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Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

TOBI Podhaler

tobramycin

Procedure no: EMEA/H/C/002155/P46/029

Note

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

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1. Introduction

On 5 April 2016, the MAH submitted a completed paediatric study for tobramycin inhalation powder, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

The MAH states that the efficacy and safety data from study CTBM100C2403 do not warrant an update of the product information of TOBI Podhaler.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study CTBM100C2403 *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*, is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

The dose was 112 mg tobramycin (4x 28mg capsules), administered twice daily for 28 days followed by 28 days off treatment.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- study CTBM100C2403 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.

A total of 60 patients were enrolled of which there were 4 paediatric patients.

2.3.2. Clinical study

Study CTBM100C2403 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

Description

This open-label, crossover, interventional phase IV study was designed to evaluate the ease of use of tobramycin inhalation powder (TIP) administered via the T-326 inhaler compared with tobramycin inhalation solution (TIS) and colistimethate (COLI) administered via nebuliser in CF patients with pulmonary infection due to *P. aeruginosa*.

A total of 60 patients were enrolled and received at least one dose of study treatment; there were 4 paediatric patients enrolled, all of whom completed the study.

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 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.

CHMP comment

The objectives seem appropriate to evaluate the ease of use of TIP vs TIS/COLI.

Study design

This was an open-label, crossover, interventional Phase IV study in patients with cystic fibrosis (CF), aged ≥6 years. Approximately 60 patients were planned to be enrolled globally. 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.

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 ≥25% and ≤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:

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. Commercially available product was used and was overlabelled as per local requirements. 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.

Commercially available TIP was used in this study; therefore, batch number is not applicable.

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 ontreatment 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.

The doses used in this study were the standard doses for this indication per the product labels or were in line with the proposed labeling and/or CF guidelines where the treatment was under Health Authority review. The duration of switch-over treatment, a single cycle for '28-day on-treatment' and '28-day off-treatment' periods, reflected the labeling.

Treatment assignment was based on the patient's usual nebulized antibiotic treatment (COLI, TIS, or TIP). At Visit 2, patients were assigned to continue to receive their usual nebulized antibiotic treatment for the first treatment cycle, and all patients were assigned to receive TIP for the second treatment cycle.

Outcomes/endpoints

Efficacy assessments included the following:

- 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
- MIC of selected antibiotics for *P. aeruginosa* from patients' specimens
- Use of antibiotic treatment for *P. aeruginosa* other than study treatments

The ease-of-use assessments included the following:

- 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]). **This was the primary variable of this study.**
- 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.
- Patient-reported outcomes (reported by caregivers for minors, as applicable)

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.

The number of *P. aeruginosa* (CFU) in sputum, the absolute change after 28 days of treatment, the semiquantitative culture data (light, moderate or heavy growth), and the MIC of the study antibiotic for *P. aeruginosa* after 28 days of each treatment, were all 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.

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 hemoptysis) were summarized by arm and treatment. Discontinuation rates were summarized by arm and treatment.

Assessor's comment

Only descriptive statistics were used, no hypothesis was tested.

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 (Table 10-1).

Most patients (51 patients, 85.0%) from all treatment arms completed the study. Nine patients (15%) discontinued the study: 2 patients (14.3%) from the TIS/TIP arm (both withdrew consent), 3 patients (10.7%) from the COLI/TIP arm (2 due to AEs and 1 due to protocol deviation), and 4 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 (1006/00006) discontinued before entering cycle 2. Patient# 1006/00006 (in the TIP/TIP arm) discontinued from cycle 2 due to AE.

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.
Source: Table 14.1-1.1.

Baseline data

Demographic characteristics were comparable across the treatment arms (Table 11-2). The mean (SD) age of patients overall was 27.6 years (±8.40) and the majority of the patients (93.3%) were ≥18 years of age. There were 4 paediatric patients enrolled, 2 patients each in the 6 – 12 years and 13 – 17 years age groups. There were a higher proportion of males than females (65.0% versus 35.0%). All patients were Caucasian.

Demographic characteristics in safety set 1 and safety set 2 were consistent with the full analysis set.

Table 11-2 Demographic summary (Full analysis set)

Variable	TIS/TIP N=14	COLI/TIP N=28	TIP/TIP N=18
Age (years)			
N	14	28	18
Mean (SD)	27.4 (6.82)	28.4 (9.86)	26.6 (7.25)
Median	27.5	26.0	27.0
Min-Max	13-39	12-62	9-37
Age category (years), n (%)			
6-12	0 (0.0)	1 (3.6)	1 (5.6)
13-17	1 (7.1)	0 (0.0)	1 (5.6)
≥18	13 (92.9)	27 (96.4)	16 (88.9)
Sex, n (%)			
Male	10 (71.4)	18 (64.3)	11 (61.1)
Female	4 (28.6)	10 (35.7)	7 (38.9)
Race, n (%)			
Caucasian	14 (100.0)	28 (100.0)	18 (100.0)
Weight (kg)			
n	14	28	18
Mean (SD)	61.0 (11.89)	61.3 (12.75)	59.8 (16.19)
Median	59.1	60.9	56.4
Min-Max	42.4-84.3	39.0-84.6	26.5-92.0
Height (cm)			
n	14	28	18
Mean (SD)	167.0 (10.02)	168.5 (10.01)	166.8 (16.48)
Median	169.0	172.0	169.5
Min-Max	149-186	147-184	126-194
Body mass index (kg/m^2)			
n	14	28	18
Mean (SD)	21.7 (3.19)	21.4 (3.12)	21.2 (3.83)
Median	20.5	20.4	20.9
Min-Max	19.1-29.5	16.2-29.3	15.5-28.1
Source of subject referral, n (%)			
Physician's own practice	10 (71.4)	11 (39.3)	13 (72.2)
Physician referral	1 (7.1)	9 (32.1)	2 (11.1)
ER or hospital	1 (7.1)	1 (3.6)	0 (0.0)
Patient database	0 (0.0)	7 (25.0)	1 (5.6)
Other	2 (14.3)	0 (0.0)	2 (11.1)

Body mass index: weight (kg) / [height (m)^2].
Source: Table 14.1-3.1.

Baseline disease characteristics are summarized in Table 11-3. Patients had a mean FEV1 % predicted that ranged from 55.0% (TIS/TIP arm) to 62.6% (TIP/TIP arm), which corresponds to moderate airway obstruction (Cystic Fibrosis Foundation Patient Registry 2013 Annual Data Report). Percent predicted values were recalculated according to Quanjer et al. 2012. The mean *P. aeruginosa* sputum density (sum of all biotypes) at baseline was slightly higher in the TIS/TIP (7.8 log10 CFU/mL) arm than in the COLI/TIP (6.9 log10 CFU/mL) and TIP/TIP (6.8 log10 CFU/mL) arms. The majority of patients had pseudomonal isolates with tobramycin MIC ≤8 μg/mL at baseline (41 patients, 68.3% overall, ranging from 57.1% in the TIS/TIP arm to 75.0% in the COLI/TIP arm). Most of the patients did not use long- or short-acting bronchodilators in the TIS/TIP and COLI/TIP arms at baseline compared to 55.6% and 61.1% of patients in the TIP/TIP arm, respectively.

Table 11-3 Disease characteristics at baseline (Full analysis set)

Variable	TIS/TIP N=14	COLI/TIP N=28	TIP/TIP N=18
FEV_1 % predicted (recalculated)[a]			
N	14	28	18
Mean (SD)	55.0 (17.02)	59.1 (19.42)	62.6 (17.78)
Median	52.3	64.1	65.5
Min-Max	26.8-87.2	24.0-99.5	32.6-88.5
FVC % predicted (recalculated)[a]			
N	14	28	18
Mean (SD)	67.7 (18.34)	80.1 (19.44)	78.6 (15.45)
Median	68.9	83.6	79.9
Min-Max	30.0-99.3	33.9-109.4	45.1-104.8
FEF_{25-75} % predicted (recalculated)[a]			
N	13	23	18
Mean (SD)	30.6 (21.19)	32.5 (22.27)	37.3 (26.79)
Median	25.1	30.0	28.8
Min-Max	9.0-91.3	8.2-98.3	13.5-101.8
Sputum density of *P. aeruginosa* (log_{10} CFU/mL) - sum of all biotypes[#]			
N	13	23	12
Mean (SD)	7.8 (1.88)	6.9 (2.22)	6.8 (2.46)
Median	8.8	7.8	7.6
Min-Max	3.6-9.1	1.3-9.1	1.3-8.9
P. aeruginosa tobramycin MIC, n (%)			
>8 µg/mL	6 (42.9)	6 (21.4)	6 (33.3)
≤8 µg/mL	8 (57.1)	21 (75.0)	12 (66.7)
Missing	0 (0.0)	1 (3.6)	0 (0.0)
Current use of long-acting bronchodilator, n (%)			
No	13 (92.9)	23 (82.1)	8 (44.4)
Yes	1 (7.1)	5 (17.9)	10 (55.6)
Current use of short-acting bronchodilator, n (%)			
No	11 (78.6)	21 (75.0)	7 (38.9)
Yes	3 (21.4)	7 (25.0)	11 (61.1)

Baseline is defined as the last value before first dose of study drug.

FEV_1 % predicted/ FVC % predicted/ FEF_{25-75} % predicted are derived according to Quanjer et al. 2012.

Overall density, defined as the sum of biotypes (mucoid, dry and small colony variants).

[a]: Recalculated: In order to avoid calculation errors and use of different formulas to calculate %predicted values by local labs, FEV_1 % predicted/ FVC % predicted/ FEF_{25-75} % predicted are derived according to Quanjer et al. 2012.

Source: Tables 14.1-3.2.

Overall, 38 patients (63.3%) experienced pulmonary exacerbations prior to study start, with the majority being observed in the TIS/TIP and COLI/TIP arms (78.6% in each). Of these, 26 patients (68.4%) were hospitalized in the previous 12 months. Five patients (13.2%) were hospitalized <1 month prior to study start. Relevant medical history and medical conditions were higher in the TIP/TIP and COLI/TIP arms (83.3% and 82.1%, respectively) than in the TIS/TIP arm (57.1%). The most frequently reported medical history/condition was asthma, reported by 10% of patients overall. All other medical conditions were reported in <10% of patients overall.

All patients (100%) received anti-pseudomonal antibiotics at baseline (Table 14.1-3.8). The most frequently used anti-pseudomonal antibiotics (any route of administration) were COLI (35 patients [all inhaled], 58.3%) and tobramycin (33 patients [32 inhaled, 1 i.v.], 55.0%). Overall 31 patients

(51.7%) received macrolides (reasons listed mainly as prophylaxis) at baseline and the percentage was higher in the TIP/TIP (61.1%) arm than in the COLI/TIP (57.1%) and TIS/TIP (28.6%) arms. The most frequently reported macrolide was azithromycin (31 patients, 51.7 %).

CHMP comment

Baseline characteristics were overall balanced between the three treatment arms. The observed differences are not expected to have any influence on the primary objective of the study (ease of use of TIP vs TIS/COLI).

Efficacy results

The primary objective of this study was to compare the mean total time required to set up the delivery device, administer the drug, and clean the delivery device for TIP administered with the T-326 Inhaler with the mean cumulative time (including disinfection of nebulizers where applicable) to perform the same activities for the patient's usual nebulized, antibiotic treatment for *P. aeruginosa*. Analysis of mean total (cumulative) administration time is presented in Table 11-6.

Table 11-6 Analysis of mean total administration time in minutes (Full analysis set)

Cycle Statistic	TIS/TIP (N=14)	COLI/TIP (N=28)	TIP/TIP (N=18)
Cycle 1			
n	8	17	14
Mean (SD)	37.0 (22.06)	16.4 (9.54)	4.2 (2.02)
Median	35.6	12.7	4.0
90th Percentile	80.0	28.5	6.5
Min-Max	10.8 - 80.0	5.5 - 37.1	1.2 - 8.5
Cycle 2			
n	10	16	11
Mean (SD)	5.0 (2.04)	3.8 (1.70)	3.4 (2.06)
Median	5.3	3.5	3.0
90th Percentile	7.0	6.4	5.9
Min-Max	0.2 - 7.3	1.3 - 7.0	1.2 - 8.1
Patients time difference between Cycle 1 and 2			
n	7	11	11
Mean (SD)	-32.7 (23.90)	-13.3 (10.35)	-0.2 (0.92)
Median	-35.5	-9.2	-0.3
90th Percentile	-3.5	-2.4	0.6
Min-Max	-74.1 - -3.5	-32.8 - 1.1	-2.0 - 1.5
Cycle comparison			
95% CI	(-54.8, -10.6)	(-20.3, -6.4)	(-0.8, 0.4)
p-value	0.0112	0.0016	0.4380

Patient's mean total administration time (min) is calculated from e-diary data.

Patient's mean total administration time (min) is calculated from e-diary data.

Total administration time = Device set-up time + administration time + device cleaning time + disinfection time (if available).

If at least once in a day disinfection time was reported all total administration times of that day were considered in the calculation of patient's mean total administration time. This applies for patients on TIS or COLI treatment in cycle 1.

Time difference in mean total administration time is calculated using within patient differences, cycle 2 - cycle 1.

Only data of patients with non-missing mean total administration time of initial and second cycle are considered.

P-value calculated from paired t-test and 95% confidence intervals for the mean difference are displayed.

Source: Tables 14.2-1.1, 14.2-1.2.

CHMP comment

The mean total administration time for TIP is significantly shorter than for TIS/COLI. A considerable number of subjects did not contribute data for this analysis (35% missing for cycle 1, 38% missing for cycle 2), for unknown reasons.

- *P. aeruginosa* quantitative culture data (CFU from patients' sputum) or semiquantitative culture data (light, moderate or heavy growth, from patients' deep cough throat swabs) (Secondary objective # 1)

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 compared to cycle 1 was slightly less for the TIS/TIP arm and was similar in the other two arms. 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.

Table 11-7 Change from start to end of on/off treatment period in *P. aeruginosa* sputum density - log_{10} CFU (/mL) of sum of all biotypes within a cycle (Full analysis set)

Treatment arm / Cycle	Visit		n	Mean (SD)	Min-Max
TIS/TIP (N=14)					
Cycle 1	Visit 2 (BSL)	Value	13	7.8 (1.88)	3.6 - 9.1
	Visit 3	Change	11	-1.4 (1.85)	-3.3 - 3.0
	Visit 4	Change	10	0.2 (1.98)	-3.5 - 4.1
Cycle 2	Visit 4	Value	10	8.3 (1.16)	5.6 - 9.3
	Visit 5	Change	9	-0.9 (1.66)	-3.6 - 1.9
	Visit 6	Change	9	0.0 (0.95)	-0.8 - 2.2
COLI/TIP (N=28)					
Cycle 1	Visit 2 (BSL)	Value	23	6.9 (2.22)	1.3 - 9.1
	Visit 3	Change	22	-0.6 (1.88)	-7.0 - 1.8
	Visit 4	Change	20	-0.6 (2.36)	-7.0 - 2.7
Cycle 2	Visit 4	Value	18	6.3 (2.60)	1.3 - 9.1
	Visit 5	Change	16	-0.5 (1.65)	-3.1 - 2.4
	Visit 6	Change	18	0.5 (2.55)	-5.4 - 6.5
TIP/TIP (N=18)					
Cycle 1	Visit 2 (BSL)	Value	12	6.8 (2.46)	1.3 - 8.9
	Visit 3	Change	9	-1.7 (2.87)	-5.4 - 2.3
	Visit 4	Change	8	-0.2 (1.56)	-3.3 - 1.6
Cycle 2	Visit 4	Value	6	5.4 (2.48)	2.3 - 8.4
	Visit 5	Change	5	-1.6 (1.53)	-2.9 - 0.8
	Visit 6	Change	5	0.0 (0.91)	-1.0 - 1.2

Baseline (BSL) is defined as the last value before first dose of study drug. SD = Standard deviation.
n = Number of patients with a quantitative result.
Change = Value of end of on/off-treatment period of the cycle – pre-dose value at start of that cycle.
Source: Table 14.2-2.1.

CHMP comment

The study was not designed nor powered to compare efficacy of TIP relative to COLI/TIS. The observed change in *P. aeruginosa* sputum density for TIP/TIP is however in line with data from previous studies.

- Microbial contamination of delivery device: *P. aeruginosa* and other pathogens (semiquantitative culture data: light, moderate or heavy growth)

Overall 2 patients in the TIS/TIP arm (14%), 9 patients in the COLI/TIP arm (32%) and 1 patient in the TIP/TIP arm (6%) had any contaminated device across the treatment cycles.

In the TIS/TIP arm, the only pathogen observed after using T-326 Inhaler was *S. aureus* (light growth at cycle 2 [Visit 5] in one device). 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. The pathogens isolated twice were *Acinetobacter lwoffi* and *Pseudomonas fluorescens* (light growth) at Visits 2 and 3, respectively. Three pathogens (*Acinetobacter baumannii*, *Ochrobactrum anthropic* and *Sphingomonas paucimobilis*) were isolated with heavy growth.

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. The medication administered through this device was not specified. No contaminated T-326 Inhaler was observed in both cycle 1 and cycle 2.

The emergence of organisms in delivery device cultures at the end of an on-treatment period that were not present at start of the cycle were *S. aureus* (TIS/TIP arm), and *Acinetobacter species* unspecified, *Chryseobacterium indologenes*, *Delftia acidovorans*, PSFL – *Pseudomonas fluorescens*, *Sphingomonas paucimobilis* and *S. aureus* (all COLI/TIP arm).

- Semiquantitative culture data (light, moderate or heavy growth) from patients` specimens for non-*P. aeruginosa* pathogens

The majority of the pathogens were present in only a small percentage of patients and there was no consistent trend of increase or decrease in density for most of the pathogens across the treatment arms. Other than *P. aeruginosa*, *Staphylococcus aureus* was the organism most frequently isolated from sputum/throat swab samples post baseline. In the majority of patients *S. aureus* was present in the culture obtained at screening visit and persisted throughout the study.

- MIC of selected antibiotics for *P. aeruginosa* from patients' specimens

In general, the results showed that there was 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. 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.

- Use of antibiotic treatment for *P. aeruginosa* other than study treatments

In cycle 1, a total of 5 patients (35.7%) in the TIS/TIP arm, 10 patients (35.7%) in the COLI/TIP arm and 4 patients (22.2%) in the TIP/TIP arm received any new anti-pseudomonal antibiotics. The median duration of use was 14 to 19 days across the treatment arms. After crossover to TIP, in cycle 2, the frequency of new antibiotic usage was reduced from cycle 1 for the TIS/TIP (3 patients, 25.0%) and COLI/TIP (8 patients, 32.0%) arms, and remained similar in the TIP/TIP arm (4 patients, 26.7%).

The ease-of-use assessments included the following:

- 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.

The time difference in mean device set-up time was significantly shorter in cycle 2 (after crossover to TIP) than in cycle 1 for the COLI/TIP arm (mean time difference, within patient differences cycle 2 – cycle 1: -2.6 min, P=0.0003). However, the difference in device set-up time between the treatment cycles remained similar for the TIS/TIP (mean time difference: -0.2, P=0.5065) arm. For the TIP/TIP arm, no significant difference between the cycles were observed.

The mean administration time was 11.7 min in cycle 1 versus 2.5 min in cycle 2 for the TIS/TIP arm, 7.6 min versus 2.2 min for the COLI/TIP arm, and 2.5 min versus 2.1 min for the TIP/TIP arm. The time difference in mean administration time was significantly shorter in cycle 2 than in cycle 1 for all three treatment arms (P=0.0005 (TIS/TIP, P=0.0001 COLI/TIP, P=0.0464 TIP/TIP).

The difference in mean cleaning time was significantly shorter in cycle 2 than in cycle 1 for the TIS/TIP (mean time difference, within patient differences cycle 2 – cycle 1: -5.6 min, P=0.0173) and COLI/TIP (mean time difference, within patient differences cycle 2 – cycle 1: -2.7 min, P<0.0001) arms, but remained similar for the TIP/TIP arm.

The mean disinfection time was 16.1 min in the TIS/TIP arm and 3.6 min in the COLI/TIP arm in cycle 1, and not applicable for TIP/TIP.

- In paediatric patients (<18 years): patient versus caregiver performing the various steps.

Overall five patients, two of which were paediatric (3007/00001 [9 years], 4003/00002 [13 years]) needed help for any of the categories of device set-up, administration, cleaning and disinfection.

- Patient-reported outcomes (reported by caregivers for minors, as applicable):

The summary of the TSQM questionnaire showed that the median scores were high at cycle 1, Visit 3 and were either sustained or improved at cycle 2, Visit 5 for the majority of domains for all three arms.

Paediatric summery:

There were 4 paediatric patients enrolled, all of whom completed the study.

There are no efficacy data presented or summarised specifically for these patients in the clinical study report. Therefore, the individual patient listings were presented. The mean total (cumulative) administration time for the 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. 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. The mean total administration time for the patient in the COLI/TIP arm was missing.

There were reductions seen in *P.aeruginosa* sputum density in these 4 patients consistent with the reductions seen in the overall study population. There were no significant changes in tobramycin 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.

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

In terms of FEV1 % predicted in cycle 1 (Visit 3), at the end of the first on -treatment period 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%. In cycle 2 (Visit 5) at the end of the second on-treatment period 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.

CHMP comment

The data from these 4 paediatric patients are generally in line with data reported for the overall population.

Safety results

Adverse Events

The treatment emergent AEs by SOCs that occurred in the on- and off-treatment period of a cycle are summarized in Table 12-3.

Table 12-3 Adverse events, regardless of study drug relationship, by primary system organ class and cycle (Safety set 1 and 2)

	TIS/TIP n (%)	COLI/TIP n (%)	TIP/TIP n (%)
Cycle 1			
Number of patients treated in cycle in the analysis set	14 (100.0)	28 (100.0)	18 (100.0)
Patients with AE(s)	**6 (42.9)**	**19 (67.9)**	**11 (61.1)**
Ear and labyrinth disorders	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	0 (0.0)	3 (10.7)	0 (0.0)
General disorders and administration site conditions	0 (0.0)	0 (0.0)	2 (11.1)
Hepatobiliary disorders	0 (0.0)	2 (7.1)	0 (0.0)
Immune system disorders	0 (0.0)	0 (0.0)	1 (5.6)
Infections and infestations	5 (35.7)	13 (46.4)	6 (33.3)
Injury, poisoning and procedural complications	0 (0.0)	0 (0.0)	0 (0.0)
Investigations	0 (0.0)	2 (7.1)	2 (11.1)
Metabolism and nutrition disorders	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	0 (0.0)	1 (3.6)	2 (11.1)
Nervous system disorders	2 (14.3)	2 (7.1)	4 (22.2)
Psychiatric disorders	0 (0.0)	0 (0.0)	1 (5.6)
Respiratory, thoracic and mediastinal disorders	2 (14.3)	2 (7.1)	5 (27.8)
Skin and subcutaneous tissue disorders	0 (0.0)	1 (3.6)	0 (0.0)
	TIS/TIP n (%)	**COLI/TIP n (%)**	**TIP/TIP n (%)**
Cycle 2			
Number of patients treated in cycle in the analysis set	12 (100.0)	25 (100.0)	15 (100.0)
Patients with AE(s)	**8 (66.7)**	**12 (48.0)**	**10 (66.7)**
Ear and labyrinth disorders	0 (0.0)	0 (0.0)	1 (6.7)
Gastrointestinal disorders	1 (8.3)	1 (4.0)	2 (13.3)
General disorders and administration site conditions	1 (8.3)	3 (12.0)	2 (13.3)
Hepatobiliary disorders	0 (0.0)	0 (0.0)	0 (0.0)
Immune system disorders	0 (0.0)	1 (4.0)	1 (6.7)
Infections and infestations	3 (25.0)	9 (36.0)	6 (40.0)
Injury, poisoning and procedural complications	0 (0.0)	1 (4.0)	0 (0.0)
Investigations	1 (8.3)	1 (4.0)	1 (6.7)
Metabolism and nutrition disorders	0 (0.0)	1 (4.0)	1 (6.7)
Musculoskeletal and connective tissue disorders	1 (8.3)	0 (0.0)	0 (0.0)
Nervous system disorders	0 (0.0)	1 (4.0)	3 (20.0)
Psychiatric disorders	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	3 (25.0)	3 (12.0)	4 (26.7)
Skin and subcutaneous tissue disorders	0 (0.0)	0 (0.0)	1 (6.7)

Treatment emergent adverse events which occurred in the on and off treatment period of a cycle are summarized.

Primary SOCs are presented alphabetically.

A patient with more than one adverse event within a primary SOC is counted only once for that class.

Percentages are based on the number of patients treated in cycle in the analysis set.

Source: Tables 14.3.1-1.1.

In cycle 1, the most commonly reported AEs (reported by >2 patients in any arm) by preferred terms were infective pulmonary exacerbation of cystic fibrosis (11.1% in the TIP/TIP, 35.7% in the COLI/TIP, and 35.7% in the TIS/TIP arms), headache and sputum increased (each ranging from 0% in the COLI/TIP to 16.7% in the TIP/TIP arms), nasopharyngitis (0% in the TIS/TIP to 11.1% in the TIP/TIP arms), and cough (7.1% in the COLI/TIP to 14.3% in the TIS/TIP arms). In cycle 2, the most commonly reported AEs by preferred terms were infective pulmonary exacerbation of cystic fibrosis (ranging from 6.7% in the TIP/TIP to 28.0% in the COLI/TIP arms), headache and nasopharyngitis (each 0% in the TIS/TIP and COLI/TIP and 20.0% in the TIP/TIP arms), and cough (0% in the COLI/TIP to 13.3% in the TIP/TIP arms).

AEs possibly related to Tobi Podhaler® according to the investigators' opinion

In cycle 1, among the AEs reported, few (4 patients) were considered to be related to the study treatment. None of the treatment related AEs in cycle 1 was considered to be severe in intensity. In cycle 2, 8 patients (15.4%) reported AEs that were considered to be related to the study treatment. All treatment related events were reported in single cases and majority of them were either mild or moderate in intensity. Out of 8, a total of 3 patients had severe AEs. These were forced expiratory volume decreased and upper respiratory tract infection (patient# 3001/00002), acoustic stimulation tests abnormal and tinnitus (patient# 1006/00006), and cough (patient# 3007/00002).

Serious Adverse Events

In cycle 1, a total of 3 patients (21.4%) experienced any SAEs in the TIS/TIP arm, 9 patients (32.1%) in the COLI/TIP arm and 3 patients (16.7%) in the TIP/TIP arm. Two of these patients discontinued treatment from the COLI/TIP arm and 1 patient discontinued treatment from TIP/TIP arm. In cycle 2, overall 8 patients (15.4%) reported any SAEs; of whom 1 patient (patient# 1006/00006) discontinued the study treatment.

There were no deaths reported during this study.

Paediatric safety summery:

- 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. An 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.

CHMP comment

The reported AEs and SAEs are in line with the known safety profile of Tobi Podhaler and the patient population under study. No new safety signals are identified from this small study, neither in adults nor in the 4 paediatric patients enrolled in the study.

2.3.3. 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, of which 4 patients were paediatric patients. All 60 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.

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. Suppression of *P. aeruginosa* and stability in FEV1 % predicted was observed. 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. 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.

3. Rapporteur's overall conclusion and recommendation

On the basis of the paediatric results of study CTBM100C2403, there is no change in the benefit-risk profile of TOBI or TOBI Podhaler for the existing indication worldwide. The efficacy and safety data from this study do not warrant an update of the product information of TOBI or TOBI Podhaler at this stage.

☒ Fulfilled:

No regulatory action required.