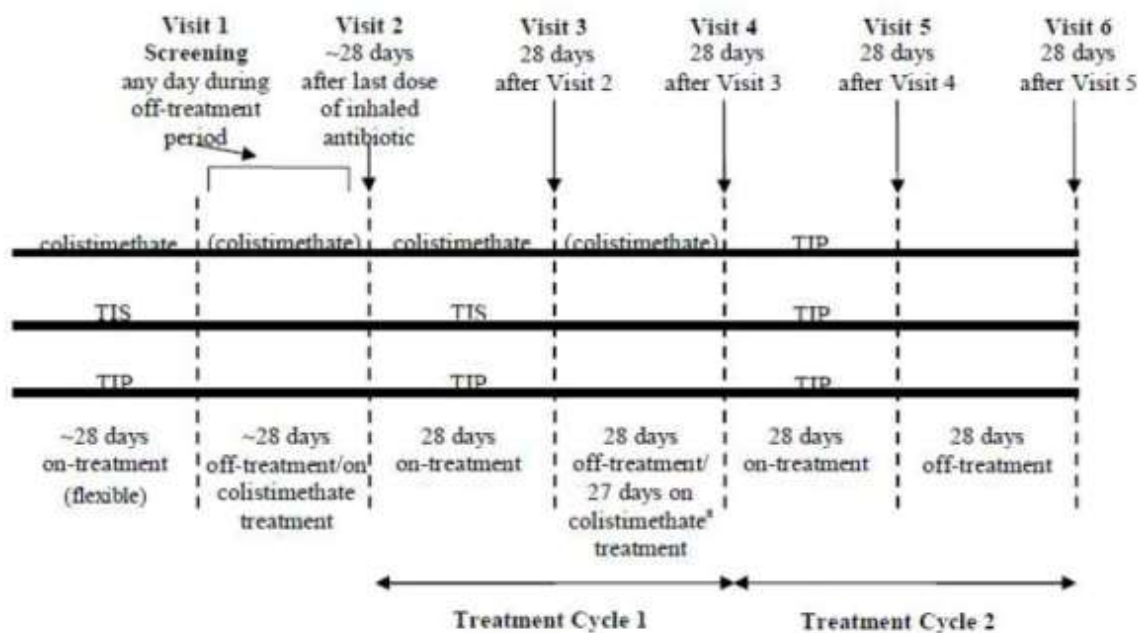
Primary objective

- To compare as a primary indicator for ease of use the mean cumulative time required to set up the delivery device (including preparation of the treatment), administer the drug, and clean the delivery device for Tobramycin inhalation powder hard capsule 28 mg (**TIP**) administered with the T-326 Inhaler, with the mean cumulative time to perform the same activities (including disinfection of the device, where applicable) for the patient's usual (pre-study prescribed) inhaled antibiotic treatment for *P. aeruginosa*.

Secondary objectives

- To assess the absolute change in the number of *P. aeruginosa* colony forming units (CFU) in sputum after up to a period of 28 days of treatment in each treatment arm.
 - To assess the frequency and type of microbial contamination of the T-326 Inhaler used to administer TIP after lifetime use (7 days of treatment) compared with the contamination of the nebulizer, used for the patient's usual nebulized antibiotic treatment for *P. aeruginosa* or for any other nebulized medication (e.g. mucolytics), at baseline (Visit 2) and at each subsequent study visit.
 - To assess the overall tolerability and safety of TIP versus tobramycin inhalation solution (**TIS**) and TIP versus colistimethate sodium/colistin sulfate (hereafter referred to as **COLI**) over both the on-treatment and off-treatment periods of the study by comparison of adverse event (AE) rates, severity, and discontinuations due to AEs.
 - To evaluate the change in the minimum inhibitory concentration (MIC) of the relevant antibiotic for *P. aeruginosa* after a period of up to 28 days of treatment of TIP versus TIS and TIP versus COLI.
 - To evaluate the safety profile of TIP versus TIS and TIP versus COLI in terms of clinical laboratory results and post-inhalational bronchospasm.
 - Study design
- This was an open-label, crossover, interventional, Phase IV study in patients with cystic fibrosis (CF), aged ≥6 years. This study consisted of a screening visit (Visit 1), cycle 1 (Visit 2 and Visit 3) and cycle 2 (Visit 4, Visit 5, and Visit 6). Each cycle consisted of a '28-day on-treatment' period followed by a '28-day off-treatment' period. Each patient was assigned to 1 of the 3 treatment arms (COLI/TIP, TIS/TIP, and TIP/TIP) with the first

treatment cycle based on the patient's usual inhaled antibiotic treatment. All patients were then crossed over to receive TIP with the T-326 Inhaler at cycle 2.



Abbreviations: TIS=tobramycin inhalation solution; TIP=tobramycin inhalation powder

Note: Patients on colistimethate may follow a cyclical or non-cyclical regimen dependent on local treatment practice.

^a Patients on continuous colistimethate are to observe a 24-hour colistimethate-free period before the start of TIP at Visit 4.

- Study population /Sample size

The study population was comprised of males and females aged 6 years and older at the time of screening with a diagnosis of CF, with an FEV1 $\geq 25\%$ and $\leq 90\%$ normal predicted values for age, sex and height based on the National Health and Nutrition Examination Survey (NHANES) III (Hankinson et al. 1999) values for adults (adjusted appropriately with Wang's corrections for patients younger than 18 years of age (Wang et al. 1993), who had a pulmonary infection with *P. aeruginosa* within 6 months prior to screening (Visit 1) and confirmed at screening and were being treated with 1 of the 3 inhaled antibiotic treatments for *P. aeruginosa* (COLI by nebulizer, TIS by nebulizer, or TIP by T-326 Inhaler). It was intended that approximately 60 patients would be recruited globally and 60 were actually enrolled.

- Treatments

The following treatments were used in this study:

Commercially available TIP was used and over-labelled as per local requirements. The TIP drug-device combination product consisted of tobramycin dry powder for inhalation in capsules administered by the T-326 Inhaler. The test product consisted of capsules of TIP at 28 mg dosage strength. Only TIP used in the second cycle of treatment was provided to the patient.

Commercial nebulized TIS, 300 mg, as prescribed by the treating physician, was used. TIS was administered using the nebulizer used by the patient for this treatment at the time of entrance into the study.

Commercial nebulized COLI, 1 million or 2 million units, as sodium salt was supplied as vials of sterile lyophilized cake or as vials of powder, depending on the supplier. It was reconstituted in 0.9% sterile sodium chloride, in water for injection, or in 0.45% sodium chloride, depending upon the supplier and country, and had to be reconstituted and administered in accordance with national PI. COLI was administered by inhalation using the patient's usual nebulizer for this treatment.

Each patient was assigned to 1 of the following 3 treatment arms, with the first treatment cycle based on the patient's usual inhaled antibiotic treatment:

COLI/TIP

First cycle: nebulized COLI, 1 million or 2 million units twice or thrice per day (or the patient's usual dose and regimen) for 56 days (no off-treatment period) or 28 days on treatment followed by 28 days off-treatment (cycling regimen), depending on local treatment guidelines.

Second cycle: TIP, 112 mg (4, 28-mg capsules) twice per day for 28 days followed by 28 days off-treatment.

TIS/TIP

First cycle: Nebulized TIS, 300 mg twice per day for 28 days followed by 28 days off-treatment.

Second cycle: TIP, 112 mg (4, 28-mg capsules) twice per day for 28 days followed by 28 days off-treatment.

TIP/TIP

First cycle: TIP, 112 mg (4, 28-mg capsules) twice per day for 28 days followed by 28 days off-treatment.

Second cycle: TIP, 112 mg (4, 28-mg capsules) twice per day for 28 days followed by 28 days off-treatment.

- Outcomes/endpoints:

Ease of use (main criteria for evaluation):

- Time required to administer study treatment, including device set-up/preparation, administration, and device cleaning (includes the time needed to work hands-on with the device during dismantling, cleaning [but not air drying or use of the dishwasher], disinfection activity [where applicable]).
- Readiness of use of study treatment: expressed in preparation time which was defined as the time of start to time of completion of delivery device preparation plus the time of start to time of completion of study treatment preparation.
- In paediatric patients (<18 years): patient versus caregiver performing the various steps

Efficacy:

- Microbial contamination of delivery device: *P. aeruginosa* and other pathogens (semiquantitative culture data: light, moderate or heavy growth).
- *P. aeruginosa* quantitative culture data (CFU, from patients' sputum) or semiquantitative culture data (light, moderate or heavy growth, from patients' deep cough throat swabs).
- Semiquantitative culture data (light, moderate or heavy growth) from patients' specimens for non-*P.aeruginosa* pathogens.
- Minimum inhibitory concentration (MIC) of selected antibiotics for *P. aeruginosa* from patients' specimens

Safety:

- Adverse events occurring before starting study treatment but after signing the informed consent form are recorded on the Relevant Medical History/Current Medical Conditions case report form (CRF).
- Physical examination and vital sign measurements.
- Haematology, clinical chemistry and urinalysis.
- Audiology (for patients with a history of abnormal audiology and for any patients with new or worsened hearing abnormalities during the study).
- Spirometry (FEV1, forced vital capacity [FVC], and forced expiratory flow between 25% and 75% of FVC [FEF25%-75%]).

- Statistical Methods:

For the primary variable, summary statistics was provided for the mean total administration time per cycle and by treatment arm and for within patient differences in mean total administration time between treatments (cycle 2 – cycle 1) by treatment arm. In case the recording period starts earlier than 7 days prior the site Visit3/5 all data were used for analysis.

Efficacy:

- The number of *P. aeruginosa* (CFU) in sputum and the absolute change after 28 days of treatment were summarized by arm and treatment.
- The semiquantitative culture data (light, moderate or heavy growth) was summarized by arm and treatment.
- The frequency and type of microbial contamination of the T-326 Inhaler used to administer TIP after seven days of treatment compared with the contamination of the nebulizer used for the nebulized antibiotic treatment or for any other nebulized treatment (e.g. mucolytics) by the patient.
- The MIC of the study antibiotic for *P. aeruginosa* after 28 days of each treatment was summarized by arm and treatment.

Safety:

- All safety data, including AEs, AEs resulting in withdrawal of treatment, serious adverse events (SAEs) (all coded using the Medical Dictionary for Regulatory Activities [MedDRA] version 18.1 terminology), laboratory test results, audiology (where assessed), airway reactivity, and vital signs were summarized descriptively for each treatment and treatment cycle by arm.
- Safety analysis was based on descriptive statistics for patients who had received at least one dose of study medication. Rates of cough, inhalation-associated cough, and other post-inhalation AEs (including haemoptysis) were summarized by arm and treatment.
- Discontinuation rates were summarized by arm and treatment.

• Results

- Recruitment/ Number analysed:

A total of 60 patients were enrolled and received at least one dose of study treatment; 14 patients entered the TIS/TIP arm, 28 patients entered the COLI/TIP arm, and 18 patients entered the TIP/TIP arm.

Of the 60 patients enrolled, 4 were paediatric patients. The paediatric data are discussed separately.

Table 10-1 Patient disposition (All subjects)

Disposition Reason	TIS/TIP n (%)	COLI/TIP n (%)	TIP/TIP n (%)
Entered the study	14	28	18
Received at least one dose of study drug	14 (100.0)	28 (100.0)	18 (100.0)
Completed	12 (85.7)	25 (89.3)	14 (77.8)
Discontinued study	2 (14.3)	3 (10.7)	4 (22.2)
Adverse event(s)	0 (0.0)	2 (7.1)	2 (11.1)
Abnormal lab value(s)	0 (0.0)	0 (0.0)	0 (0.0)
Abnormal test procedure result(s)	0 (0.0)	0 (0.0)	0 (0.0)
Unsatisfactory therapeutic effect	0 (0.0)	0 (0.0)	0 (0.0)
Subject's condition no longer requires study drug	0 (0.0)	0 (0.0)	0 (0.0)
Subject withdrew consent	2 (14.3)	0 (0.0)	0 (0.0)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)
Administrative problems	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)
Protocol deviation	0 (0.0)	1 (3.6)	2 (11.1)
Patient's inability to use the device	0 (0.0)	0 (0.0)	0 (0.0)

Percentages are based on the number of patients who received at least one dose of study drug.

- Baseline data:

The mean age of patients was 27.6 years (± 8.40) and the majority of patients (93.3%) were ≥ 18 years of age. All patients were Caucasian and the majority of patients were male (65%).

Most patients (51 patients, 85.0%) from all treatment arms completed the study.

Nine patients (15%) discontinued the study:

- Two patients (14.3%) from the TIS/TIP arm (both withdrew consent)
- Three patients (10.7%) from the COLI/TIP arm (2 due to AEs and 1 due to protocol deviation)
- Four patients (22.2%) from the TIP/TIP arm (2 due to AEs and 2 due to protocol deviations).

All these patients mentioned above except 1 patient discontinued before entering cycle 2. One patient (in the TIP/TIP arm) discontinued from cycle 2 due to AE.

- Primary Objective: Ease of use:

The mean total administration time was 37.0 minutes in cycle 1 versus 5.0 min in cycle 2 for the TIS/TIP arm, 16.4 min versus 3.8 min for the COLI/TIP arm, and 4.2 min versus 3.4 min for the TIP/TIP arm. The difference in mean total administration time was significantly shorter in cycle 2 (after crossover to TIP) than in cycle 1 for the TIS/TIP (mean time difference, within patient differences cycle 2 – cycle 1: -32.7 min, $p=0.0112$) and COLI/TIP arms (mean time difference, within patient differences cycle 2 – cycle 1: -13.3 min, $p=0.0016$). The difference in cumulative administration time between the treatment cycles remained similar for the TIP/TIP arm (mean time difference, within patient differences cycle 2 – cycle 1: -0.2 min, $p=0.4380$).

Overall, patients on TIP took significantly less time than patients on COLI or TIS to set up the delivery device, administer the drug, and clean the delivery device.

- Secondary Objectives:

Absolute change in the number of *P. aeruginosa* CFUs in sputum after up to a period of 28 days of treatment:

At Visit 3, after the end of on-treatment period in cycle 1, the mean log reduction of *P. aeruginosa* for sum of all biotypes was 1.4 log₁₀ CFU in the TIS/TIP arm, 0.6 log₁₀ CFU in the COLI/TIP arm and 1.7 log₁₀ CFU in the TIP/TIP arm. At Visit 5 (cycle 2), the mean log reduction was slightly less for the TIS/TIP arm and was similar in the other two arms (TIS/TIP: 0.9 log₁₀ CFU, COLI/TIP: 0.5 log₁₀ CFU and TIP/TIP: 1.6 log₁₀ CFU). At Visit 6 (i.e., 28 days after off-treatment period in cycle 2), the recovery of CFUs returned to Visit 4 values or was similar to Visit 4 across the treatment arms.

The change in MIC of the relevant antibiotic for *P. aeruginosa* after a period of up to 28 days of treatment:

In general, after a period of up to 28 days of treatment with TIP versus TIS and TIP versus COLI assessed by MIC₅₀ and MIC₉₀, the results showed a one dilution-fold increase in tobramycin MICs at Visit 5 compared to Visit 3 for the TIS/TIP and COLI/TIP arms. Improvement of MICs was observed at Visit 6.

In the TIS/TIP arm, tobramycin MICs were higher at Visit 5 than in Visit 3 (MIC₅₀: 4 $\mu\text{g/mL}$ versus 2 $\mu\text{g/mL}$, MIC₉₀: 512 $\mu\text{g/mL}$ versus 256 $\mu\text{g/mL}$). However, at Visit 6, at the end of off treatment period, MIC₅₀ and MIC₉₀ values decreased to 2 $\mu\text{g/mL}$ and 32

µg/mL, respectively. Similar results were observed in the COLI/TIP arm. The MIC50 and MIC90 values observed at Visit 3 (2 µg/mL and 16 µg/mL, respectively) further increased at Visit 5 (4 µg/mL and 32 µg/mL, respectively) after crossover to TIP. However, at Visit 6, MIC50 value decreased to 2 µg/mL and MIC90 remained the same as it was at Visit 5 (32 µg/mL). For patients who received TIP in both cycles (TIP/TIP), the MIC50 and MIC90 tobramycin values were stable up to Visit 5 (2 µg/mL and 64 µg/mL, respectively) and further decreased to 1 µg/mL and 32 µg/mL at the end of Visit 6.

Microbial contamination of the T-326 Inhaler/nebulizer:

Overall 2 patients in the TIS/TIP arm, 9 patients in the COLI/TIP arm and 1 patient in the TIP/TIP arm had any contaminated device across the treatment cycles

The assessment of the unused commercial T-326 Inhaler showed no microbial contamination at cycle 2 (Visit 4). In the TIS/TIP arm, no pathogen was isolated from cycle 1 (Visits 2 and 3). The only pathogen observed after using T-326 Inhaler was *S. aureus*. That patient did not have *S. aureus* isolated from the sputum. During cycle 2 (Visit 4) light growth of *P. aeruginosa* was isolated from the tubing used with a Pari LC Sprint nebulizer. In the COLI/TIP arm, the majority of the pathogens were isolated from the device used to administer COLI in cycle 1. Most of these were isolated only once. Overall 9 patients in the COLI/TIP arm had any contaminated delivery device and none of the patient had same pathogen isolated from their sputum, except for 1 patient.

No contaminated T-326 Inhaler was shown in the COLI/TIP arm in cycle 2. In the TIP/TIP arm, in cycle 1 (Visit 2, baseline visit) moderate growth of *P. aeruginosa* was isolated from the mouthpiece used with a Pari eflow Rapid nebulizer.

- Exploratory Objective:

The relative mean change from baseline to post-baseline in FEV1 % predicted:

In cycle 1 (Visit 3), at the end of the first on-treatment period, the mean FEV1 % predicted showed a relative increase from baseline in the TIS/TIP (2.2%) and COLI/TIP (3.9%) arms, and a slight decrease from baseline in the TIP/TIP (-2.8%) arm. In cycle 2 (Visit 5) at the end of the second on-treatment period, the FEV1 % predicted remained stable as was observed at Visit 4 pre-dose value across the treatment arms.

Antipseudomonal antibiotic usage and hospitalization:

The number of patients using new anti-pseudomonal antibiotics was comparatively lower in cycle 2 than in cycle 1 for the TIS/TIP (25.0% versus 35.7%) and COLI/TIP (32.0% versus 35.7%) arms. The number of patients with new anti-pseudomonal antibiotics overall in cycle 2 was low (15 patients, 28.8%).

In cycle 1, 2 patients (11.1%) were hospitalized due to respiratory related SAEs in the TIP/TIP arm, 3 patients (21.4%) in the TIS/TIP arm and 7 patients (25.0%) in the COLI/TIP arm for a median duration of 10 to 17 days. In cycle 2, a total of 7 patients (13.5%) were hospitalized for a median duration of 15 days.

- Safety results

All Patients:

No deaths were reported in this study.

Patients with any adverse events (AEs) were higher in cycle 2 than in cycle 1 for the TIS/TIP arm (Cycle 2: 66.7% versus cycle 1: 42.9%). The percentage was comparable for the TIP/TIP arm (cycle 2: 66.7% versus cycle 1: 61.1%). The percentage of patients with any AEs was lower in cycle 2 than in cycle 1 for the COLI/TIP arm (cycle 2: 48.0% versus cycle 1: 67.9%).

In cycle 1, the most frequently reported events were under the following system organ classes (SOCs): infections and infestations, nervous system disorders and respiratory, thoracic and mediastinal disorders. The most commonly reported AEs by preferred terms were infective pulmonary exacerbation of cystic fibrosis, headache, sputum increased, nasopharyngitis, and cough.

In cycle 2, the most frequently reported events were under the following SOC: infections and infestations, respiratory, thoracic and mediastinal disorders, and general disorders and administration site conditions. The most commonly reported AEs by preferred terms were infective pulmonary exacerbation of cystic fibrosis, headache, nasopharyngitis, and cough.

Patients with any SAEs were comparatively lower in cycle 2 than in cycle 1 for the COLI/TIP and TIP/TIP arms but were slightly higher in the TIS/TIP arm. The SAE reported most frequently in cycle 1 and cycle 2 was infective pulmonary exacerbation of cystic fibrosis.

None of the SAEs reported in cycle 1 were suspected to be related to the study treatment. The SAEs that were suspected to be related to the study treatment in cycle 2 were acoustic stimulation tests abnormal, tinnitus, forced expiratory volume decreased, and upper respiratory tract infection.

Haematology parameters showed no clinically significant changes from baseline to Visit 4 and Visit 6. No notable changes in vital signs were observed from baseline to various post-baseline visits.

At Visit 4, 2 patients in the TIS/TIP arm and 1 patient in the COLI/TIP arm had $\geq 100\%$ increase in BUN from screening. No patient in the TIP/TIP arm had any notable values of renal laboratory parameters. At Visit 6, 2 patients in the TIS/TIP arm and 1 patient in the COLI/TIP arm had $\geq 100\%$ increase in BUN from screening. One patient each in the TIS/TIP and COLI/TIP arms had $\geq 100\%$ increase in BUN and $>ULN$ from screening. One patient in the TIS/TIP arm had positive results for urine protein ($\geq ++$) at Visit 6. Patients with elevations of LFTs at any time post-baseline were very limited: 1 patient each in TIS/TIP and TIP/TIP arms.

The majority of patients across treatment cycles and treatment arms had negative urine protein, glucose or blood on urine dipstick.

The frequency of airway reactivity (i.e. decrease of 20% or more in post dose FEV1 % predicted as compared to the pre-dose) from pre-dose to 15 to 45 minutes post-dose was low: 1 patient each at Visit 2 and Visit 3 in the COLI/TIP arm and 1 patient at Visit 4 in the TIP/TIP arm.

For assessment of events during inhalation, in patients who received TIP in both the cycles (TIP/TIP arm), there was a clear trend in decrease in frequency of cough over time from cycle 1 to cycle 2 and that led to few patients with cough at cycle 2 compared to other treatment arms across treatment cycles.

No events other than cough during and within 5 minutes following inhalation of study medication were reported.

Audiology abnormalities were reported in a low proportion of patients: one patient in the COLI/TIP arm at Visits 3, 5 and 6 and 2 patients in the TIP/TIP arm at Visits 5 and 6 reported audiology abnormalities.

- **Paediatric patients:**

There were 4 paediatric patients enrolled; 2 patients each in the 6-12 years and 13-17 years age groups. Those enrolled were:

- 13-year-old male and a 9-year-old female in the TIP/TIP group.
- 13-year-old female in the TIS/TIP group.
- 12-year-old female in the COLI/TIP group.

All paediatric patients completed the study.

There are no efficacy data presented or summarised specifically for the paediatric patients in the clinical study report. Thus individual patient data were reviewed

- Primary endpoint: Ease of use

13-year-old male and a 9-year-old female in the TIP/TIP group:

The mean total (cumulative) administration times in the TIP/TIP arm was 3.6 minutes in cycle 1 and 3.1 minutes in cycle 2 for one patient, and 1.4 minutes in cycle 1 and 2.1 minutes in cycle 2 for the second patient.

13-year-old female in the TIS/TIP group:

The mean total (cumulative) administration time for this patient in the TIS/TIP arm was 14.7 minutes for TIS in cycle 1 and 4.6 minutes for TIP in cycle 2, which represented a 10.1 minute decrease in administration time with use of TIP in cycle 2.

12-year-old female in the COLI/TIP group:

The mean total administration time for the patient in the COLI/TIP arm was missing

- Secondary endpoints:

There were reductions seen in *P.aeruginosa* sputum density in the 4 paediatric patients consistent with the reductions seen in the overall study population.

There were no significant changes in tobramycin minimum inhibitory concentration (MICs) with the exception of a sputum isolate of *P.aeruginosa* biotype dry from one patient, which increased to >512 µg/mL at the completion visit from 0.5 µg/mL at baseline. Despite this increase in MIC, this patient had a reduction in *P. aeruginosa* density noted at the completion visit in their sputum culture.

At the end of the first on -treatment period (Cycle 1) for the two patients in the TIP/TIP arm, the mean FEV1 % predicted showed a relative change from baseline of 17.6% for

one patient and 1.1% for the second patient. For the patient in the TIS/TIP arm there was a relative change of -5.1%, and for the patient in the COLI/TIP arm there was a relative change of -1.5%.

At the end of the second on-treatment period (Cycle 2 -Visit 5) to the completion visit for the two patients in the TIP/TIP arm the mean FEV1% predicted showed a relative change of -5.5% for one patient and 13.9% for the second patient. For the patient in the TIS/TIP arm there was a relative change of -9.1%, and for the patient in the COLI/TIP arm there was a relative change of -16%.

A review of the FEV1 historical records for these patients in the 12 months prior to study entry showed that these changes were consistent with previously reported values for these patients with the exception of the change in FEV1 values demonstrated for the COLI/TIP patient.

Overall there was some variability demonstrated by the relative change in FEV1% predicted for the 4 paediatric patients, but in 3 of the 4 patients this variability was consistent with what was reported in the year prior to study entry.

Safety:

There were also no clinically significant changes in haematology or chemistry parameters in these paediatric patients.

The AE's are noted below:

- 13-year-old male in the TIP/TIP group. An (AE) of cough was reported for this patient. The cough was mild for which no action was taken and was not suspected to be related to study drug.
- 13-year-old female in the TIS/TIP group. No AEs were reported for this patient.
- 9-year-old female in the TIP/TIP group. A serious adverse event (SAE) of infective pulmonary exacerbation of CF was reported for which the patient was hospitalized. The pulmonary exacerbation resolved and was not suspected to be related to study medication.
- 12-year-old female in the COLI/TIP group. There were no AEs listed for this patient.

There were no reports of airway hyperactivity noted for any of these patients.

There were no new or unexpected safety findings from the 4 paediatric patients enrolled in this study. The safety results observed in this study were generally consistent with the known established safety profiles of TIP and TIS.

Rapporteur's comments:

This is a small study that was designed to assess ease of use. Though it was not powered for efficacy, a few supplementary endpoints were included for this.

The majority of the patients enrolled were over 18 years of age. Overall it demonstrated that TIP was easier to use, with less time to administer compared to TIS or COLI. The AE's documented were in keeping with the expected AEs of the formulations used; no new signals were observed.

There was a reduction in *P. aeruginosa* after TIP, with fewer episodes of bacterial contamination of the TIP delivery device compared with the devices used for COLI.

Four paediatric patients were enrolled and all completed the study; due to this small number only individual assessments could be made.

For ease of use (primary endpoint):

There was no change in the mean total (cumulative) administration times in the two paediatric patients in the TIP/TIP arm and a reduction was noted in the single patient enrolled in the TIS/TIP arm. No data is presented for the patient in the COLI/TIP arm. Overall no clear assessment of ease of use in the paediatric patients could be made from this limited data.

Safety

Two of the four paediatric patients reported some adverse events (AE) which were consistent to AEs reported in adults and for the formulations used. Overall no new safety concerns were noted.

Efficacy

There were reductions seen in *P. aeruginosa* sputum density at the completion phase in the 4 paediatric patients that were consistent with the reductions seen in the overall study population after the treatment with TIP. The MICs for tobramycin for all but one patient remain unchanged. For the patient that had an increase in the Tobramycin MIC, there was no effect on the reduction of the *P. aeruginosa* sputum density at the end of the completion phase of the study.

The predicted FEV1% showed variability in 3 of the 4 paediatric patients that were not similar to the adult study population; where FEV1% showed an increase after cycle 2. However it was noted, by retrospective review of their medical charts, that these three patients had a similar variability in their FEV1% in the year prior to the study.

In summary:

This study demonstrated that overall, TIP took less time to set up and administer than the other established treatments for CF (TIS and COLI). The paediatric data from this study are insufficient to inform efficacy and ease of use of TOBI Podhaler (TIP) in the paediatric age group. There was suppression of *P. aeruginosa* growth in culture, but variability in the FEV 1% predicted for these patients. No new safety signals were noted in either TIS or TIP arms. Thus there is no change to the benefit: risk profile for either Tobramycin inhaled powder or Tobramycin nebulised solution in the paediatric population.

3. Discussion on clinical aspects

This open-label, crossover, interventional Phase IV study was designed to compare the ease of use of TIP with TIS and nebulized COLI for the treatment of pulmonary *P. aeruginosa* in patients with CF. The first treatment cycle was designed to compare the pre-study prescribed inhaled antibiotic treatments in terms of time spent on administration and contamination of the device used in a close to real-world setting. The second cycle allowed the direct assessment of the 'switch experience' from nebulized antibiotics to TIP in terms of patient satisfaction, efficacy, and safety.

A total of 60 patients were enrolled - 4 of whom were paediatric patients - received at least one dose of study treatment and, 51 patients completed the study. The baseline demographic characteristics were balanced among the treatment arms. Patients had mean

baseline FEV1 % predicted of 55.0% to 62.6% across the treatment arms indicating moderate airway obstruction. *P. aeruginosa* sputum density at baseline was comparable across the treatment arms (ranging from 6.8 log₁₀CFU/mL in the TIP/TIP arm to 7.8 log₁₀ CFU/mL in the TIS/TIP arm) and 30% of patients had MIC >8 µg/mL. The baseline burden of *P. aeruginosa* sputum density is consistent with previous TIP trials, as is the baseline distribution of MIC values.

Patients on TIP took significantly less time than patients on COLI or TIS to set up the delivery device, administer the drug, and clean the delivery device. Additional evidence for the efficacy of TIP was shown by sustained suppression of *P. aeruginosa* and stability in FEV1 % predicted. For 3 of the 4 paediatric patients there was some variability in the FEV1% predicted but this pattern was consistent to what was reported in those patients in the year prior to the study. The safety results observed in this study were generally consistent throughout the study group including for the paediatric patients. They were also comparable among the treatment arms and with the known safety profile of TIP and TIS.

V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

This study was designed to assess ease of use, comparing TOBI Podhaler with TOBI and Colistimethate sodium/colistin sulfate. There were a few paediatric patients enrolled in submitted study; based on the results from these patients there is no change to the positive benefit: risk profile of either TOBI or TOBI Podhaler for their current paediatric indications.

- **Recommendation**

No further regulatory action is required.