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Human Medicines Division

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/P46/031

Note

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

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1. Introduction

On 2 June 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 CTBM100CUS03 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 CTBM100CUS03, *A 24-week, open-label, parallel-group, interventional Phase IV study comparing Tobramycin Inhalation Powder (TIP) administered once daily continuously versus TIP administered BID in 28 day on / 28 day off cycles for the treatment of pulmonary Pseudomonas aeruginosa in patients with cystic fibrosis*, is a stand alone study.

The study was not listed in the TOBI Podhaler PIP (EMEA-000184-PIP01-08-M02).

2.2. Information on the pharmaceutical formulation used in the study

The dose was 112 mg tobramycin (4x 28mg capsules), administered once daily continuously or 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 CTBM100CUS03, A 24-week, open-label, parallel-group, interventional Phase IV study comparing Tobramycin Inhalation Powder (TIP) administered once daily continuously versus TIP administered BID in 28 day on / 28 day off cycles for the treatment of pulmonary *Pseudomonas aeruginosa* in patients with cystic fibrosis.

A total of 32 patients were randomized of which there were 3 paediatric patients.

2.3.2. Clinical study

Study CTBM100CUS03, A 24-week, open-label, parallel-group, interventional Phase IV study comparing Tobramycin Inhalation Powder (TIP) administered once daily continuously versus TIP administered BID in 28 day on / 28 day off cycles for the treatment of pulmonary *Pseudomonas aeruginosa* in patients with cystic fibrosis.

Description

This open-label, parallel-group, interventional phase IV study was a 24 weeks study comparing TIP administered once daily on a continuous (i.e., non-cycled) basis, versus TIP administered twice daily in 28 day on / 28 day off cycles for the treatment of pulmonary *P. aeruginosa* in patients 6 years or older

with cystic fibrosis. The study was conducted in 14 US centres and was prematurely discontinued due to recruitment challenges. In total, 32 patients were enrolled, including 3 paediatric patients.

Methods

Objective(s)

Primary objective

To estimate the difference in mean (absolute) change from baseline in forced expiratory volume in 1 second (FEV1) % predicted at Day 168 (Visit 9) with Tobramycin Inhalation Powder (TIP) 112 mg once daily (continuous) vs TIP 112 mg BID in 28 day on / 28 day off cycles.

Secondary objectives

- To estimate the difference in mean (absolute) change from baseline in FEV1 % predicted at Day 140 (Visit 8) and at all other post-baseline visits for TIP 112 mg once daily (continuous) vs TIP 112 mg BID in 28 day on / 28 day off cycles.
- To estimate the difference in mean percent (relative) changes from baseline in FEV1 % predicted, forced vital capacity (FVC) % predicted, and forced expiratory flow rate over 25% to 75% of forced vital capacity (FEF25-75) % predicted at Day 140 (Visit 8), Day 168 (Visit 9) and at all other scheduled post-baseline visits with TIP 112 mg once daily (continuous) vs TIP 112 mg BID in 28 day on / 28 day off cycles.
- To estimate the difference in mean change from baseline in *P. aeruginosa* sputum density (log10 colony forming units [CFU] per gram sputum) at Day 140 (Visit 8), Day 168 (Visit 9) and at all other scheduled post-baseline visits with TIP 112 mg once daily (continuous) vs TIP 112 mg BID in 28 day on / 28 day off cycles.
- To estimate the difference in mean change from baseline in tobramycin minimal inhibitory concentration (MIC) for *P. aeruginosa* at Day 140 (Visit 8), Day 168 (Visit 9) and at all other scheduled post-baseline visits with TIP 112 mg once daily (continuous) vs TIP 112 mg BID in 28 day on / 28 day off cycles.
- To evaluate safety through Day 168 (Visit 9) in patients receiving TIP 112 mg once daily (continuous) vs TIP 112 mg BID in 28 day on / 28 day off cycles.
- To estimate the difference in time to first hospitalization, incidence of hospitalization, and mean length of hospital stay due to respiratory-related events through Day 168 (Visit 9) in patients receiving TIP 112 mg once daily (continuous) vs TIP 112 mg BID in 28 day on / 28 day off cycles.
- To estimate the difference in time to first use, incidence of use, and duration of use of an antipseudomonal antibiotic (overall, oral, intravenous) other than prophylactic treatment planned before enrolment, through Day 168 (Visit 9) in patients receiving TIP 112 mg once daily (continuous) vs TIP 112 mg BID in 28 day on / 28 day off cycles.

Study design

This study consisted of a screening visit (Visit 1) and 8 follow-up visits (Visits 2-9). The screening visit (Visit 1) could take place any time within 28 days prior to study drug administration (Visit 2). If the patient had previously received inhaled aminoglycoside for *P. aeruginosa* , initiation of study drug could only occur if at least 28 days had elapsed since the patient's last dose of inhaled aminoglycoside.

Upon randomization, patients were assigned to receive either TIP four 28-mg capsules (112 mg) administered once daily on a continuous (i.e., non-cycled) basis or TIP four 28-mg capsules (112 mg) administered twice daily in 28 day on / 28 day off cycles; each cycle consisted of a 28-day on-treatment period followed by a 28-day off-treatment period. The duration of study duration was 168 days (24 weeks).

Study population

The study population consisted of males and females >6 years of age who had a confirmed diagnosis of cystic fibrosis. At screening, patients were required to have FEV1 ≥25% and ≤ 80% of normal predicted values for age, sex, and height. In addition, patients were required to have chronic *P. aeruginosa* infection in their respiratory tracts. As such, *P. aeruginosa* was required to be present in a sputum/deep cough throat swab culture or bronchoalveolar lavage (BAL) within 6 months prior to screening and in the sputum/deep-throat cough swab culture at screening.

Sample size

Enrolment of 200 patients was planned. A total of 32 patients were randomized, 16 to each treatment group. A total of 5 patients completed the study, and 6 patients were discontinued before the sponsor ended the study. The remaining 21 patients were discontinued due to the sponsor's decision to terminate the study prematurely. The 31 patients who received at least one dose of study medication were included in the Safety and Full Analysis Sets, 16 in the TIP once daily (continuous) treatment group and 15 in the TIP BID (cycled) treatment group.

CHMP comment

The study was terminated prematurely due to recruitment problems. As a result, the planned sample size was far from reached and only 5 subjects completed the study. No conclusions can be drawn based on these few subjects.

Treatments

For both treatment arms, each dose was four 28-mg capsules (112 mg) of tobramycin dry powder for inhalation administered by the T-326 Inhaler for 168 days (24 weeks). Patients were randomized to one of the following two treatment arms in a 1:1 ratio:

- TIP once daily (continuous) treatment group: A total daily dose of 112 mg administered once daily in the morning on a continuous (ie, non-cycled) basis.
- TIP BID (cycled) treatment group: A total daily dose of 224 mg administered BID in 28-day on / 28-day off cycles (a total of three 56-day cycles).

Outcomes/endpoints

The primary efficacy variable was the change from baseline in FEV1 % predicted. The primary analysis time point was at Day 168 (Visit 9). The following secondary efficacy variables were planned:

1. Percent change from baseline in FEV1 % predicted
2. Percent change from baseline in FVC % predicted
3. Percent change from baseline in FEF25-75 % predicted
4. Change from baseline in *P. aeruginosa* sputum density
5. Time to first hospitalization due to respiratory-related events

6. Hospitalization due to respiratory-related events

7. Length of hospital stay due to respiratory-related events

8. Time to first usage of anti-pseudomonal antibiotic

9. Usage of anti-pseudomonal antibiotic

10. Duration of use of anti-pseudomonal antibiotic

Safety assessments consisted of physical examinations, vital signs, clinical laboratory tests, audiology testing (at selected sites), adverse event assessments, acute change in airway reactivity (FEV1 percent predicted) from pre-dose to 30 minutes after completion of first dose of study drug (where a relative change of 20% or more is considered a clinically significant change indicating bronchospasm), inhalation-associated cough rate, and use of concomitant medications/significant nondrug therapies.

Statistical Methods

Due to the premature termination of the study and the reduction in patient data, many of the summaries and analyses planned in the protocol were eliminated in the statistical analysis plan prior to database lock. Data were summarized descriptively and no inferential analysis was provided. For safety analysis, only adverse events were summarized. Descriptive statistics for the primary efficacy variable and secondary efficacy variable 1 were provided. All the data collected in the CRF were provided as listings.

Results

Recruitment/ Number analysed

A total of 32 patients were randomized, 16 to each treatment group. A total of 5 patients completed the study, and 6 patients were discontinued before the sponsor ended the study. The remaining 21 patients were discontinued due to the sponsor's decision to terminate the study prematurely due to poor recruitment (listed under "Administrative problems" in the table below).

Table 10-1 Patient disposition (Randomized set)

	TIP Once Daily – Continuous N=16 n (%)	TIP BID – Cycled N=16 n (%)	Total N=32 n (%)
Completed	1 (6.3)	4 (25.0)	5 (15.6)
Discontinued from study	15 (93.8)	12 (75.0)	27 (84.4)
Reason for discontinuation			
Administrative problems	10 (62.5)	11 (68.8)	21 (65.6)
Adverse Events	3 (18.8)	0 (0.0)	3 (9.4)
Protocol deviation	0 (0.0)	1 (6.3)	1 (3.1)
Patient withdrew consent	1 (6.3)	0 (0.0)	1 (3.1)
Unsatisfactory therapeutic effect	1 (6.3)	0 (0.0)	1 (3.1)

N = Number of patients in the randomized set; n = Number of patients meeting the criterion.
Reasons for discontinuation are sorted alphabetically.
Percentage (%) is calculated using the Randomized set as the denominator.
Randomized set: All patients randomized are included in the randomized set.
Source: Table 14.1-1.1

Patient 0503-00006 was randomized to the TIP BID (cycled) treatment group, but never received study medication, and was excluded from the Safety and Full Analysis Sets. The 31 remaining patients received at least one dose of study medication and were included in the Safety and Full Analysis Sets.

Table 11-1 Analysis sets (Randomized set)

	TIP Once Daily – Continuous N=16 n (%)	TIP BID – Cycled N=16 n (%)	Total N=32 n (%)
Randomized Set [1]	16 (100.0)	16 (100.0)	32 (100.0)
Safety Set [2]	16 (100.0)	15 (93.8)	31 (96.9)
Full Analysis Set [3]	16 (100.0)	15 (93.8)	31 (96.9)

Note: The denominator for the percentages is the number of patients randomized.

[1] The Randomized Set consists of all patients who were randomized.

[2] The Safety Set consists of all patients who received at least one dose of study medication.

[3] The Full Analysis Set consists of all patients to whom study medication was assigned. Patient 0503-00006 (inappropriately randomized) was excluded from the Full Analysis Set.

Source: Table 14.1-2.1

There were 3 paediatric patients enrolled. One patient (13 years old, female, Caucasian) was randomized to the TIP once daily (continuous) group, and two patients (14 years old, female, Caucasian; 10 years old, male, Caucasian) were randomized to the TIP twice daily (cycled) group. All 3 paediatric patients discontinued the study due to the sponsor's decision to terminate the study prematurely.

Baseline data

Patients ranged from 10 to 74 years of age. The mean age was slightly higher in the TIP once daily (continuous) treatment group (34.9 years) than in the TIP BID (cycled) treatment group (26.5 years) and the proportion of males was also higher (62.5% vs. 50%, respectively). All but 2 of the patients were Caucasian. The two treatment groups were similar at baseline; mean FEV1 % predicted was 54.5% in the TIP once daily (continuous) treatment group and 57.3% in the TIP BID (cycled) treatment group.

Efficacy results

The primary efficacy variable was the change from baseline in FEV1 % predicted. The primary analysis time point was at Day 168 (Visit 9). The two treatment groups were similar at baseline; mean FEV1 % predicted was 54.5% in the TIP once daily (continuous) treatment group and 57.3% in the TIP twice daily (cycled) treatment group. Only 5 patients had spirometry at Visit 9 and there are no meaningful results. Changes over time and differences between the two treatment groups could not be adequately assessed, as these observations were limited by the small and decreasing sample size over the study period.

As with the absolute changes in FEV1 % predicted, assessment of between-group differences for the secondary efficacy variables could not be adequately assessed, as these observations were limited by the small and decreasing sample size over the study period.

CHMP comment

It is agreed with the MAH that no meaningful results or conclusions can be generated based on only 5 subjects.

Safety results

The overall duration of exposure ranged from 6 to 167 days, with an overall mean of 74.3 days and a median of 84 days.

No deaths were reported in this study.

The overall incidence of adverse events was similar in the TIP once daily (continuous) treatment group (81.3%) and TIP twice daily (cycled) treatment group (80.0%). The most commonly affected primary system organ classes (SOCs) were respiratory, thoracic and mediastinal disorders (primarily cough, dyspnoea, and oropharyngeal pain), gastrointestinal disorders (primarily abdominal pain, diarrhoea, and nausea), and infections and infestations (primarily infective pulmonary exacerbation of cystic fibrosis).

A total of 4 patients experienced hospitalizations that were considered serious adverse events. All were worsening pre-existing conditions; 3 patients with worsening cystic fibrosis and 1 patient with worsening endometriosis. None of the SAEs was suspected to be related to study treatment.

Three patients experienced AEs leading to discontinuation, all in the TIP once daily (continuous) treatment group. One patient experienced mildly decreased hearing at 0.25 kHz on Day 15 and permanently discontinued study treatment due to this AE, although the investigator did not suspect that the AE was related to study drug. A second patient experienced mild dose-related coughing on Day 2 and permanently discontinued study treatment due to this AE. The third patient experienced mild non-cardiac chest tightness on Day 7 and permanently discontinued study treatment due to this AE. Both of these AEs were suspected to be related to study drug.

No audiologic impairment suspected to be related to study treatment was observed. No worsening in renal function was reported.

A total of 14 patients, 7 in each treatment group, experienced a cough during inhalation at one or more visits. A total of 11 patients, 6 in the TIP once daily (continuous) group and 5 in the TIP twice daily (cycled) group, experienced a cough within 5 minutes after inhalation at one or more visits. Most of the coughing occurred within 15 seconds after inhalation. One patient was treated with albuterol to reduce coughing.

Paediatric patients

There were 3 paediatric patients enrolled in the study, each of whom discontinued the study due to the sponsor's decision to terminate the study prematurely. There is no safety or efficacy data presented or summarized specifically for these patients in the clinical study report. Therefore, the individual patient listings were reviewed and are discussed below:

13-year-old female in the TIP once daily (continuous) group:

The patient discontinued on Day 84 of the study.

Cough was reported as an AE three times for this patient. The cough was experienced either during inhalation or post inhalation of TIP. The cough was mild in all cases, no action was taken, and it was suspected to be related to study drug. Increased coughing was also reported once. The increased coughing was mild, no action was taken and it was suspected to be related to study drug.

Aphonia and oropharyngeal pain were each reported once for this patient. These AEs were mild, non-drug therapy was given, and they were suspected to be related to study drug. Constipation and abdominal pain were each reported once for this patient. These AEs were mild. A concomitant medication was given for the constipation and no action was taken for the abdominal pain. They were not suspected to be related to study drug.

There were no clinically significant changes in haematology, chemistry, or urinary laboratory values in this patient.

In terms of efficacy, pre-dose relative change from baseline in FEV1 % predicted ranged from +5.0% to +15.0% during visits prior to discontinuation. At the discontinuation visit, the relative change was 0.0%.

14-year-old female in the TIP twice daily (cycled) group:

The patient discontinued on Day 85 of the study.

Cough was reported as an AE four times for this patient. The cough was mild in all cases, no action was taken, and it was suspected to be related to study drug.

Increased coughing, increased sputum production, dyspnoea, and wheezing were each reported once during the same 37-day time frame. These AEs were moderate, and concomitant medication was given. They were not suspected to be related to study drug.

Post-tussive vomiting was reported twice for this patient. This AE was mild in both cases, and no action was taken. It was suspected to be related to study drug in one of the two cases.

Constipation was reported once for this patient. This AE was moderate, and a concomitant medication was given. It was not suspected to be related to study drug. Diarrhoea was reported once for this patient. This AE was moderate, and no action was taken. It was not suspected to be related to study drug.

There were no clinically significant changes in haematology, chemistry, or urinary laboratory values in this patient.

In cycle 1 (Visit 4), at the end of the on-treatment period, the mean FEV1 % predicted showed a pre-dose relative change from baseline of +19.0%. In cycle 2 (Visit 6 and the discontinuation visit for this patient), at the end of the on-treatment period, the mean FEV1 % predicted showed a pre-dose relative change from baseline of +16.0%.

10-year-old male in the TIP twice daily (cycled) group:

The patient discontinued on Day 35 of the study.

Increased coughing was reported as an AE twice for this patient. In one case, this AE was mild, no action was taken, and it was suspected to be related to study drug. In the second case, this AE was moderate, no action was taken, and it was not suspected to be related to study drug.

Rhonchi were reported twice for this patient. In both cases, this AE was mild, no action was taken, and it was not suspected to be related to study drug.

There were no clinically significant changes in haematology, chemistry, or urinary laboratory values in this patient.

In cycle 1 (Visit 3), during the on-treatment period, the mean FEV1 % predicted showed a predose relative change from baseline of +25.0%. At the discontinuation visit (Day 35), the mean FEV1 % predicted showed a pre-dose relative change from baseline of -2.0%.

CHMP comment

No new safety signals are identified from this small study, neither in adults nor in the 3 paediatric patients enrolled in the study.

2.3.3. Discussion on clinical aspects

The main objectives of the study, changes over time in lung function and differences in lung function between the two treatment groups could not be adequately assessed, due to the small and decreasing sample size over the study period.

There were no new or unexpected safety findings overall or from the 3 paediatric patients enrolled in this study. The safety results observed in this study were generally consistent with the known established safety profile of TIP.

3. Rapporteur's overall conclusion and recommendation

It is agreed with the MAH that the product information of TOBI Podhaler does not warrant an update based on the results from study CTBM100CUS03.

Fulfilled:

No regulatory action required.

4. Additional clarification requested

N.A.

MAH responses to Request for supplementary information

N.A.