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Procedure Management and Committees Support 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/P46/024

Note

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

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1. Introduction

On 12 May 2015, 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.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that TBM100C2401E1 is a stand alone study.

The MAH stated that study CTBM100C2401E1 (C2401E1) is an extension to the core study CTBM100C2401. The core study was a post approval measure for TOBI Podhaler but not part of the Paediatric Investigation Plan. The extension study is not part of the post approval measure for TOBI Podhaler.

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. The dose was the same for all patients, regardless of age or weight.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report(s) for:

- study CTBM100C2401E1: A 48 week extension to CTBM100C2401, a single arm open-label, multicenter, phase IV trial, to assess long term safety of tobramycin inhalation powder (TIP) in patients with Cystic Fibrosis

2.3.2. Clinical study

Study CTBM100C2401E1: A 48 week extension to CTBM100C2401, a single arm open-label, multicenter, phase IV trial, to assess long term safety of tobramycin inhalation powder (TIP) in patients with Cystic Fibrosis

Description

An open label, multi-center, uncontrolled, single arm extension study (phase IV) to assess long term safety of tobramycin inhalation powder (TIP) in patients suffering from cystic fibrosis, aged 6 years and older who have completed their study participation in the core study CTBM100C2401. The extension study consisted of 6 additional cycles of a 28-day on-treatment period followed by a 28-day off-treatment period per cycle, for a total of 48 weeks.

The core study CTBM100C2401 has been assessed and described in the assessment report for paediatric study submitted in accordance with article 46 of regulation (EC) No 1901/2006.

Methods

Objective(s)

Primary objective

The primary objective of the study was to assess the safety of Tobramycin Inhalation Powder (TIP) across 12 treatment cycles (6 treatment cycles in the core study and 6 treatment cycles in the extension study). The incidence of treatment emergent adverse events (AEs), including pulmonary exacerbations, over 12 cycles of treatment was the primary variable of interest.

Secondary objective

Secondary objective was assessment of efficacy of TIP across 12 cycles (6 treatment cycles in the core study and 6 treatment cycles in the extension study) by:

- the change in forced expiratory volume in 1 second (FEV1%) predicted (relative and absolute)
- the absolute change in *P. aeruginosa* colony forming unit (CFU) per gram of sputum
- the change of *P. aeruginosa* tobramycin minimum inhibitory concentration (MIC)
- the time to first and the rate of the usage (overall, oral, intravenous) of anti-pseudomonal
- antibiotic (other than those regularly scheduled as prophylactic treatment)
- the time to first and the rate of hospitalization due to serious respiratory-related AEs
- to evaluate the safety profile of TIP in terms of clinical laboratory results and audiology (in a
- subset of patients)
- the safety profile of TIP in terms of acute change in FEV1 from pre-dose to 30 minutes post dose

To evaluate the above endpoints of interest (including the primary endpoint of incidence of AEs) across the 6 cycles of treatment in this extension study.

Exploratory objectives included to explore the rate of pulmonary exacerbations across 12 cycles of TIP treatment and to explore the characteristics of post inhalation events across 6 cycles of the extension.

Study population /Sample size

The study population was comprised of cystic fibrosis patients 6 years of age and older who completed the core study CTBM100C2401 and were able to comply with all protocol requirements of the extension study.

The number of patients planned to be enrolled in this extension study was bound by the number of patients enrolled in the core study. A total of 45 patients were enrolled in this extension study, out of 96 patients who completed the core study. A lower number of patients were enrolled than anticipated as some sites chose not to participate in this study, and a number of patients did not choose to enter this trial possibly due to the longer duration of the trial.

CHMP's comment:

It seems that the risk of selection bias is low, because the efficacy data of the overall safety population for the first 6 cycles are similar to the efficacy data of the extension safety population for the first 6 cycles. In addition, the baseline disease characteristics at the start of the core study of the overall study population were similar to the baseline characteristics of the subgroup entering the extension study.

Treatments

Eligible patients from the core study received the study drug for 6 additional treatment cycles. Patients received four TIP capsules (112 mg of tobramycin, 28 mg / capsule) via the T-326 Inhaler twice daily (morning and evening) in repeated cycles of 28 days on-treatment, followed by 28 days off-treatment period. Total duration of treatment was up to 48 weeks.

Outcomes/endpoints

Safety

- incidence of treatment emergent adverse events (AEs) over 12 cycles of treatment (1air);
- incidence of treatment emergent adverse events (AEs) over 6 extension treatment cycles from start of extension study;
- changes in hematology and clinical chemistry parameters from baseline;
- vital signs;
- airway reactivity;
- post-inhalation events;
- audiology testing in a subset of patients.

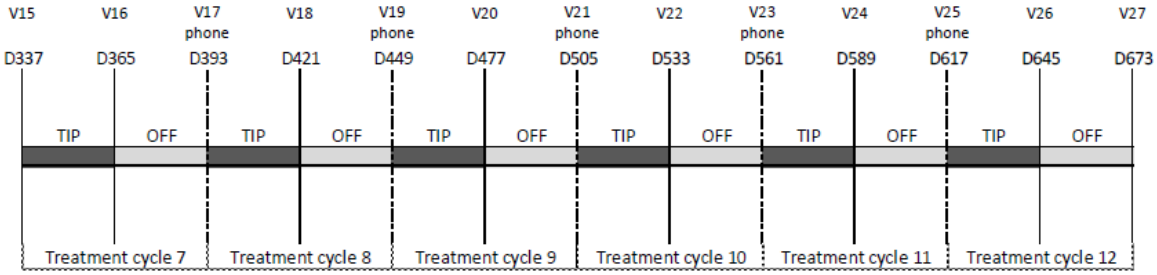
Efficacy

- change in FEV1% predicted, forced vital capacity (FVC%) predicted and forced expiratory flow between 25% and 75% of FVC (FEF25-75%) predicted, across 12 treatment cycles from baseline in core study and across 6 extension treatment cycles from start of extension study;
- change in P. aeruginosa CFU per gram of sputum across 12 treatment cycles from baseline in core study and across 6 extension treatment cycles from start of extension study;
- change in P. aeruginosa tobramycin MIC across 12 treatment cycles from baseline in core study and across 6 treatment cycles from start of extension study;
- time to first and rate of anti-pseudomonal antibiotic use and hospitalization due to serious respiratory-related AEs, across 12 treatment cycles and across 6 extension treatment cycles.

Measurement of the endpoints

The study design included 8 site visits and 5 telephone calls (Figure 9-1). Visits 16, 18, 20, 22, 24 and 26 were site visits and took place at the end of on-treatment period and before the off-treatment period started for each cycle. Visits 17, 19, 21, 23 and 25 were telephone calls made after each cycle, at the end of off-treatment period for that cycle.

Figure 9-1 Study design



Statistical Methods

There were three populations defined for analysis purpose:

- overall safety population (all patients who entered the core study and received at least one dose of study drug);
- extension safety population (all patients who entered the extension study and received at least one dose of study drug within the extension);
- audiology population (all patients in the extension safety population for whom at least one audiology test was performed).

Since all patients received TIP in this single arm design, there was no formal statistical testing performed in the study.

There was no imputation for missing data and no interim analysis was planned.

To note: baseline refers to baseline in the core study, unless specifically mentioned as baseline in the extension study.

Results

Recruitment/ Number analysed

The first patient enrolled on 27 Feb 2013 and the last patient completed the study 18 Nov 2014.

The study was conducted at 22 centers in the following 9 countries: Argentina (3 centers), Australia (2 centers), Canada (1 center), Germany (2 centers), Hungary (1 center), Italy (5 centers), Mexico (2 centers), Spain (2 centers), United States (4 centers).

From the 157 patients who entered the core study (overall safety population), 45/157 patients (28.7%) (extension safety population) consented to enter this extension study. 34/45 patients (75.6%) completed this extension study (6 cycles of TIP treatment). The most commonly reported reason for discontinuation was withdrawal of consent, reported by 5/45 patients (11.1%).

Table 10-1 Patient disposition (Overall and extension safety population)

	Overall safety population n (%)	Extension safety population n (%)
Entered the core study	157 (100.0)	45 (100.0)
Completed the core study	96 (61.1)	45 (100.0)
Discontinued core prematurely	61 (38.9)	0 (0.0)
Entered the extension study	45 (28.7)	45 (100.0)
Completed extension	34 (21.7)	34 (75.6)
Discontinued extension prematurely	11 (7.0)	11 (24.4)
Adverse event(s)	1 (0.6)	1 (2.2)
Abnormal lab value(s)	0 (0.0)	0 (0.0)
Abnormal test procedure result(s)	0 (0.0)	0 (0.0)
Unsatisfactory therapeutic effect	2 (1.3)	2 (4.4)
Subject's condition no longer requires study drug	0 (0.0)	0 (0.0)
Subject withdrew consent	5 (3.2)	5 (11.1)
Lost to follow-up	0 (0.0)	0 (0.0)
Administrative problems	0 (0.0)	0 (0.0)
Death	1 (0.6)	1 (2.2)
Protocol deviation	2 (1.3)	2 (4.4)

Source: Table 14.1-1.1; Table 14.1-1.2

Percentages are based on the number of patients who entered the core study in the population of interest.

CHMP's comment:

The discontinuation rate in the extension safety population was 24.4%. The most frequently reported reason for discontinuation was withdrawal of consent (N=5; 11.1%). The reasons were not directly related to the study medication (change of patient's residents (N=2); opportunity for a different clinical trial (N=1); personal problems (N=1); alternation of Tobi Podhaler with Cayston monthly (N=1). Additional reasons for premature discontinuation from the study were unsatisfactory therapeutic effect (N=2; 4.4%) and protocol deviations (N=2; 4.4%). There was 1 patient (2.2%) reported with AE related discontinuation and there was 1 death (2.2%) recorded during this extension study that was not assessed as causally related to the study medication.

The discontinuation rate in the overall safety population for the first 6 cycles was nearly 40%. The main reasons for discontinuations were due to AEs (29 patients (18,5%)) and from withdrawal of consent. The main reasons for withdrawing consent were that the inhalation of study drug was unpleasant and that patients were not satisfied with the effect of the study drug.

In the extension study less patients stopped study medication due to AEs and no patient stopped treatment due to unpleasant inhalation of study drug.

Baseline data

Demographic characteristics

At baseline, the mean age of the extension safety population was 24.5 (±10.79) years and 29 % of them were younger than 20 years. The majority of patients included were males (55.6%).

Table 11-2 Demographic summary (Extension safety population)

Variable	Total N=45
Age (years)	
N	45
Mean (SD)	24.5 (10.79)
Median	23.0
Min-Max	6-60
Age group (years), n (%)	
6-<13	2 (4.4)
13-<20	11 (24.4)
≥ 20	32 (71.1)
Sex, n (%)	
Male	25 (55.6)
Female	20 (44.4)
Race, n (%)	
Caucasian	41 (91.1)
Other	4 (8.9)
Weight (kg)	
N	45
Mean (SD)	54.6 (14.12)
Median	53.2
Min-Max	20.0-86.8

Variable	Total N=45
Height (cm)	
N	45
Mean (SD)	164.3 (13.76)
Median	163.5
Min-Max	119-196
Body mass index (kg/m^2)	
N	45
Mean (SD)	19.9 (3.27)
Median	19.3
Min-Max	12.1-27.0

Source: Table 14.1-3.1

Body mass index: weight (kg) / [height (m) ^{2}].

Disease characteristics at the start of the extension study

The mean FEV1% predicted of the patients at the start of the extension study was slightly lower compared to baseline (48.6% versus 52.2% respectively). The mean sputum density of P. aeruginosa for sum of all biotypes, at the start of the extension study was lower than at the baseline (6.4 log10 CFU/gram versus 7.3 log10 CFU/gram respectively).

Table 11-3 Disease characteristics at baseline and at the start of extension (Extension safety population)

	Total N=45	
Variable	**Baseline**	**Start of extension**
FEV_1 % predicted		
n	45	45
Mean (SD)	52.2 (15.01)	48.6 (14.84)
Median	52.4	47.4
Min-Max	29.0-85.6	21-72.1
FVC % predicted		
n	45	45
Mean (SD)	73.2 (17.49)	68.6 (17.12)
Median	72.0	68.4
Min-Max	37.6-116.3	37.3-114
FEF_{25-75} % predicted		
n	45	45
Mean (SD)	24.7 (14.86)	23.4 (14.17)
Median	20.1	18.6
Min-Max	7.8-59.3	5.9-63.5
Sputum density of P. aeruginosa (log10 CFU) – mucoid		
n	36	35
Mean (SD)	7.1 (1.67)	6.1 (2.71)
Median	7.7	7.5
Min-Max	1.3-8.8	1.3-8.8
Sputum density of P. aeruginosa (log10 CFU) – dry		
n	34	29
Mean (SD)	6.4 (2.29)	4.3 (3.21)
Median	7.0	3.7
Min-Max	1.3-8.8	1.3-8.8
Sputum density of P. aeruginosa (log10 CFU) - small colony variant		
n	15	10
Mean (SD)	6.5 (2.37)	4.3 (3.21)
Median	7.1	3.7
Min-Max	1.3-8.8	1.3-8.8
Sputum density of P. aeruginosa (log10 CFU) - sum of all biotypes[a]		
n	44	44
Mean (SD)	7.3 (1.76)	6.4 (2.66)
Median	7.9	7.9
Min-Max	1.3-8.8	1.3-9.1
P. aeruginosa tobramycin MIC, n (%)		
> 8 µg/mL	12 (26.7)	
≤ 8 µg/mL	33 (73.3)	

	Total N=45	
Variable	**Baseline**	**Start of extension**
Current use of long acting bronchodilator, n (%)		
Yes	9 (20.0)	
Current use of short acting bronchodilator, n (%)		
Yes	23 (51.1)	
Macrolide use, n (%)		
Yes	22 (48.9)	
Previous experience to inhaled TOBI, n (%)		
Yes	29 (64.4)	
Previous experience to inhaled TIP, n (%)		
Yes	2 (4.4)	

Source: Table 14.1-3.2; Table 14.1-3.2b

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

MIC = Minimum inhibitory concentration.

Baseline refers to baseline of the core study.

CHMP's comment:

The extension safety population (mean age 24.5 years) was a bit younger than the overall safety population (mean age 28 years). At the start of the extension study patients had a lower mean FEV1% predicted (48.6%) compared to at the baseline (52.2%) but were less colonized with P. aeruginosa (mean sputum density for sum of all biotypes of *P. aeruginosa* 6.4 log10 CFU/gram versus 7.3 log10 CFU/gram).

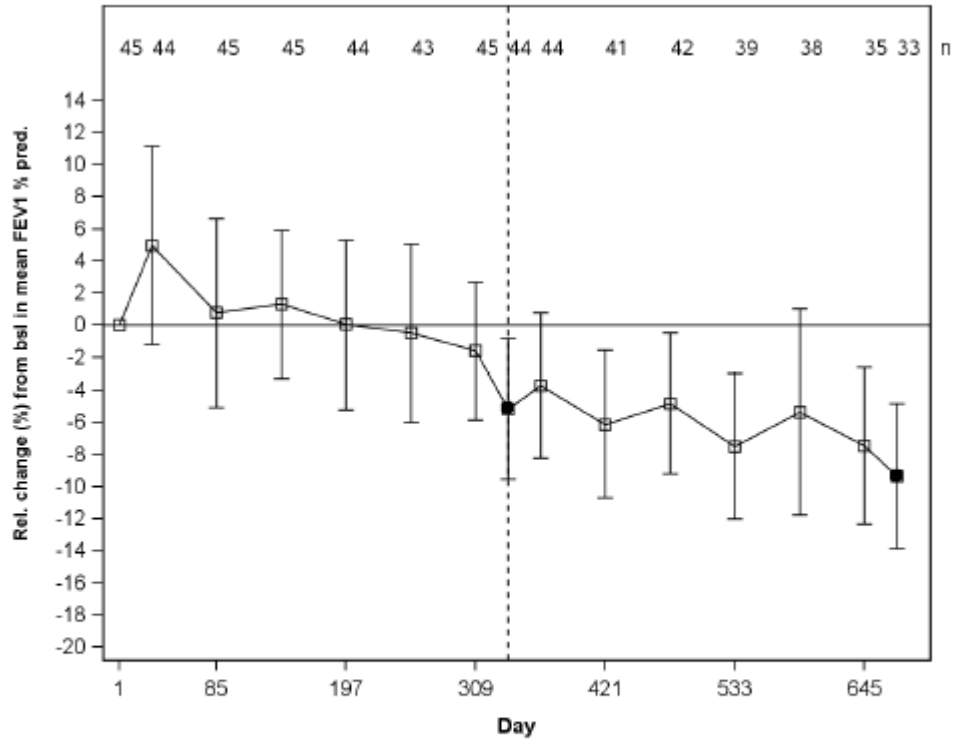
Efficacy results

Relative change in FEV1% predicted:

The mean FEV1% predicted for the extension study population increased from baseline for the first 3 core treatment cycles after which there were slight decreases observed in core Cycles 5 and 6 (Figure 11-1). At the end of Cycle 6 dosing in the core study, there was a mean decrease of 1.6% in FEV1% predicted from baseline. None of the changes from baseline were statistically significant.

There were decreases from baseline in the mean FEV1% predicted throughout extension Cycles 7 to 12. At the end of last treatment cycle dosing (Cycle 12), there was a mean relative decrease of 7.5% in FEV1% predicted from baseline over the 96 week study period. This was not tested for significance. When compared with the FEV1% predicted at the start of the extension study, there was a mean relative decrease of 0.6% in FEV1% predicted. None of the changes in FEV1% predicted from the start of the extension study were statistically significant.

Figure 11-1 Relative change from baseline in mean FEV_1% predicted over time (Extension safety population)



Note: The vertical bar is the 95% confidence interval.
Day 1 refers to baseline of the core study.
The dashed line at Day 337 represents the start of the extension study.
Days 337 and 673 (denoted by shaded boxes) represent the last day in last off-treatment period in core/extension study, other time points represent the end of on-treatment periods.
Source: Figure 14.2-1.1

Subgroup analysis

Subgroup analysis of changes in FEV1% predicted showed that the subgroup of patients ≥20 years, the subgroup with baseline FEV1% predicted ≥ 50% and the subgroup with azithromycin use, had better lung function at the end of the study than the subgroups of younger age (6 to <13 years and 13 to <20 years), baseline FEV1% predicted <50% and the subgroup that did not use azithromycin respectively.

FEV1% predicted by age

From baseline, all age subgroups showed decreases in mean FEV1% predicted at the last treatment Cycle 12. The decrease in FEV1% predicted at the end of dosing in Cycle 12 from baseline was 6.3% for the age subgroup 6 to <13 years (N=2), 13.4% for the 13 to <20 years age subgroup (N=11) and 4.6% for the ≥20 years age group (N=23).

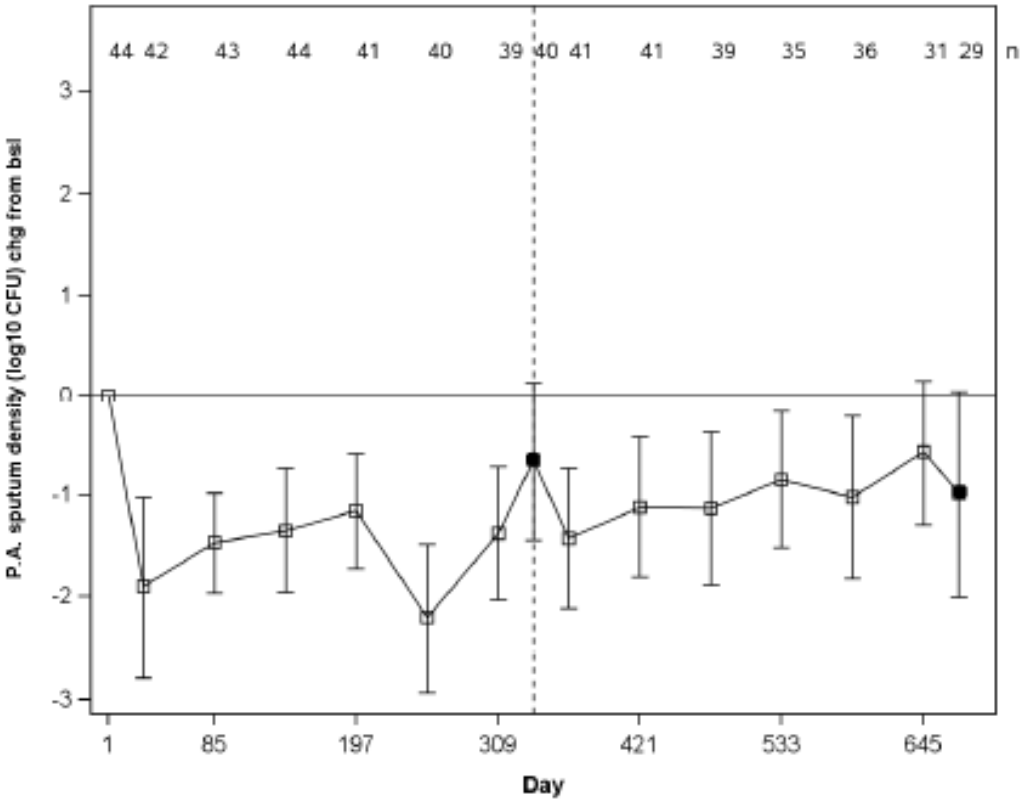
Absolute change in P. aeruginosa sputum density:

From baseline, there were decreases in the mean *P. aeruginosa* sputum density for sum of all biotypes at the end of dosing periods across 12 treatment cycles (6 cycles in the core study and 6 cycles in the extension study). As expected there was a tendency of an increase in P. aeruginosa sputum density at the end of the off-treatment periods of the core and extension treatment cycles (Figure 11-2).

From the baseline, there was a decrease of 1.4 log10 CFU/gram at the end of dosing in the core study treatment Cycle 6, and there was a decrease of 0.6 log10 CFU/gram at the end of dosing in the last treatment cycle in the extension study (Cycle 12). The decreases in the sputum density of P.

aeruginosa were statistically significant across the core and extension study cycles ($p<0.05$), except at extension Cycle 12 (Table 11-6).

Figure 11-2 Change from baseline in mean *P. aeruginosa* sputum density for sum of all biotypes (log10 CFU) over time (Extension safety population)



Note: The vertical bar is the 95% confidence interval.
Day 1 refers to baseline of the core study.
The dashed line at Day 337 represents the start of the extension study.

Days 337 and 673 represent the last day in last off-treatment period in the core/extension study, other time points represent the end of on-treatment periods.
If no *P. aeruginosa* is isolated for a visit, log10 CFU is imputed with log10(19) for all biotypes.
Source: Figure 14.2-1.7.

Tobramycin MIC:
At the completion of the extension study, 24.1% of patients (7 patients) showed no change in tobramycin MIC values, 44,8% ≥2-fold increase and 34.5% ≥4-fold increase. However, most of them still showed MIC values <8µg/mL at the extension study completion.

At the completion of the core study (see Rapporteur's preliminary assessment report), 18% of patients had no change in tobramycin MIC (minimum inhibitory concentration) from baseline, 43% experienced at least a 2-fold increase in tobramycin MIC, and 27% had at least a 4-fold increase. For patients with a baseline MIC ≤ 8 µg/ml, 16.9% had an increase to a MIC > 8 µg/ml.

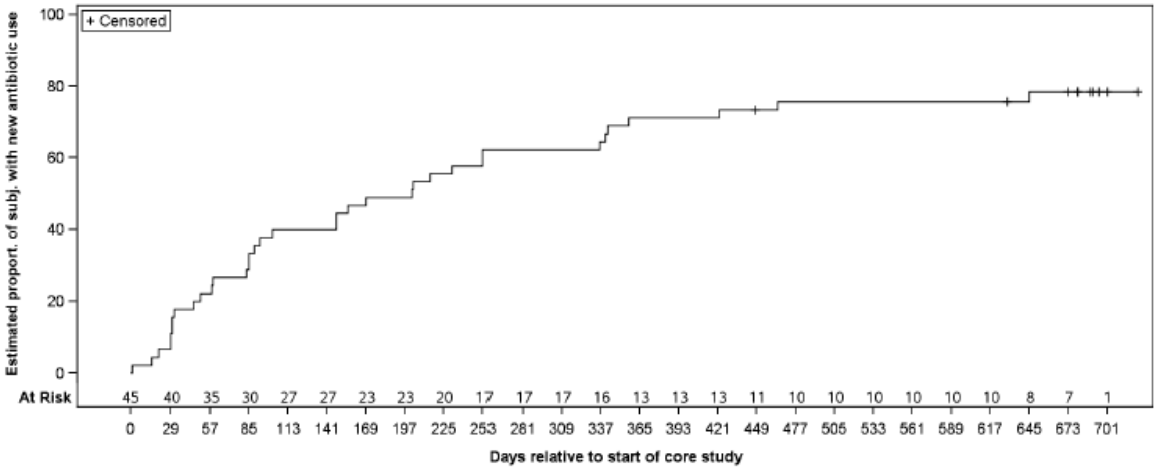
New anti-pseudomonal antibiotic usage and hospitalization:
Overall, 35 patients (77.8%) were treated with new additional anti-pseudomonal antibiotics (68.9% oral use, 55.6% IV use and 2.2% inhaled use) through 12 treatment cycles with a median total

duration of 59 days. The rate of usage was comparable between core and extension treatment cycles (66.7% versus 68.9% respectively). Also the rates of route of administration (oral/IV) were comparable between the core and extension study.

The Kaplan-Meier estimates for the time to first new anti-pseudomonal antibiotic use showed that most patients reported first anti-pseudomonal antibiotic use in the core study cycles and during the initial cycles of the extension study, while a lower number of patients reported use during the later time-points in the extension study.

Figure 14.2-2.1 (Page 1 of 4)
Kaplan-Meier curves of time to first new anti-pseudomonal antibiotic use during core and extension study, by route (overall, IV, oral, inhaled)
Extension safety population

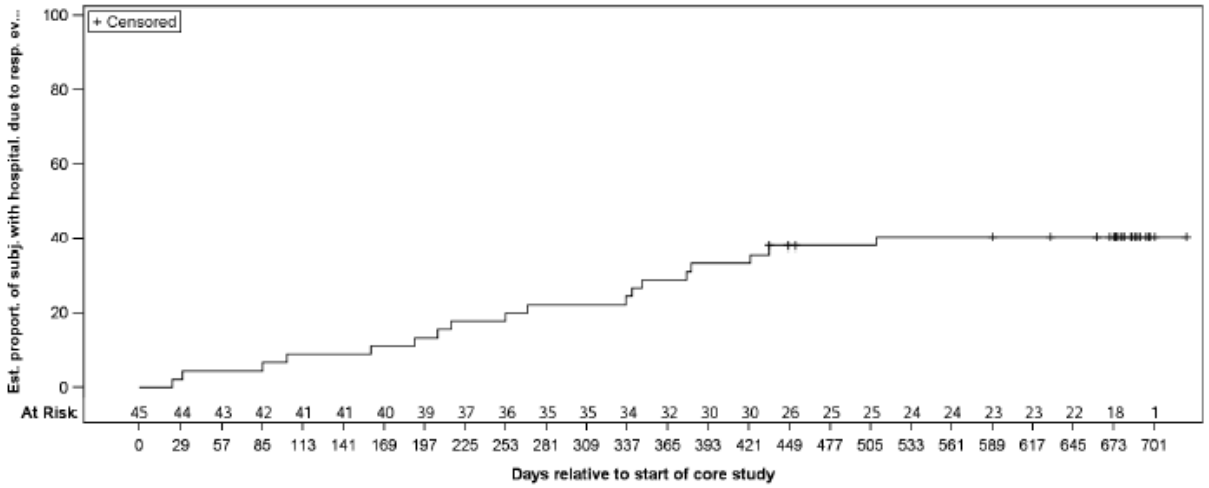
Route: Overall



Overall, respiratory-related hospitalizations were reported for a total of 18 patients (40%) through 12 treatment cycles with a median total duration of hospitalization of 17 days. The rate of hospitalizations was slightly higher during the extension treatment cycles compared to the core study cycles (35.6% versus 26.7%). Also the duration of hospitalization was slightly higher during the extension cycles (median 16 days) than during the core study cycles (median 13.5 days).

The Kaplan-Meier estimates of time to first hospitalization due to respiratory-related events show that there were gradual increases in the cumulative number of new hospitalizations across core cycles and initial treatment cycles of the extension study, after which the rates remained constant.

Figure 14.2-2.3 (Page 1 of 1)
Kaplan-Meier curve of time to first hospitalization due to respiratory-related serious adverse events during core and extension study
Extension safety population



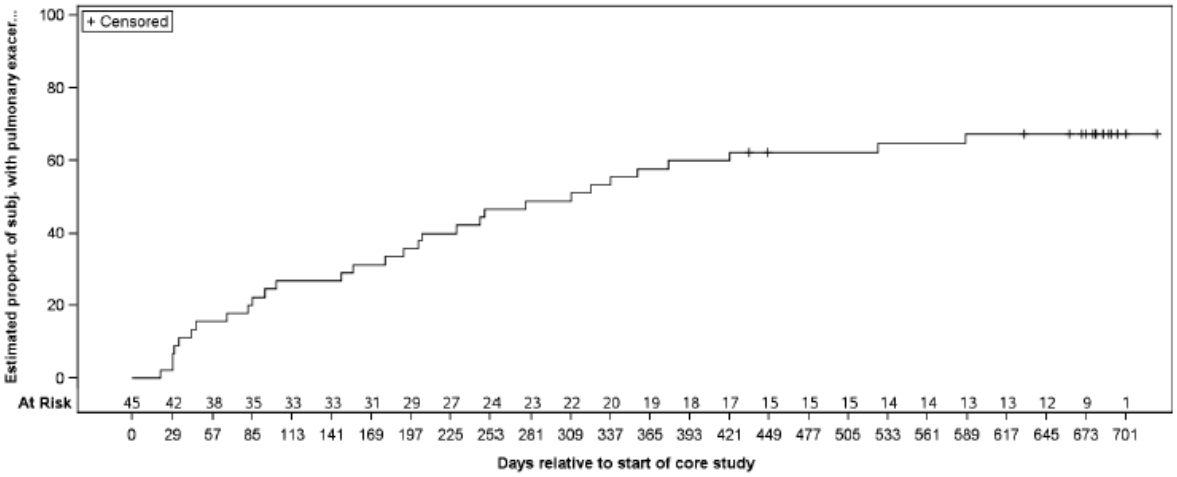
Pulmonary exacerbations:
Pulmonary exacerbations were reported by a total of 30 patients (66.7%) across 12 treatment cycles. Overall, these patients reported 89 episodes of exacerbations, most were mild or moderate in severity.

A total of 34 (38.2%) episodes of exacerbations were assessed as SAEs and hospitalization was reported for a total of 36 (40.4%) exacerbation events.

The rates of moderate and serious pulmonary exacerbation periods were slightly higher during the extension cycles (47.5% moderate periods/12.5% serious periods) compared to the core study cycles (38.8% moderate periods/8.2% serious periods). This was not tested for significance. The median duration of the episodes was 16 days for both the extension and core study cycles.

Most patients reported the first exacerbation episode during core cycles. The frequency of new reports of exacerbation remained low and relatively constant from the dosing period of extension treatment Cycle 8 until off-treatment period of treatment Cycle 12.

Figure 14.2-2.5 (Page 1 of 1)
Kaplan-Meier curve of time to first pulmonary exacerbation during core and extension study
Extension safety population



CHMP's comment:

The efficacy data from the single arm extension study show a non-significant decrease of efficacy of TIP during the second year of treatment, measured as predicted mean FEV1 %. This decrease in FEV1 % predicted is supported by a higher rate of moderate and serious pulmonary exacerbations compared to the core study (47.5% moderate periods/12.5% serious periods versus 38.8% moderate periods/8.2% serious periods), a higher rate of respiratory-related hospitalizations compared to the core study (35.6% versus 26.7%) and a slightly longer duration of hospitalization periods compared to the core study (median: 16 vs. 13.5 days).

The Kaplan Meier curves of "time to first pulmonary exacerbation" (Fig 14.2-2.5), "first hospitalization due to respiratory-related serious adverse events" (Fig. 14.2-2.3) and "time to first new additional anti-pseudomonal antibiotic usage" show that the proportions of patients with pulmonary exacerbation episodes, respiratory-related serious adverse events and new additional anti-pseudomonal antibiotic usage increase across cycle 1 to 12. These increases are flattening out towards the end of the study.

The antibacterial effect of TIP was maintained across the study as measured by the reduction in *P. aeruginosa* bacterial load.

With regard to resistance development, the changes in tobramycin MIC values at the end of the extension study (cycles 7-12) were similar to that of the core study (cycles 1-6).

Overall, the provided data suggest a decrease of efficacy over time (12 treatment cycles). The decrease is seen in FEV1% and also reflected in an increase in hospitalisations and exacerbations – albeit the rate appears to slow down with time as suggested by figure 14.2-2.5. It is important that loss of efficacy is monitored. As agreed in the risk management plan, the MAH should follow up all reports suggestive of lack of efficacy with use of a follow up questionnaire and should discuss the analyses of lack of efficacy cases in the PSURs.

Safety results

AEs:

Across 12 treatment cycles (6 cycles in the core and 6 cycles in the extension study), a total of 86.7% (39/45 patients) reported AEs across on and off treatment periods, regardless of the study drug relationship (Table 12-2). The incidence of AEs was comparable across core (35 patients, 77.8%) and extension cycles (36 patients, 80%).

AEs by preferred term:

The most frequently reported adverse event across 12 treatment cycles was infective pulmonary exacerbation of cystic fibrosis (30 patients, 66.7%); this was also the most commonly reported AE in the core and extension cycles (Table 12-3). Other commonly reported AEs were nasopharyngitis (13 patients, 28.9%), hemoptysis (12 patients, 26.7%), cough (11 patients, 24.4%) and sputum increased (10 patients, 22.2%).

Table 12-3 **Most frequent adverse events (>3% percent overall, on and off treatment), regardless of study drug relationship, by preferred term and study period (Extension safety population)**

	Core (Cycles 1-6) N=45 n (%)	Extension (Cycles 7-12) N=45 n (%)	Overall (Cycles 1-12) N=45 n (%)
Patients with AE(s)	35 (77.8)	36 (80.0)	39 (86.7)
Preferred term			
Infective pulmonary exacerbation of cystic fibrosis	25 (55.6)	23 (51.1)	30 (66.7)
Nasopharyngitis	9 (20.0)	9 (20.0)	13 (28.9)
Haemoptysis	8 (17.8)	10 (22.2)	12 (26.7)
Cough	8 (17.8)	8 (17.8)	11 (24.4)
Sputum increased	7 (15.6)	5 (11.1)	10 (22.2)
Oropharyngeal pain	6 (13.3)	3 (6.7)	9 (20.0)
Forced expiratory volume decreased	4 (8.9)	6 (13.3)	9 (20.0)
Diarrhoea	5 (11.1)	5 (11.1)	8 (17.8)
Abdominal pain	4 (8.9)	4 (8.9)	7 (15.6)
Headache	4 (8.9)	4 (8.9)	6 (13.3)
Upper respiratory tract infection	2 (4.4)	2 (4.4)	4 (8.9)
Sinusitis	1 (2.2)	3 (6.7)	4 (8.9)
Dysphonia	4 (8.9)	1 (2.2)	4 (8.9)
Pyrexia	3 (6.7)	2 (4.4)	4 (8.9)
Fatigue	2 (4.4)	3 (6.7)	4 (8.9)
Bacterial disease carrier	1 (2.2)	3 (6.7)	3 (6.7)
Rhinorrhoea	0 (0.0)	3 (6.7)	3 (6.7)
Vomiting	2 (4.4)	1 (2.2)	3 (6.7)
Constipation	0 (0.0)	3 (6.7)	3 (6.7)
Staphylococcus test positive	3 (6.7)	0 (0.0)	3 (6.7)
Ear infection	2 (4.4)	0 (0.0)	2 (4.4)
Pharyngitis	2 (4.4)	0 (0.0)	2 (4.4)
Rhinitis	2 (4.4)	0 (0.0)	2 (4.4)
Urinary tract infection	2 (4.4)	0 (0.0)	2 (4.4)
Influenza	0 (0.0)	2 (4.4)	2 (4.4)
Productive cough	2 (4.4)	0 (0.0)	2 (4.4)
Wheezing	1 (2.2)	1 (2.2)	2 (4.4)
Nausea	2 (4.4)	1 (2.2)	2 (4.4)
Dyspepsia	0 (0.0)	2 (4.4)	2 (4.4)

	Core (Cycles 1-6) N=45 n (%)	Extension (Cycles 7-12) N=45 n (%)	Overall (Cycles 1-12) N=45 n (%)
Pulmonary function test decreased	2 (4.4)	0 (0.0)	2 (4.4)
Chest discomfort	1 (2.2)	2 (4.4)	2 (4.4)
Back pain	1 (2.2)	1 (2.2)	2 (4.4)
Musculoskeletal chest pain	1 (2.2)	1 (2.2)	2 (4.4)
Hyperglycaemia	0 (0.0)	2 (4.4)	2 (4.4)
Dysmenorrhoea	1 (2.2)	1 (2.2)	2 (4.4)
Hypertension	2 (4.4)	0 (0.0)	2 (4.4)

Source: Table 14.3.1-1.1 to Table 14.3.1-1.3

Preferred terms are sorted in descending order of frequency.

A patient with multiple occurrences of the same preferred term is counted only once in the preferred term in the period of interest.

AEs by severity/serious adverse events:

Across 12 treatment cycles, 40% of the reported AEs (reported by 18 patients) were moderate in severity, 24% (11 patients) were reported as severe AEs and 22.2% (10 patients) were reported as mild AEs. Most of the severe AEs were reported under SOC infections and infestations and was mostly reported as infective pulmonary exacerbations of cystic fibrosis (8 patients, 17.8%). All other severe AEs were isolated cases, not reported by more than 1 patient.

There was 1 death, a 15 year old female, reported due to pulmonary exacerbation during the off-treatment period of last treatment cycle (Cycle 12). The primary precipitating factor for pulmonary exacerbation was a viral respiratory infection reported in the off-treatment period of Cycle 12. The patient went on to experience hypercapnic respiratory failure, respiratory acidosis, hemodynamic instability, cardiogenic shock and cardiac failure resulting in death. The AE (pulmonary exacerbation) was not suspected to be related to the study treatment.

The SAEs were reported at a higher frequency in the extension study (16 patients, 35.6%) compared with the frequency in the core study (12 patients, 26.7%).

Table 12-5 Serious adverse events, by preferred term (Extension safety population)

	Core (Cycles 1-6) N=45 n (%)	Extension (Cycles 7-12) N=45 n (%)	Overall (Cycles 1-12) N=45 n (%)
Patients with SAE(s)	12 (26.7)	16 (35.6)	19 (42.2)
Preferred term			
Infective pulmonary exacerbation of cystic fibrosis	11 (24.4)	14 (31.1)	17 (37.8)
Bronchopneumonia	1 (2.2)	0 (0.0)	1 (2.2)
Influenza	0 (0.0)	1 (2.2)	1 (2.2)
Pneumonia	0 (0.0)	1 (2.2)	1 (2.2)
Hyperamylasaemia	1 (2.2)	0 (0.0)	1 (2.2)
Ovarian cyst	1 (2.2)	0 (0.0)	1 (2.2)
Prostatitis	0 (0.0)	1 (2.2)	1 (2.2)
Cardiac failure	0 (0.0)	1 (2.2)	1 (2.2)
Cardiogenic shock	0 (0.0)	1 (2.2)	1 (2.2)
Distal intestinal obstruction syndrome	0 (0.0)	1 (2.2)	1 (2.2)
Forced expiratory volume decreased	0 (0.0)	1 (2.2)	1 (2.2)
Syncope	0 (0.0)	1 (2.2)	1 (2.2)
Dyspnoea exertional	0 (0.0)	1 (2.2)	1 (2.2)
Haemoptysis	0 (0.0)	1 (2.2)	1 (2.2)
Respiratory acidosis	0 (0.0)	1 (2.2)	1 (2.2)
Respiratory failure	0 (0.0)	1 (2.2)	1 (2.2)
Haemodynamic instability	0 (0.0)	1 (2.2)	1 (2.2)

Source: Table 14.3.1-2.1; Table 14.3.1-2.2; Listing 14.3.2-1.2.

Preferred terms are sorted in descending order of frequency.

A patient with multiple occurrences of the same preferred term is counted only once for the preferred term.

AEs suspected to be study drug related

A total of 15 patients (33.3%) reported AEs suspected to be related to the study treatment across 12 treatment cycles. Most of the AEs suspected to be related to the study-drug were reported in the on-treatment period (12 patients, 26.7%) and commonly reported during the core treatment cycles (11 patients, 24.4%).

Airway reactivity

Airway reactivity (≥ 20% decrease in pre-dose to 30 minutes post-dose) was reported by 2 patients overall (one in Cycle 3 and one in Cycle 4) with no occurrences in the extension cycles.

Table 12-9 Airway reactivity: greater than or equal to 20% relative decrease in FEV_1% predicted from pre dose to 30 minute post dose (Extension safety population)

Study period/Cycle/Visit/Day	Total N=45 n/total (%)
Core Cycle 1 - Visit 2/Day 1	0/ 44 (0.0)
Core Cycle 1 - Visit 3/Day 29	0/ 41 (0.0)
Core Cycle 2 - Visit 5/Day 85	0/ 39 (0.0)
Core Cycle 3 - Visit 7/Day 141	1/ 42 (2.4)
Core Cycle 4 - Visit 9/Day 197	1/ 40 (2.5)
Core Cycle 5 - Visit 11/Day 253	0/ 41 (0.0)
Core Cycle 6 - Visit 13/Day 309	0/ 39 (0.0)
Extension Cycle 7 - Visit 16/Day 365	0/ 37 (0.0)
Extension Cycle 8 - Visit 18/Day 421	0/ 36 (0.0)
Extension Cycle 9 - Visit 20/Day 477	0/ 37 (0.0)
Extension Cycle 10 - Visit 22/Day 533	0/ 36 (0.0)
Extension Cycle 11 - Visit 24/Day 589	0/ 35 (0.0)
Extension Cycle 12 - Visit 26/Day 645	0/ 30 (0.0)

Source: Table 14.3-3.14

Relative change = 100 * (30-m-post-dose value– pre-dose value)/pre-dose value

n is number of patients with event, total is number of patients with pre and post dose values at visit.

Post inhalation events:

The most commonly reported event post inhalation within 5 minutes was cough across all the study cycles. The duration of the event was short and the median duration ranged from 0.08 to 0.25 minutes. The duration of cough was generally higher during the core study cycles than in the extension study cycles. There were 4 patients with cough ongoing at the completion of the visit during the core study, while there was 1 such ongoing event reported during the extension study.

Audiology

Hearing loss of ≥ 10dB decrease at 2 consecutive frequencies was reported by 1 patient during Cycle 6 of the core study, 1 patient during extension Cycle 7, 1 patient during extension Cycle 8 and 1 patient during extension Cycles 9, 10 and 12. For this last patient, the reported decrease was ≥15dB at 2 consecutive frequencies during extension Cycles 9 and 10. At the extension study completion visit there was 1 report of a patient with ≥20dB decrease at 0.25 kHz frequency who had previously reported an AE of deafness (based on a reported 15dB decrease) during Cycle 9 which subsequently resolved.

One patient was reported with neurosensory hearing loss in the right ear at core completion. In the extension study there was 1 patient with neurosensory hearing loss in the right ear during extension Cycles 7, 9 and 10.

CHMP's comment:
SAEs were reported at a higher frequency in the extension study compared with the frequency in the core study. This was likely driven by a difference in infective pulmonary exacerbations (table 12-5) which is also highlighted under the efficacy part. Overall, the reported AEs and their frequencies are comparable to the known safety profile of the product.

2.3.3. Discussion on clinical aspects

The completed single arm, open-label, multicentre, Phase IV 48 weeks extension trial to assess long term safety of tobramycin inhalation powder (TIP) in patients with Cystic Fibrosis shows that TIP was reasonably well tolerated. SAEs were reported at a higher frequency in the extension study compared with the frequency in the core study. This was likely driven by a difference in infective pulmonary exacerbations. Overall, the reported AEs and their frequencies are comparable to the known safety profile of the product.

The efficacy data show a decrease in FEV1 % during the second year of treatment. This decrease in FEV1 % predicted is reflected in higher rates of moderate and serious pulmonary exacerbations, respiratory-related hospitalizations and a longer duration of hospitalization periods compared to the first year of treatment. The proportions of patients with pulmonary exacerbation episodes, respiratory-related serious adverse events and new additional anti-pseudomonal antibiotic usage increase across cycle 1-12, although these increases are flattening out with time as suggested by figure 14.2-2.5. There was no evidence of antibiotic resistance development during the extension study. Resistance development remains, however, an important potential risk for TIP. It is important that loss of efficacy is monitored. As agreed in the risk management plan, the MAH should follow up all reports suggestive of lack of efficacy with use of a follow up questionnaire and should discuss the analyses of lack of efficacy cases in the PSURs.

3. CHMP's overall conclusion and recommendation

Overall conclusion

The 48 week extension study CTBM100C2401E1 aimed to evaluate the long-term safety profile of tobramycin inhalation powder over six additional treatment cycles. The newly available data on safety are consistent with the data of the core study CTBM100C2401 and the known safety profile.

No new safety concerns have been identified.

The findings from the extension study CTBM100C2401E1 do not warrant any changes to the product information.

x Fulfilled:

No regulatory action required.