25 January 2018
EMA/220904/2023
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/P46/033

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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1. Introduction

On 2 October 2017, the MAH submitted a completed paediatric study for Tobi Podhaler, 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 study title and number CTBM100CDE02, an 8 week open-label interventional multicenter study to evaluate the lung clearance index as endpoint for clinical trials in cystic fibrosis patients ≥ 6 years of age, chronically infected with *Pseudomonas aeruginosa* is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- CTBM100CDE02, an 8 week open-label interventional multicenter study to evaluate the lung clearance index as endpoint for clinical trials in cystic fibrosis patients ≥ 6 years of age, chronically infected with *Pseudomonas aeruginosa*.

2.3.2. Clinical study

CTBM100CDE02; An 8 week open-label interventional multicenter study to evaluate the lung clearance index as endpoint for clinical trials in cystic fibrosis patients ≥ 6 years of age, chronically infected with *Pseudomonas aeruginosa*

Description

The only parameter of lung function that is currently recognized as a surrogate endpoint in CF trials is the forced expiratory volume in one second (FEV1). However, FEV1 mainly reflects large conducting airways and is relatively insensitive to changes in the small airways, where CF lung disease starts. Accordingly, there is a need for parameters that are more sensitive and allow detection of changes in disease severity. Previous studies suggest that LCI may be a more sensitive surrogate parameter to assess early lung disease, treatment effects in patients with milder lung disease and/or disease progression in CF patients.

This was an open-label, single arm design study in patients with cystic fibrosis (CF), aged 6 to 50 years, representing the typical CF patient population, with chronic *P. aeruginosa* infection in a clinically stable condition and treated by standard inhaled Tobramycin mono-therapy in an on-off regimen as either tobramycin inhalation solution (TIS) or tobramycin inhalation powder (TIP). The main aim of the study was to assess the change of lung clearance index (LCI) after 4 weeks following onset of study drug inhalation versus Baseline.

This study was terminated prematurely. The reason for study termination was challenge with enrollment and patient recruitment.

Methods

Objectives

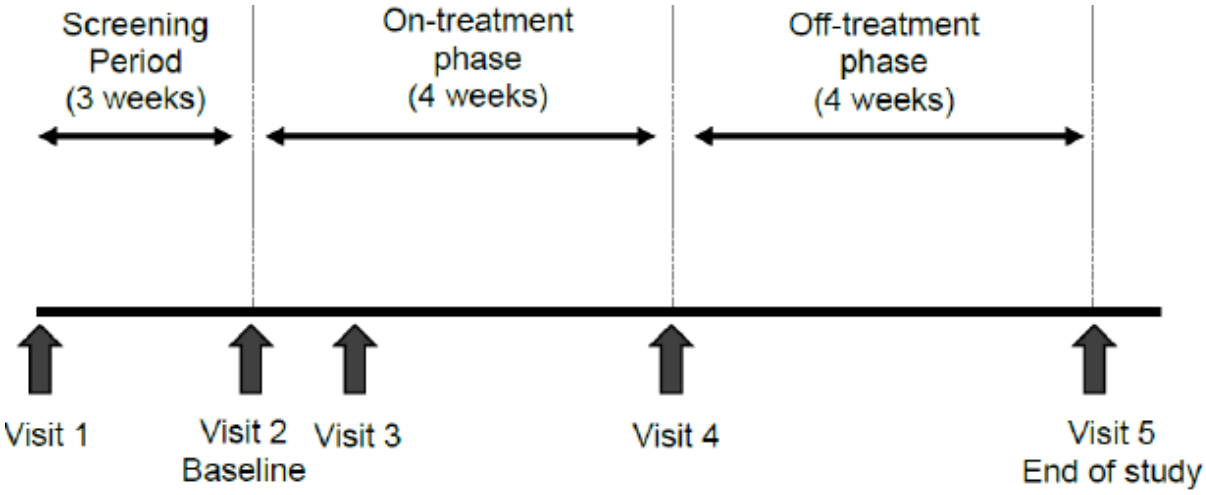
Primary objective: To assess the change of lung clearance index (LCI) after 4 weeks following onset of study drug inhalation versus Baseline.

Secondary objectives: The secondary objectives of the study were to assess:

- Change of forced expiratory volume at 1 second (FEV1) after 4 weeks following onset of study drug inhalation versus Baseline.
- Change in colony-forming units (CFU) after 4 weeks following onset of study drug inhalation versus Baseline.
- Change of LCI after 1 week following onset of study drug inhalation versus Baseline. The multiple breath washout device Exhalyzer D was used to assess the LCI, a system that is recommended by the European Cystic Fibrosis Society clinical trial network.
- Change of LCI, FEV1 and CFU between week 4 (end of study drug inhalation in the current treatment cycle) and week 8 (prior to start of study drug inhalation in the following treatment cycle).
- Correlation between the changes of LCI, FEV1 and CFU after 1 week, 4 weeks, and 8 weeks versus Baseline, respectively.

Study design

An open-label, single arm design study. This study was designed to evaluate LCI by a standardized procedure in a well characterized study setting to assess feasibility of LCI as a more sensitive method to measure effectiveness of antibiotic therapy in patients with mild lung disease. After a screening period to test the presence of *P.aeruginosa,* participants received treatment for 28 days and were followed for another 28 days off-treatment.



Study population /Sample size

It was anticipated that 35 patients (children, adolescents and young adults) were to be recruited in the Germany, Austria and Switzerland (DACH) region at approximately 8 study sites, however in actual only 17 patients from Germany were recruited and analysed in this study

Male and female patients aged 6 to 50 years at screening (Visit 1) and had confirmed diagnosis of CF, elevated LCI of ≥ 7.5, FEV1 of ≥ 50% predicted at screening and had *P.aeruginosa* in two sputum or deep cough throat swab cultures or bronchoalveolar lavage within 12 months prior to screening or in one culture within 12 months prior to screening were enrolled in the study and patients who had history of sputum culture or deep cough throat swab (or bronchoalveolar lavage) culture yielding *Burkholderia cepacia* complex within 2 years prior to screening, hemoptysis > 60 mL at any time within 30 days prior to screening were excluded from the study.

Drugs that support lung clearance e. g. pulmozyme (DNAse) or hypertonic saline or drugs that treat obstructive airways, e. g. long acting ß-Agonists could impact the LCI as well. In order to minimize the influence of these concomitant medications on the treatment effect of inhaled antibiotics, initiation or discontinuation of these therapies in the last 56 days (8 weeks) prior to screening Baseline visit and during the study was not allowed.

Treatments

Tobramycin either as TIS (300 mg/5mL or 300 mg/4mL) was to be nebulized or as TIP (112 mg), as prescribed by the treating physician. Neither TIS nor TIP was provided to the patient, therefore formulations and batch number details are unknown.

The study duration of 8 weeks comprised a complete on / off treatment cycle starting with 28 days inhalation followed by 28 days without study drug inhalation.

Outcomes/endpoints

Efficacy

Primary efficacy variable time course and changes in LCI from Baseline (Visit 2) to Week 4 (Visit 4).

The secondary efficacy variables were the changes in FEV1 % predicted, CFU and LCI and the comparison among themselves at respective visit were performed for safety set.

Safety:

Safety analyses including treatment emergent adverse events (TEAEs), vital signs, lab parameters and their change from baseline were evaluated based on safety set. All listings were ordered according to age categories 6 to 12, > 12 to 17 and > 17 for safety set.

Statistical Methods

The primary efficacy endpoint was assessed by changes in LCI from Baseline to Week 4. Baseline LCI was the assessment taken prior to the start of TBM100, which was typically the value at Visit 2. Between visits comparison for changes in LCI from baseline was analyzed using an analysis of variance (ANOVA) model with factors patient and visit. Estimates over time were presented as least square (LS) means, pairwise LS-Mean differences along with 95% confidence intervals (CIs) and two sided p-values for the pairwise differences between visits. Similarly for secondary efficacy variables, estimates of change over time was presented as LS means, pairwise LS-mean differences along with 95% CIs and two sided p-values for the pairwise differences between visits. For determining the correlation between

changes from baseline in LCI, FEV1 % predicted, CFU at Week 1, Week 4 and Week 8, estimates as Pearson correlation coefficient with their 95% CIs and p-values were presented.

The safety set was used for all analyses in the study, which consisted of all patients that entered the study (provided informed consent) and had been exposed to at least one dose of study drug.

Results

Recruitment/ Number analyse

In total, 17 patients entered into the study and were treated with TIS (5 patients) and TIP (12 patients). None of the patient discontinued from the study and all 17 patients completed the study. Two patients (16.7%) in TIP group had at least one protocol deviation in the study. Protocol deviation criteria included prohibited concomitant medication and other reason (1 patient (8.3%) each).

Baseline data

Table 11-2 Demographics (Safety set)

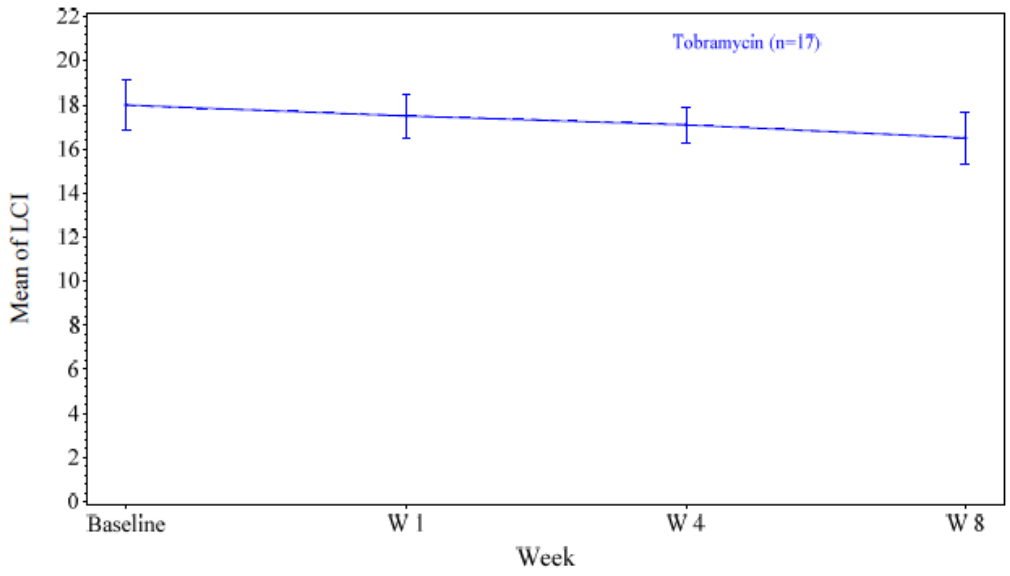
Variable Statistic/Category	TIS (N=5)	TIP (N=12)	Overall (N=17)
Age categories, n (%)			
6 to 12 years	1 (20.0)	0 (0.0)	1 (5.9)
>12 to 17 years	1 (20.0)	1 (8.3)	2 (11.8)
>17 years	3 (60.0)	11 (91.7)	14 (82.4)
Age (years)			
n	5	12	17
Mean	20.2	28.9	26.4
SD	8.26	9.79	9.99
Median	22.0	29.0	24.0
Min, Max	8, 30	17, 43	8, 43
Sex, n (%)			
Male	2 (40.0)	9 (75.0)	11 (64.7)
Female	3 (60.0)	3 (25.0)	6 (35.3)
Race, n (%)			
Caucasian	5 (100.0)	12 (100.0)	17 (100.0)
Black	0 (0.0)	0 (0.0)	0 (0.0)
Asian	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)
Weight (kg)			
n	5	12	17
Mean	51.280	67.283	62.576
SD	13.4719	9.7475	12.9302
Median	54.000	67.450	62.000
Min, Max	29.00, 63.00	53.50, 83.20	29.00, 83.20
Height (cm)			
n	5	12	17
Mean	162.600	174.675	171.124
SD	18.4472	8.2028	12.7866
Median	170.000	176.000	174.000
Min, Max	131.0, 175.0	160.0, 185.0	131.0, 185.0
BMI (kg/m^2)			
n	5	12	17
Mean	19.010	21.987	21.112
SD	1.7581	2.2060	2.4646
Median	19.050	22.450	20.900
Min, Max	16.90, 20.90	18.69, 25.68	16.90, 25.68

There were three paediatric patients enrolled (aged 8, 17, 17), all patients completed the study.

Efficacy results

Change in LCI was statistically non-significant at Week 1 (p=0.5910), Week 4 (p=0.4099) and Week 8 (p=0.1492) when compared with Baseline. Results were similar when change in LCI was analyzed as Week 1 vs Week 4 and Week 8 and also Week 4 vs Week 8. The mean LCI was decreased slightly over time when compared to Baseline (17.985), Week 1 (17.506), Week 4 (17.101) and Week 8 (16.489).

Figure 11-1 LCI mean over time up to Week 8 (Safety set)

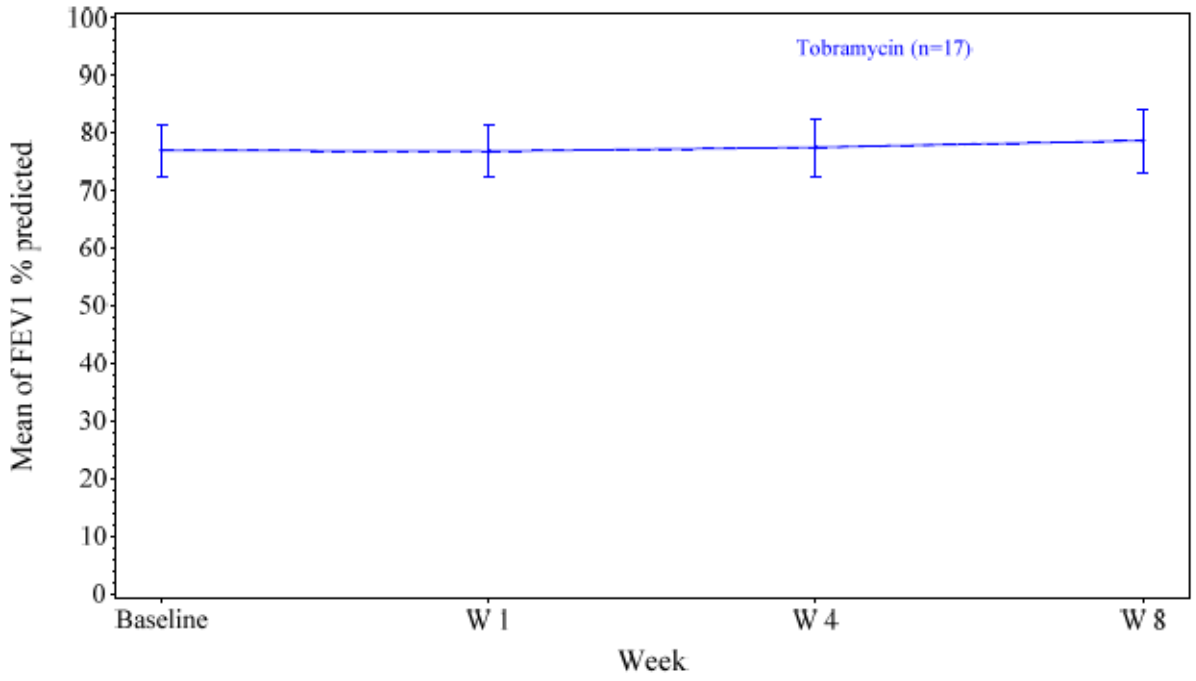


SE = standard error of the mean.
Mean ± SE are displayed
Source: Table 14.2-1.1

Change from Baseline in FEV1 after 4 weeks following onset of study drug inhalation

Change in FEV1 was statistically non-significant at Week 1 (p=0.9254), Week 4 (p=0.6961) and Week 8 (p=0.2783) when compared with Baseline. Results were similar when change in LCI was analyzed as Week 1 vs Week 4 and Week 8 and also Week 4 vs Week 8. The mean FEV1 was slightly decreased at Week 1 as compared to Baseline (76.838 vs 76.964), however there was a slight increase in mean FEV1 at Week 4 (77.481) and Week 8 (78.705)

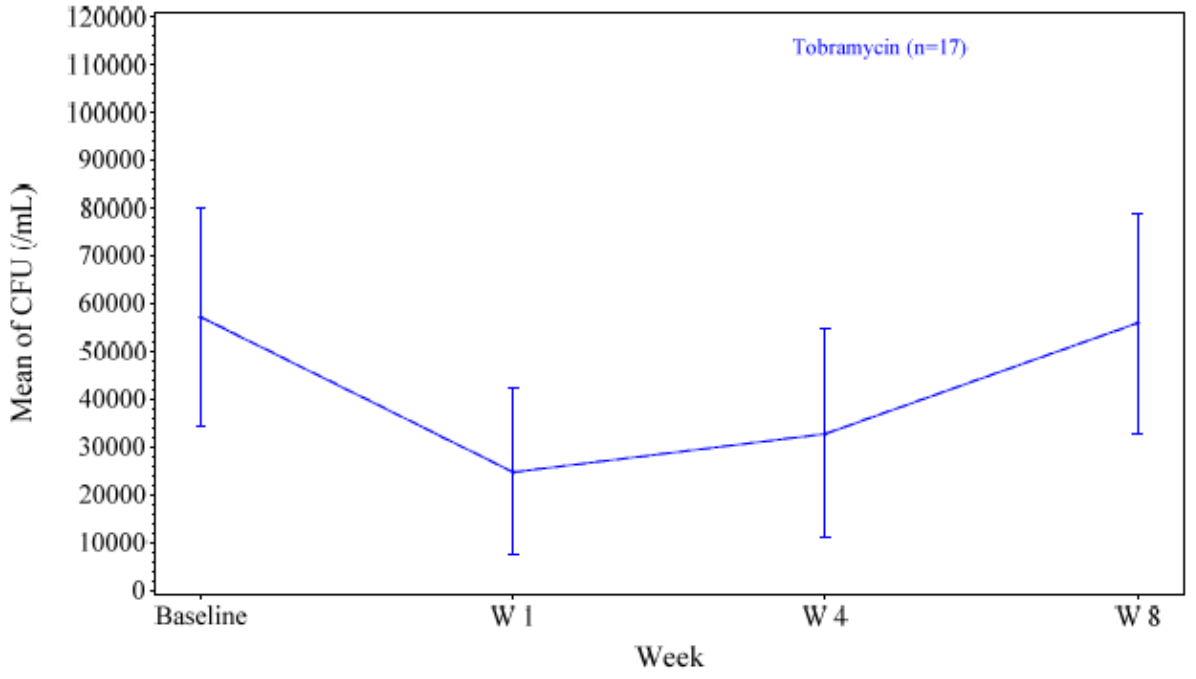
Figure 11-2 FEV1 % predicted mean over time up to Week 8 (Safety set)



Change from Baseline in CFU after 4 weeks following onset of study drug inhalation

Change in CFU was statistically non-significant at Week 1 (p=0.3019), Week 4 (p=0.3540) and Week 8 (p=0.9933) when compared with Baseline. Results were similar when change in CFU was analyzed as Week 1 vs Week 4 and Week 8 and also Week 4 vs Week 8. Mean CFU was decreased at Week 1 (23389.9) and Week 4 (26113.0) as compared to Baseline (56594.3), however at Week 8 mean CFU was comparable (56285.0) with Baseline.

Figure 11-3 CFU (/mL) mean over time up to Week 8 (Safety set)



Correlation between the changes of LCI, FEV1 and CFU after 1 week, 4 weeks, and 8 weeks versus Baseline, respectively

Change after Week 1 from Baseline: The correlation between LCI and CFU was moderately positive (r=0.59) and correlation was statistically significant (p=0.0321). Correlations between LCI and FEV1 and between FEV1 and CFU were statistically non-significant (p=0.8337 and p=0.1808 respectively).

Change after Week 4 from baseline: The correlation between LCI and CFU was moderately positive (r=0.79) and correlation was statistically significant (p=0.0046). Also the correlation between FEV1 and CFU was moderately negative (r= -0.64) and it was considered to be statistically significant (p=0.0462). There was moderately negative correlation between LCI and FEV1 (r= -0.39) and correlation was statistically non-significant. Change after Week 8 from baseline: The correlations between any of the paired parameters were statistically non-significant (p≥0.0617).

Due to the small sample size exploratory endpoints will not be discussed.

Safety results

Exposure

The overall mean (SD) duration of exposure was 28.1 (1.52) days. Majority of patients (76.5%) were exposed from 21 to 28 days and rest of the patients (23.5%) were exposed for >28 days. Mean exposure was comparable between both the treatment groups (TIS: 26.8 days vs TIP: 28.6 days).

Adverse events

Overall, 5 patients (29.4%) had experienced adverse events: TIP (3 patients (25.0%) and TIS (2 patients (40.0%)). Most commonly affected primary system organ classes (SOCs) were respiratory, thoracic and mediastinal disorders (3 patients (17.6%)) followed by gastrointestinal disorders, injury, poisoning and procedural complications, and investigations (1 patient each (5.9%)). Most commonly reported AEs by preferred term included abdominal pain upper, sunburn, forced expiratory volume decreased, cough, haemoptysis, obstructive airways disorder (1 patient each (5.9%)).

Table 12-2 Number (%) of patient with treatment emergent adverse events by primary system organ class, preferred term and treatment dose form (Safety set)

MedDRA system organ class Preferred term	TIS (N=5) n (%)	TIP (N=12) n (%)	Overall (N=17) n (%)
Any MedDRA system organ class	2 (40.0)	3 (25.0)	5 (29.4)
Gastrointestinal disorders	0 (0.0)	1 (8.3)	1 (5.9)
Abdominal pain upper	0 (0.0)	1 (8.3)	1 (5.9)
Injury, poisoning and procedural complications	1 (20.0)	0 (0.0)	1 (5.9)
Sunburn	1 (20.0)	0 (0.0)	1 (5.9)
Investigations	1 (8.3)	0 (0.0)	1 (5.9)
Forced expiratory volume decreased	1 (8.3)	0 (0.0)	1 (5.9)
Respiratory, thoracic and mediastinal disorders	2 (16.7)	1 (20.0)	3 (17.6)
Cough	1 (8.3)	0 (0.0)	1 (5.9)
Haemoptysis	0 (0.0)	1 (20.0)	1 (5.9)
Obstructive airways disorder	1 (8.3)	0 (0.0)	1 (5.9)

TIS = Tobramycin inhalation solution, TIP = Tobramycin inhalation powder.

All patients had AEs of mild severity except for 1 patient (patient ID: 1005003). This patient (41 years old male) was into TIP treatment group and experienced an AE of headache, which was of moderate severity.

Only 1 patient (5.9%) had a TEAE suspected to be study drug related. Patient ID 1001004 (23-year-old male): Patient was into TIP treatment group and experienced 2 TEAEs: forced expiratory volume decreased and obstructive airways disorder. Both the events were of mild severity and considered to

be related to study drug as assessed by the Investigator. Both the events were resolved and no medication was administered due to events.

There were no deaths or SAEs in the study.

No notable clinically significant abnormality in clinical chemistry, vital signs, and physical findings were observed.

Microbiology results

At Week 1 and Week 4, overall mean Pseudomonas aeruginosa tobramycin MIC was reduced by 1.267 µg/mL and 4.536 µg/mL respectively, as compared to Baseline. Overall mean Pseudomonas aeruginosa tobramycin MIC at Week 8 was increased by 1.036 µg/mL when compared to Baseline.

Discussion on clinical aspects

This open label single armed study included 17 patients, half of the planned number, and was terminated early due to recruitment difficulties.

The study did not meet its primary efficacy objective. The main efficacy results of the study have shown that changes in LCI, FEV1 or CFU were not statistically significant at Week 1, Week 4 and Week 8 when compared with baseline. There was no specific trend observed with respect to correlation between the changes of LCI, FEV1 and CFU after 1 week, 4 weeks, and 8 weeks versus Baseline.

All 17 patients had pathological LCI at Baseline and Week 4. There was a slight improvement in mean pathological LCI at Week 4 as compared to Baseline. Eight patients had pathological FEV1 at Baseline and Week 4. The mean pathological FEV1 was comparable between Baseline and Week 4. Nine patients had normal FEV1 at Baseline and Week 4. Mean normal FEV1 was slightly improved at Week 4 when compared to Baseline.

There were no untoward safety findings in this small study.

The MAH suggests that LCI alone does not seem to be an appropriate clinical endpoint for efficacy studies with antibiotic treatment (either i.v. or inhaled) in small groups of CF patients, based on the findings in this study and in the light of recently published literature (Vanderhelst et al, 2014; Horsley et al, 2013.

The MAH concludes that on the basis of the paediatric results of study CTBM100CDE02, 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. This can be agreed.

Horsley AR, Davies JC, Gray RD, et al (2013) Changes in physiological, functional and structural markers of cystic fibrosis lung disease with treatment of a pulmonary exacerbation. Thorax; 68: 532–539.

Vanderhelst E, Letter to the Editor (2014): The Lung Clearance Index as a probe for the effectiveness of short-term therapies in cystic fibrosis lung disease. Journal of Cystic Fibrosis.

3. Rapporteur's overall conclusion and recommendation

Fulfilled:

No regulatory action required.