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Procedure Management and Committees Support Division

CHMP's 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/P46/027

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1. Introduction

On 2 November 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.

The MAH states that the efficacy and safety data from study CTBM100CFR01 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 CTBM100CFR01*, Observational study on the compliance and quality of life of patients with cystic fibrosis treated with Tobi Podhaler® for a pulmonary infection due to Pseudomonas aeruginosa*, 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 CTBM100CFR01: Observational study on the compliance and quality of life of patients with cystic fibrosis treated with Tobi Podhaler® for a pulmonary infection due to *Pseudomonas aeruginosa*

2.3.2. Clinical study

Study CTBM100CFR01: Observational study on the compliance and quality of life of patients with cystic fibrosis treated with Tobi Podhaler® for a pulmonary infection due to Pseudomonas aeruginosa

Description

Study CTBM100CFR01 is a post-marketing, non-interventional, prospective, multicenter study, performed in a real-life setting with specialized physicians, to evaluate the compliance with Tobi Podhaler, as measured with the Morisky score (see below), reported during the last treatment cycle preceding the visit performed at 12th month. Out of the 126 patients that were enrolled in the study, 40 patients were paediatric patients.

Methods

Objective(s)

Primary Objective:

To evaluate the compliance to Tobi Podhaler, as measured with Morisky score, reported during the treatment cycle before the visit performed at 12 months (a compliant patient corresponding to a Morisky score ≥ 3).

Assessor's comment

The Morisky score is a structured four-item self-reported adherence measure. The following 4 questions are included:

1. Do you ever forget to take your medicine?

2. Are you careless at times about taking your medicine?

3. When you feel better do you sometimes stop taking your medicine?

4. Sometimes if you feel worse when you take the medicine, do you stop taking it?

The Morisky score can be considered a generally accepted self-reported adherence measure. The questions asked in the current study are in line with the original 4 questions described by Morisky as listed above. As such, the primary objective is acceptable.

Secondary Objectives

- To describe the changes in compliance (Morisky score) throughout the 12-month follow-up period, and the factors responsible for non-compliance.
- To describe the compliance to Tobi Podhaler in terms of: number of missing days of treatment per week, number of inhaled capsules per dose, reasons of missing days of treatment, timing of inhalations, relative compliance in comparison with the previous treatment.
- To describe the change in quality of life of patients treated with Tobi Podhaler, using the Cystic Fibrosis Questionnaire-Revised (CFQ-R) at 6 months and 12 months after initiation of Tobi Podhaler.
- To describe the characteristics of the patients: demographics, characteristics of cystic fibrosis and pulmonary *P.aeruginosa* infection, and the previous antipseudomonal antibiotic treatments.
- To describe the conditions of use of Tobi Podhaler: treatment duration, number of cycles.
- To describe the method of use of Tobi Podhaler as evaluated by the physician: search of critical errors of use, number of partially empty capsules and duration of the inhalation of 4 capsules.
- To describe patient's opinion about the ease of use of Tobi Podhaler, the interest in the dose visual control, and patients' preference in comparison with previous inhaled treatments.
- To describe the change in clinical parameters of cystic fibrosis from baseline to 6 month and 12 months after the initiation of the TOBI Podhaler: body weight, forced expiratory volume in one second (FEV1), microbiology (sputum/deep-throat swab).
- To describe the safety and tolerability of Tobi Podhaler:

- All adverse events (AEs) including serious adverse events (SAEs), AEs or SAEs considered to be study-drug related according to the investigator, except those related to CF symptoms or progression,
- Reasons for treatment discontinuation.

Study design

This was a prospective, non-interventional, multicenter study in France, performed in a reallife setting with specialized physicians (pulmonologists, paediatricians, gastroenterologists) from cystic fibrosis centers.

The study included three visits occurring at standard scheduled clinic appointments: one baseline visit (Visit 1) and two follow-up visits at 6 months and 12 months.

Information was collected from electronic Case Report Forms (e-CRFs) filled out by the physicians and electronic self-assessment questionnaires (e-diary) filled out by the patients or their legal representatives.

Study population

Patients eligible for inclusion in this study had to fulfil all of the following criteria:

- Outpatients aged ≥6 years, male or female,
- Suffering from cystic fibrosis,
- With a *P.aeruginosa* pulmonary infection documented with positive bacteriological culture of sputum or deep cough throat swab within the six weeks preceding inclusion,
- Previously treated with nebulized antipseudomonal antibiotic within the preceding six months,
- Treated with Tobi Podhaler®, initiated at Visit 1 at the latest or within the 2 months preceding Visit 1 (1 cycle of 28 days maximum preceding Visit 1), following recommended posology and method of administration (i.e. 4 capsules of 28 mg, taken twice a day, within alternate cycles of 28 days of treatment followed by 28 days without treatment). The treatment with another inhaled antibiotic was allowed during the 28 days period without treatment with Tobi Podhaler®,
- Follow-up consultation planned at least each six months.

Patients awaiting for pulmonary transplantation were excluded from the study.

Sample size

There was no existing data of compliance based on Morisky score determined by using the Morisky Medication Adherence Scale (MMAS) in CF patients' population. In a recent study, the rate of compliance to inhaled tobramycin at 12 months assessed with the medication possession ratios (MPR) was about 60% (Eakin MN et al. Journal of Cystic Fibrosis (2011)). Therefore the expected value of the primary endpoint was 60%.

The required absolute precision for the primary endpoint was ± 7.5%, corresponding to a length of the 95% confidence interval of 15%.

Based on these assumptions, 164 patients had to be assessed. It was assumed that about 20% of included patients did not respect inclusion criteria of the study or had no value for the primary endpoint. Therefore a total of 210 patients were to be included.

Each participating specialist was asked to include the first 3 consecutive patients corresponding to inclusion criteria of the study. Therefore 70 active specialists were needed.

Assessor's comment

The assumptions leading to the proposed sample size of 210 patients are considered reasonable.

Treatments

Patients received four TIP capsules (112 mg of tobramycin, 28 mg / capsule) twice a day, within alternate cycles of 28 days of treatment followed by 28 days without treatment.

Outcomes/endpoints

Primary criterion:

12-month compliance to inhaled anti-*P.aeruginosa* antibiotherapy assessed using the self-reported scale measuring medication-taking behaviour described by Morisky which includes 4 items. The Morisky score was calculated by adding 1 when "no" was answered to any item. The sum of the 4 items gave the Morisky score. A patient was considered compliant to the study treatment when his/her Morisky score was ≥3.

Assessor's comment

a Morisky score ≥3 to be considered compliant to the study treatment is acceptable.

Secondary criteria:

- Other compliance assessments: number of missing doses per week, number of inhaled capsules per dose, reasons of missing doses, timing of inhalations, relative compliance in comparison with the previous treatment at 6 and 12 months.
- Quality of life with Tobi Podhaler®: CFQ-R at 6 and 12 months.
- Characteristics of the CF patients, treated with Tobi Podhaler® for a pulmonary infection due to *P.aeruginosa* in a real-life setting: demographics, disease characteristics, previous antipseudomonal antibiotics.
- Conditions and method of use of Tobi Podhaler®:, treatment duration, number of cycles, search of critical errors of use, duration of the inhalation of the 4 capsules.
- Ease of use of Podhaler® inhaler, interest of the dose visual control, patients' preference in comparison with previous inhaled treatments.
- Course of CF: body weight, FEV1, microbiology (sputum/deep-throat cough swab).
- Safety and tolerability of Tobi Podhaler®: adverse events suspected to be drug-related, reasons for treatment discontinuations.

Statistical Methods

The reference population for the analysis consisted of all patients included, respecting major selection criteria of the study and still being treated at 12 months. Premature discontinuations of treatment before 12 months were described according to the reason for discontinuation.

Descriptive statistics were used to describe patient characteristics and study results (mean, standard-deviations (SD), median, and extreme values for quantitative parameters; absolute frequency and percentages of each modality for qualitative parameters, 95% confidence interval (CI) was calculated when relevant).

Multivariate analyses were also performed in order to determine factors that could influence the compliance at 12 months.

Results

Recruitment / Number analysed

A total of 126 patients entered the study (Included set, IS), among them 119 received at least one dose of Tobi Podhaler (Safety set, SS). The Analysis set (AS) consisted of 117 patients who did not present any major deviation in the inclusion criteria. For the primary criterion analysis only the patients having done at least 4 cycles of Tobi Podhaler treatment or, when the number of cycles was unknown, having done at least 7 months under Tobi Podhaler treatment were considered. A total of 28 patients discontinued mainly due to drug intolerance.

Table 10-1 Disposition of patients

	IS (N=126)
Entered the study **(IS)**	**126 (100%)**
Received at least one dose of study drug **(SS)**	**119 (94.4%)**
Analyzed **(mITT)**	**117 (98.3%)**
Analyzed for primary criterion **(mITT for primary criterion)**	**97 (82.9%)**
Discontinued	**28 (23.5%)**
Lack of efficacy	1 (3.6%)
Drug Intolerance	12 (42.9%)
Patient's decision	5 (17.9%)
Lung transplantation	1 (3.6%)
Other reason	9 (32.4%)

Source: post text Table 2.

Patients who did all the visits were 101 (80.2%) in IS, 101 (84.9%) in SS, 99 (84.6%) in mITT and 90 (92.8%) in mITT for the primary criterion. Among patients who did all visits, data were collected from both e-CRF and e-diary in 44 (43.6%) of the patients in IS, 44 (43.6%) of the patients in SS, 44 (44.4%) of the patients in mITT and 41 (45.6%) of the patients in mITT for the primary criterion.

Assessor's comment:

According to the sample size calculation, a total of 210 patients were to be included to be able to assess 164 patients (assuming that about 20% of included patients did not respect inclusion criteria of the study or had no value for the primary endpoint). **However, only 126 patients out of the planned 210 patients (60%) entered the study,** but no argumentation was provided in the submitted documentation. The MAH is requested to discuss this discrepancy.

Baseline data

Demographic characteristics in the mITT population are presented in Table 10-3.

At baseline, mean age was 22 ± 9 years, (77 patients (69%) ≥ 18 years, 19 patients (16%) ≥13 and <18 years, and 21 patients (18%) ≥ 6 and < 13 years. Patients were female in a slight majority (51.3%).

Table 10-3 Demographic characteristics – mITT population

	Total (N=117)	6 - 12 years (N=21)	13 - 17 years (N=19)	≥18 years (N=77)
Sex				
Male	57 (48.7%)	12 (57.1%)	8 (42.1%)	37 (48.1%)
Female	60 (51.3%)	9 (42.9%)	11 (57.9%)	40 (51.9%)
Age (years)				
Mean (SD)	22.2 (9.1)	-	-	-
Median	22.0	-	-	-
Min. ; Max.	6 ; 45	-	-	-
Height (cm)				
Mean (SD)	158.4 (14.7)	136.9 (11.7)	155.1 (9.7)	165.1 (9.7)
Weight (kg)				
Mean (SD)	49.7 (13.6)	31.1 (7.4)	44.4 (9.5)	56.1 (10.1)
Body Mass Index (kg/m²)				
Mean (SD)	19.4 (3.0)	16.4 (2.2)	18.3 (2.4)	20.5 (2.7)
Smoking status				
Never smoked	110 (94.0%)	21 (100%)	19 (100%)	70 (90.9%)
Former smoker	5 (4.3%)	-	-	5 (6.5%)
Current smoker	2 (1.7%)	-	-	2 (2.6%)

Source: post text Tables 9 and 10.

Characteristics of CF and *P.aeruginosa* infection at baseline in the mITT population are described in Table 10-4.

Patients were diagnosed with CF on average 18.5 years ago. The baseline mean FEV1% predicted was 67.2%, and mean weight was 49.7 kg. The mean sputum density of *P. aeruginosa* (sum of all biotypes) at baseline was 3.5 log10 CFU/mL, and mean tobramycin MIC was 4.5 µg/mL.

Table 10-4 Characteristics of cystic fibrosis and *P.aeruginosa* infection at baseline visit – mITT population

	Total (N=117)	6 - 12 years (N=21)	13 - 17 years (N=19)	≥18 years (N=77)
Time since cystic fibrosis diagnosis (years)				
Mean (SD)	18.5 (8.5)	9.2 (2.7)	12.9 (2.8)	22.5 (7.7)
FEV_1 (% predicted)				
Mean (SD)	67.2 (25.4)	87.3 (21.8)	77.2 (24.7)	59.3 (22.8)
Sputum density of *P.aeruginosa* (log10 CFU)				
Mean (SD)	3.5 (1.6)	2.2 (1.6)	2.7 (1.4)	4.0 (1.4)
***P.aeruginosa* Tobramycin MIC (µg/mL)**				
Mean (SD)	4.5 (4.0)	2.6 (1.6)	4.0 (0.0)	4.9 (4.5)

Source: post text Tables 11 and 12.

During the year preceding the initiation of Tobi Podhaler, 83 patients (71%) were treated with inhaled tobramycin solution (Tobi), 83 patients (71%) with colistin solution (Colimycine®) and 4 patients (3.4%) with aztreonam lysine solution (Cayston®). The co-treatment Tobi + Colimycin® was received by 42.6% patients; Colimycin® in monotherapy was received by 27.8% patients and Tobi in monotherapy by 26.1%.

At baseline, half of the patients (50.0%) were compliant (Morisky score ≥3) overall to their previous inhaled treatment. The mean ±SD Morisky score was 2.5 ±1.2. In the 6 - 12 years old age group, 56.3% of patients were compliant (mean Morisky score 3.0 ±1.0). In the 13-17 years old age group, 54.5% of patients were compliant (mean Morisky score 2.6 ±1.2). In the adult patients, 47.2% of patients were compliant (mean Morisky score 2.3 ±1.2).

Efficacy results

Primary Endpoint:

Overall at 12-month follow-up, 59.6% of patients (95% CI [45.3%; 72.4%]) were compliant with mean Morisky score of 2.7 ± 1.0.

Compliance seemed to be better in children and teenagers: the 12-month Morisky score was 3.1 ± 0.7 in 6-12 yrs., 3.0 ± 0.8 in 13-17 yrs. and 2.5 ± 1.1 in adults, with respectively 80.0%, 75.0% and 48.3% of compliant patients.

An analysis of factors which might be associated with non-compliance was performed according to logistic regression: no factors were statistically associated.

Table 10-9 Compliance with Tobi Podhaler® – mITT population for the primary criterion (N=97)

	Total (N=97)	6 - 12 years (N=18)	13 - 17 years (N=14)	≥18 years (N=65)
Morisky score at 12-month-follow-up				
n	47	10	8	29
0	1 (2.1%)	-	-	1 (3.4%)
1	3 (6.4%)	-	-	3 (10.3%)
2	15 (31.9%)	2 (20.0%)	2 (25.0%)	11 (37.9%)
3	17 (36.2%)	5 (50.0%)	4 (50.0%)	8 (27.6%)
4	11 (23.4%)	3 (30.0%)	2 (25.0%)	6 (20.7%)
Mean (SD)	2.7 (1.0)	3.1 (0.7)	3.0 (0.8)	2.5 (1.1)
Compliance with Tobi Podhaler® at 12-month-follow-up (Morisky score ≥3)				
Yes	28 (59.6%)	8 (80.0%)	6 (75.0%)	14 (48.3%)
No	19 (40.4%)	2 (20.0%)	2 (25.0%)	15 (51.7%)
95% CI (Yes)	[45.3%;72.4%]	[49.0%;94.3%]	[40.9%;92.9%]	[31.4%;65.6%]

n: number of collected Morisky scores. One Morisky score was calculated per patient.

Source: post text Tables 21 and 23.

Assessor's comment:

Data of 18 paediatric patients (N=10 and N=8 for 6-12 years and 13-17 years, respectively) was included in this analysis and showed relatively good compliance (75%-80% was compliant). Half of the adult patients were none compliant (Morisky score <3), which was comparable as reported at baseline for their previous therapy. Due to the small sample size however, especially in paediatric patients, no firm conclusions should be drawn.

The compliance in the patients ≥ 18 years of age is lower than the primary endpoint: 48.3% in stead of 60%. Although the numbers are small (n=29), the company should comment whether this compliance in this age group is in line with what can be expected in this age group or whether it is a coincidence; if this is in line what can be expected, the company is requested to comment whether this is considered acceptable.

Secondary Endpoints:

Description of compliance

At 6-month follow-up, 59.3% of patients were compliant with Tobi Podhaler (95% CI [46.0%; 71.3%]) and the mean (±SD) Morisky score was 2.7 ± 0.9. At 12-month follow-up on overall, more patients were compliant with Tobi Podhaler® than with their previous inhaled antipseudomonal treatments: 25 patients (59.5%) versus 22 (52.4%). At 6-month follow-up, more patients were compliant with Tobi Podhaler® than with their previous inhaled antipseudomonal treatments: 29 patients (56.9%) versus 26 (51.0%).

Change in compliance with inhaled antipseudomonal treatments from baseline (compliance with previous treatment) to 12-month (compliance with Tobi Podhaler®) was described in Table 10-12.

An analysis of factors which may be associated with non-compliance was performed according to an univariate logistic regression. No factors were statistically associated.

Table 10-12 Change from baseline to 12-month in compliance according to age groups – mITT population for the primary criterion (N=97)

	6 - 12 years (N=18)		13 - 17 years (N=14)		≥18 years (N=65)	
	12-month (Tobi Podhaler®)	Baseline (previous treatment)	12-month (Tobi Podhaler®)	Baseline (previous treatment)	12-month (Tobi Podhaler®)	Baseline (previous treatment)
Morisky scores						
n	8	8	7	7	27	27
0	-	-	-	-	1 (3.7%)	1 (3.7%)
1	-	-	-	-	2 (7.4%)	6 (22.2%)
2	2 (25.0%)	4 (50.0%)	1 (14.3%)	2 (28.6%)	11 (40.7%)	7 (25.9%)
3	3 (37.5%)	-	4 (57.1%)	2 (28.6%)	8 (29.6%)	8 (29.6%)
4	3 (37.5%)	4 (50.0%)	2 (28.6%)	3 (42.9%)	5 (18.5%)	5 (18.5%)
Mean (SD)	3.1 (0.8)	3.0 (1.1)	3.1 (0.7)	3.1 (0.9)	2.5 (1.0)	2.4 (1.1)
Median (Min. ; Max.)	3.0 (2 ; 4)	3.0 (2 ; 4)	3.0 (2 ; 4)	3.0 (2 ; 4)	2.0 (0 ; 4)	2.0 (0 ; 4)
Compliances						
Yes	6 (75.0%)	4 (50.0%)	6 (85.7%)	5 (71.4%)	13 (48.1%)	13 (48.1%)
No	2 (25.0%)	4 (50.0%)	1 (14.3%)	2 (28.6%)	14 (51.9%)	14 (51.9%)
95% CI (Yes)	[40.9%;92.9%]	[21.5%;78.5%]	[48.7%;97.4%]	[35.9%;91.8%]	[30.7%;66.0%]	[30.7%;66.0%]
Compliance with Tobi Podhaler® in comparison with previous treatments						
n	8		7		27	
Worsening	1 (12.5%)		1 (14.3%)		5 (18.5%)	
Same	4 (50.0%)		4 (57.1%)		17 (63.0%)	
Improvement	3 (37.5%)		2 (28.6%)		5 (18.5%)	

n: number of collected Morisky scores for patients who have fulfilled the Morisky score for both previous treatments and Tobi Podhaler® at 12-month follow-up. One Morisky score was calculated per patient.
Best previous inhaled antipseudomonal treatment was the treatment with the best compliance.

Source: post text Tables 24 and 26.

Assessor's comment

Again, less than half of the subjects contributed data for this analysis, for reasons not at all discussed by the MAH. Keeping the low subject numbers in mind though, it seems that compliance with Tobi Podhaler was equal to (or potentially slightly better than) compliance to previous therapy, especially in paediatric subjects.

Missing doses

Overall, 85 questionnaires (65.9%) reported forgotten previous treatment intakes at baseline, 49 questionnaires (59.0%) reported forgotten Tobi Podhaler® intakes at 6-month follow-up and 39 (60.0%) at 12-month follow-up (Table 10-13).

Patients who have ever forgotten their treatment missed mostly one day or less of treatment per week: 44 questionnaires (34.9%) reported one day or less of missing treatment per week for previous treatments, 34 (42.5%) for Tobi Podhaler® at 6-month follow-up or 31 (47.7%) at 12-month follow-up.

Table 10-13 Number of missing doses per week during the last cycles preceding the visits – mITT population for the primary criterion

	Previous treatments baseline visit	Tobi Podhaler® 6-month	Tobi Podhaler® 12-month
Have you ever forgotten to take your medication?			
n	129	83	65
Yes	85 (65.9%)	49 (59.0%)	39 (60.0%)
No	41 (31.8%)	31 (37.3%)	26 (40.0%)
Don't know	3 (2.3%)	3 (3.6%)	-
Number of missing doses per week during the last cycle			
n	126	80	65
0	41 (32.5%)	31 (38.8%)	26 (40.0%)
1 day or less per week	44 (34.9%)	34 (42.5%)	31 (47.7%)
More than 1 day per week	25 (19.8%)	10 (12.5%)	8 (12.3%)
Don't know	16 (12.7%)	5 (6.3%)	-

n: number of collected questionnaires. More than one questionnaire was collected per patient.
Source: post text Table 45.

Patients were questioned about their reasons of Tobi Podhaler® missing doses at 6 or 12-month follow-up. At 6-month follow-up on overall, 30 patients (55.6%) declared having ever forgotten to take Tobi Podhaler®. The principal reason was forgetfulness (10 patients, 33.3%). At 12-month follow-up on overall, 27 patients (57.4%) declared having ever forgotten to take Tobi Podhaler®. The principal reason was forgetfulness too (11 patients, 40.7%). Only one adult patient declared at 6 and 12-month follow-up that he/she did not take Tobi Podhaler® because the treatment was not suitable for him/her.

At 12-month follow-up on overall, patients were compliant in taking the 4 capsules at each dose. At the question “How many capsules have you taken on average for each treatment?”, all patients (46, 100%) answered “4”. At the question “Have you ever taken less than 4 inhaled capsules per dose”, they answered “No” at 95.7% (45 patients): all patients (10, 100%) aged between 6 and 12 years old, 7 patients (87.5%) aged between 13 and 17 years old and 28 adult patients (96.6%). Similar answers were reported at 6-month follow-up.

At 12-month follow-up on overall, a majority of patients (35, 74.5%) took Tobi Podhaler® between 7 a.m. and 9 a.m. on the morning. A majority of adult patients (18 , 62.1%) took the medication after 8 a.m. A majority of patients (26, 55.3%) took Tobi Podhaler® between 8 p.m. and 9 p.m. the evening. Comparable answers were reported at 6-month follow-up.

All patients considered that Tobi Podhaler was very easy to use or easy to use. They were a large majority (88.4%) who preferred Tobi Podhaler to their previous treatments.

Quality of life of the patients during their treatment with Tobi Podhaler®

At the end of the study, in patients aged 14 and older, CFQ-R scores from all domains tended to increase except for the digestion score who tended to decrease; similar results were observed in younger patients (children aged 13 and less) where mean scores from most of CFQ-R domains tended to increase while scores from symptom domains (respiratory, digestion) tended to slightly decrease. No clinically meaningful changes were observed.

Course of cystic fibrosis in patients treated with Tobi Podhaler®

Weight, FEV1 and tobramycin MIC were evaluated at 6 or 12-month follow-up to assess the evolution of CF during the study. Results are presented in Table 10-19.

At 12-month follow-up, the weight of children and teenagers tended to increase: mean change (±SD) in weight was 2.8 (1.8) kg in children or 4.2 (3.6) kg in teenagers. Weight of adult patients was stable.

At 12-month follow-up on overall, FEV1 (% predicted) tended to improve: FEV1 was improved in 46 patients (47.4%), stabilized in 21 (21.6%), and worsened in 30 (30.9%). FEV1 improvement was substantial in patients aged between 6 and 12 years old in whom 15 patients (78.9%) improved it. The FEV1 was improved in the majority of patients aged between 13 and 17 years old (10 patients, 62.5%). In adult, it was worsened in 23 (37.1%), remained stable in 18 (29.0%) and improved in 21 (33.9%).

Too few results were collected with tobramycin MIC to conclude.

Table 10-19 Course of cystic fibrosis in patients on Tobi Podhaler® at 6 or 12-month follow-up - MITT population (N=117)

	Total (N=117)	6 - 12 years (N=21)	13 - 17 years (N=19)	≥18 years (N=77)
Weight at baseline (kg) n	117	21	19	77
Mean (SD)	49.7 (13.6)	31.1 (7.4)	44.4 (9.5)	56.1 (10.1)
Weight at 6-month (kg) n	114	21	18	75
Mean (SD)	50.3 (13.4)	32.6 (7.8)	47.0 (11.4)	56.1 (10.1)
Weight at 12-month (kg) n	97	19	16	62
Mean (SD)	50.9 (13.1)	34.5 (7.5)	48.0 (11.1)	56.7 (10.2)
Change in weight from baseline to 12-month (kg)				
Mean (SD)	1.2 (3.0)	2.8 (1.8)	4.2 (3.6)	-0.1 (2.3)
FEV_1 at baseline (% predicted) n	117	21	19	77
Mean (SD)	67.2 (25.4)	87.3 (21.8)	77.2 (24.7)	59.3 (22.8)
FEV_1 at 6-month (% predicted) n	107	18	18	71
Mean (SD)	69.8 (27.7)	99.1 (21.8)	80.0 (24.8)	59.8 (23.4)
FEV_1 at 12-month (%predicted) n	97	19	16	62
Mean (SD)	71.8 (31.4)	100.4 (33.1)	80.7 (20.6)	60.7 (26.9)
Change in FEV_1 from baseline to 12-month (% predicted)				
Mean (SD)	3.5 (17.2)	11.0 (28.5)	7.2 (12.0)	0.2 (12.5)
Change in FEV_1 in classes at 12-month (n [%])				
Worsening	30 (30.9%)	3 (15.8%)	4 (25.0%)	23 (37.1%)
Same	21 (21.6%)	1 (5.3%)	2 (12.5%)	18 (29.0%)
Improvement	46 (47.4%)	15 (78.9%)	10 (62.5%)	21 (33.9%)
Tobramycin MIC at baseline (µg/mL) n	29	4	3	22
Mean (SD)	4.5 (4.0)	2.6 (1.6)	4.0 (0.0)	4.9 (4.5)
Tobramycin MIC at 6-month follow-up (µg/mL) n	18	5	1	12
Mean (SD)	3.9 (5.3)	2.6 (1.6)	4.0	4.5 (6.4)
Tobramycin MIC at 12-month follow-up (µg/mL)n	11	2	-	9
Mean (SD)	1.3 (2.5)	4.2 (5.4)	-	0.6 (1.3)

Source: post text Tables 79 and 80.

Assessor's comment

Especially in paediatric patients, FEV1 tended to increase from baseline to the 12-month analysis timepoint (change of 11% and 7.2% in 6-12 years and 13-17 years, respectively). In adults, FEV1 was worsened, stable, and improved in approximately 1/3rd of subjects each. No conclusions regarding tobramycin MIC can be drawn.

Treatment duration

The mean number of cycles of treatment with Tobi Podhaler® was 5.2 (±1.1) at 12-month follow-up.

Assessment of Tobi Podhaler® way of use by the investigators

Investigators evaluated the way their patients used Tobi Podhaler® during the study. Results are presented in Table 10-22 at 12-month follow-up.

On overall, at 12-month follow-up, investigators evaluated that their patients used correctly Tobi Podhaler®: 84 patients (89.4%) did not blow into the device before inhaling, 85 (90.4%) breathed correctly or put correctly the capsules, 83 patients (88.3%) used correctly the pushbutton and 84 (89.4%) emptied completely the capsules. There was no difference between age groups

The mean duration of inhalation was 3.8 ± (2.1) minutes at 6-month follow-up and 3.8 ± (2.1) minutes at 12-month follow-up increasing with age.

Table 10-22 Assessment of Tobi Podhaler® way of use by the investigators at 12-month follow-up - MITT population (N=117)

	Total (N=94)	6 - 12 years (N=18)	13 - 17 years (N=15)	≥18 years (N=61)
Did your patient blow into the device before inhaling?				
Yes	-	-	-	-
No	84 (89.4%)	15 (83.3%)	12 (80.0%)	57 (93.4%)
Don't know	10 (10.6%)	3 (16.7%)	3 (20.0%)	4 (6.6%)
Did your patient correctly breathe through the mouthpiece?				
Yes	85 (90.4%)	16 (88.9%)	12 (80.0%)	57 (93.4%)
No	-	-	-	-
Don't know	9 (9.6%)	2 (11.1%)	3 (20.0%)	4 (6.6%)
Did your patient put the capsule correctly in the space provided?				
Yes	85 (90.4%)	16 (88.9%)	12 (80.0%)	57 (93.4%)
No	-	-	-	-
Don't know	9 (9.6%)	2 (11.1%)	3 (20.0%)	4 (6.6%)
Did your patient use the push-button correctly?				
Yes	83 (88.3%)	15 (83.3%)	12 (80.0%)	56 (91.8%)
No	2 (2.1%)	1 (5.6%)	0	1 (1.6%)
Don't know	9 (9.6%)	2 (11.1%)	3 (20.0%)	4 (6.6%)
If no, how many times did this mistake occur during the 4-capsules intake?				
n	2	1	-	1
Once	1 (50.0%)	-	-	1 (100%)
Four times	1 (50.0%)	1 (100%)	-	-
Were the capsules completely emptied?				
Yes	84 (89.4%)	15 (83.3%)	12 (80.0%)	57 (93.4%)
No	1 (1.1%)	1 (5.6%)	-	-
Don't know	9 (9.6%)	2 (11.1%)	3 (20.0%)	4 (6.6%)
If no, in how many capsules was some powder remaining?				
n	1	1	-	-
1	1 (100%)	1 (100%)	-	-
Duration of 4 capsules inhalation (minutes)				
n	79	15	11	53
Mean (SD)	3.8 (1.9)	2.6 (1.1)	3.8 (1.9)	4.1 (1.9)
Median	3.2	2.2	3.0	4.0
Min. ; Max.	1 ; 10	1 ; 5	2 ; 6	2 ; 10

N: number of collected questionnaires. One questionnaire was collected per patient.
Source: post text Tables 67 and 68.

Safety results

Adverse Events

Overall 70 AEs were reported in 42 patients (35.3%) and 42 AEs were possibly related to Tobi Podhaler® according to the investigators' opinion in 33 patients (27.7%). Adult patients and patients between 13 and 17 years old reported more AEs or related AEs than patients between 6 and 12 years old.

All AEs reported by SOCs and PTs were described in Table 10-26. Adverse events were mainly classified in the SOC "Respiratory, thoracic and mediastinal disorders": 39 events in 30 patients

(25.2%) including the frequent AEs (≥1.0% of patients) cough (19 events in 18 patients, 15.1%), haemoptysis (6 events in 4 patients, 3.4%), dysphonia (3 events in 3 patients, 2.5%), dyspnea (3 events in 3 patients, 2.5%), bronchospasm (2 events in 2 patients, 1.7%), increased bronchial secretion (2 events in 2 patients, 1.7%) or throat irritation (2 events in 2 patients, 1.7%).

Other frequent AEs (≥1.0% of patients) were infective pulmonary exacerbation of cystic fibrosis (4 events in 3 patients, 2.5%), Pseudomonas infection (2 events in 2 patients, 1.7%), or tinnitus (2 events in 2 patients, 1.7%).

Table 10-26 Adverse events reported by SOCs and PTs - SS (N=119)

	Total (N=119)		6 - 12 years (N=21)		13 - 17 years (N=19)		≥18 years (N=79)	
	AEs	Patients (%)	AEs	Patients (%)	AEs	Patients (%)	AEs	Patients (%)
Patients with at least one AE	**70**	**42 (35.3%)**	**5**	**5 (23.8%)**	**12**	**7 (36.8%)**	**53**	**30 (38.0%)**
Respiratory, thoracic and mediastinal disorders	**39**	**30 (25.2%)**	**3**	**3 (14.3%)**	**5**	**5 (26.3%)**	**31**	**22 (27.8%)**
Cough	19	18 (15.1%)	2	2 (9.5%)	4	4 (21.1%)	13	12 (15.2%)
Haemoptysis	6	4 (3.4%)	-	-	-	-	6	4 (5.1%)
Dysphonia	3	3 (2.5%)	-	-	-	-	3	3 (3.8%)
Dyspnoea	3	3 (2.5%)	-	-	-	-	3	3 (3.8%)
Bronchospasm	2	2 (1.7%)	-	-	-	-	2	2 (2.5%)
Increased bronchial secretion	2	2 (1.7%)	-	-	-	-	2	2 (2.5%)
Throat irritation	2	2 (1.7%)	1	1 (4.8%)	-	-	1	1 (1.3%)
Asthmatic crisis	1	1 (0.8%)	-	-	1	1 (5.3%)	-	-
Pneumothorax	1	1 (0.8%)	-	-	-	-	1	1 (1.3%)
Infections and infestations	**11**	**10 (8.4%)**	**2**	**2 (9.5%)**	**1**	**1 (5.3%)**	**8**	**7 (8.9%)**
Infective pulmonary exacerbation of cystic fibrosis	4	3 (2.5%)	-	-	-	-	4	3 (3.8%)
Pseudomonas infection	2	2 (1.7%)	1	1 (4.8%)	1	1 (5.3%)	-	-
Bronchitis	1	1 (0.8%)	1	1 (4.8%)	-	-	-	-
Bronchopulmonary aspergillosis	1	1 (0.8%)	-	-	-	-	1	1 (1.3%)
Influenza	1	1 (0.8%)	-	-	-	-	1	1 (1.3%)
Oral fungal infection	1	1 (0.8%)	-	-	-	-	1	1 (1.3%)
Viral upper respiratory tract infection	1	1 (0.8%)	-	-	-	-	1	1 (1.3%)
Surgical and medical procedures	**7**	**4 (3.4%)**	**-**	**-**	**5**	**2 (10.5%)**	**2**	**2 (2.5%)**
Therapeutic procedure	5	2 (1.7%)	-	-	5	2 (10.5%)	-	-
Lung transplant	1	1 (0.8%)	-	-	-	-	1	1 (1.3%)
Therapeutic embolization	1	1 (0.8%)	-	-	-	-	1	1 (1.3%)
Gastrointestinal disorders	**3**	**3 (2.5%)**	**-**	**-**	**1**	**1 (5.3%)**	**2**	**2 (2.5%)**
Distal intestinal obstruction syndrome	1	1 (0.8%)	-	-	1	1 (5.3%)	-	-
Odynophagia	1	1 (0.8%)	-	-	-	-	1	1 (1.3%)
Subileus	1	1 (0.8%)	-	-	-	-	1	1 (1.3%)
Ear and labyrinth disorders	**3**	**2 (1.7%)**	**-**	**-**	**-**	**-**	**3**	**2 (2.5%)**
Tinnitus	2	2 (1.7%)	-	-	-	-	2	2 (2.5%)
Vertigo	1	1 (0.8%)	-	-	-	-	1	1 (1.3%)
General disorders and administration site conditions	**2**	**2 (1.7%)**	**-**	**-**	**-**	**-**	**2**	**2 (2.5%)**
Chest discomfort	1	1 (0.8%)	-	-	-	-	1	1 (1.3%)
Drug intolerance	1	1 (0.8%)	-	-	-	-	1	1 (1.3%)
Injury, poisoning and procedural complications	**1**	**1 (0.8%)**	**-**	**-**	**-**	**-**	**1**	**1 (1.3%)**
Wrong technique in drug usage process	1	1 (0.8%)	-	-	-	-	1	1 (1.3%)

	Total (N=119)		6 - 12 years (N=21)		13 - 17 years (N=19)		≥18 years (N=79)	
	AEs	Patients (%)	AEs	Patients (%)	AEs	Patients (%)	AEs	Patients (%)
Investigations	**2**	**1 (0.8%)**	**-**	**-**	**-**	**-**	**2**	**1 (1.3%)**
Oxygen saturation decreased	2	1 (0.8%)	-	-	-	-	2	1 (1.3%)
Nervous system disorders	**1**	**1 (0.8%)**	**-**	**-**	**-**	**-**	**1**	**1 (1.3%)**
Dysgeusia	1	1 (0.8%)	-	-	-	-	1	1 (1.3%)
Skin and subcutaneous tissue disorders	**1**	**1 (0.8%)**	**-**	**-**	**-**	**-**	**1**	**1 (1.3%)**
Hyperhidrosis	1	1 (0.8%)	-	-	-	-	1	1 (1.3%)

Source: post text Tables 83 and 84.

Assessor's comment

The reported AEs are in line with the known safety profile of Tobi Podhaler and the patient population under study. No new safety signals are identified.

Serious Adverse Events

Seven SAEs were reported in 6 patients (5.0%). The most frequent SAEs were classified in the SOC "Respiratory, thoracic and mediastinal disorders": 4 events in 4 adult patients (5.1%) including 3 events of haemoptysis in 3 patients (3.8%) and 1 event of pneumothorax in 1 patient (1.3%). The other SAEs reported each in 1 adult patients (1.3%) were "infective pulmonary exacerbation of cystic fibrosis" and "lung transplant". One SAE (distal intestinal obstruction syndrome) was reported in 1 patient (5.3%) between 13 and 17 years old. No SAE was reported in patients between 6 and 12 years old.

Table 10-27 Serious adverse events reported by SOCs and PTs - SS (N=119)

	Total (N=119)		6 - 12 years (N=21)		13 - 17 years (N=19)		≥18 years (N=79)	
	AEs	Patients (%)	AEs	Patients (%)	AEs	Patients (%)	AEs	Patients (%)
Patients with at least one SAE	**7**	**6 (5.0%)**	**-**	**-**	**1**	**1 (5.3%)**	**6**	**5 (6.3%)**
Respiratory, thoracic and mediastinal disorders	**4**	**4 (3.4%)**	**-**	**-**	**-**	**-**	**4**	**4 (5.1%)**
Haemoptysis	3	3 (2.5%)	-	-	-	-	3	3 (3.8%)
Pneumothorax	1	1 (0.8%)	-	-	-	-	1	1 (1.3%)
Infections and infestations	**1**	**1 (0.8%)**	**-**	**-**	**-**	**-**	**1**	**1 (1.3%)**
Infective pulmonary exacerbation of cystic fibrosis	1	1 (0.8%)	-	-	-	-	1	1 (1.3%)
Surgical and medical procedures	**1**	**1 (0.8%)**	**-**	**-**	**-**	**-**	**1**	**1 (1.3%)**
Lung transplant	1	1 (0.8%)	-	-	-	-	1	1 (1.3%)
Gastrointestinal disorders	**1**	**1 (0.8%)**	**-**	**-**	**1**	**1 (5.3%)**	**-**	**-**
Distal intestinal obstruction syndrome	1	1 (0.8%)	-	-	1	1 (5.3%)	-	-

Source: post text Tables 83 and 85.

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

Overall, 42 AEs in 33 patients (27.7%) were assessed as possibly related by the investigators including 33 AEs from the SOC "Respiratory, thoracic and mediastinal disorders" in 28 patients (23.5%). The most frequent AE possibly related was cough (18 events in 17 patients, 14.3%).

One SAE possibly related to Tobi Podhaler® according to the investigators' opinion was described in 1 adult patient: haemoptysis of moderate severity which led to the temporarily discontinuation of Tobi Podhaler®.

Table 10-28 Adverse events possibly related to Tobi Podhaler® according to the investigators' opinion reported by SOCs and PTs - SS (N=119)

	Total (N=119)		6 - 12 years (N=21)		13 - 17 years (N=19)		≥18 years (N=79)	
	AEs	Patients (%)	AEs	Patients (%)	AEs	Patients (%)	AEs	Patients (%)
Patients with at least one possibly related AE according to the investigators' opinion	**42**	**33 (27.7%)**	**3**	**3 (14.3%)**	**5**	**5 (26.3%)**	**34**	**25 (31.6%)**
Respiratory, thoracic and mediastinal disorders	**33**	**28 (23.5%)**	**3**	**3 (14.3%)**	**5**	**5 (26.3%)**	**25**	**20 (25.3%)**
Cough	18	17 (14.3%)	2	2 (9.5%)	4	4 (21.1%)	12	11 (13.9%)
Dysphonia	3	3 (2.5%)	-	-	-	-	3	3 (3.8%)
Haemoptysis	3	3 (2.5%)	-	-	-	-	3	3 (3.8%)
Bronchospasm	2	2 (1.7%)	-	-	-	-	2	2 (2.5%)
Dyspnoea	2	2 (1.7%)	-	-	-	-	2	2 (2.5%)
Increased bronchial secretion	2	2 (1.7%)	-	-	-	-	2	2 (2.5%)
Throat irritation	2	2 (1.7%)	1	1 (4.8%)	-	-	1	1 (1.3%)
Asthmatic crisis	1	1 (0.8%)	-	-	1	1 (5.3%)	-	-
General disorders and administration site conditions	**2**	**2 (1.7%)**	**-**	**-**	**-**	**-**	**2**	**2 (2.5%)**
Chest discomfort	1	1 (0.8%)	-	-	-	-	1	1 (1.3%)
Drug intolerance	1	1 (0.8%)	-	-	-	-	1	1 (1.3%)
Ear and labyrinth disorders	**1**	**1 (0.8%)**	**-**	**-**	**-**	**-**	**1**	**1 (1.3%)**
Tinnitus	1	1 (0.8%)	-	-	-	-	1	1 (1.3%)
Gastrointestinal disorders	**1**	**1 (0.8%)**	**-**	**-**	**-**	**-**	**1**	**1 (1.3%)**
Odynophagia	1	1 (0.8%)	-	-	-	-	1	1 (1.3%)
Infections and infestations	**1**	**1 (0.8%)**	**-**	**-**	**-**	**-**	**1**	**1 (1.3%)**
Oral fungal infection	1	1 (0.8%)	-	-	-	-	1	1 (1.3%)
Injury, poisoning and procedural complications	**1**	**1 (0.8%)**	**-**	**-**	**-**	**-**	**1**	**1 (1.3%)**
Wrong technique in drug usage process	1	1 (0.8%)	-	-	-	-	1	1 (1.3%)
Investigations	**2**	**1 (0.8%)**	**-**	**-**	**-**	**-**	**2**	**1 (1.3%)**
Oxygen saturation decreased	2	1 (0.8%)	-	-	-	-	2	1 (1.3%)
Nervous system disorders	**1**	**1 (0.8%)**	**-**	**-**	**-**	**-**	**1**	**1 (1.3%)**
Dysgeusia	1	1 (0.8%)	-	-	-	-	1	1 (1.3%)

Source: post text Tables 86 and 87.

Reasons for treatment discontinuation

From the 28 patients (23.5%) who discontinued the treatment, 12 (10.1%) did it for drug intolerance and 5 (4.2%) according to patient's decision. Among the other reasons for discontinuation, undetected *P.aeruginosa* was reported in 4 patients (3.4%). One adult patient discontinued the treatment at 6 month follow-up for lack of efficacy.

Assessor's comment

The safety profile reported in the current study is in line with the known safety profile of Tobi Podhaler and the patient population under study. No new safety signals are identified.

2.3.3. Discussion on clinical aspects

The aim of this observational, prospective, post-marketing and multicenter study performed in France was to evaluate in a real-life setting the compliance with Tobi Podhaler® in cystic fibrosis patients after 12 month of treatment. Unfortunately, only 60% of the planned sample size was actually included in the study, no reason for the discrepancy between planned and actual enrolment was reported. Furthermore, only approximately half of the subjects included in the study actually contributed data for the main analyses. Due to the low subject numbers, especially in the 6-12 years (N=21) and 13-17 years (N=19) age group, no firm conclusions can be drawn.

The compliance in the patients ≥ 18 years of age is lower than the primary endpoint: 48.3% in stead of 60%.

The MAH showed that based upon the limited available data this is in line with what can be expected in the adult population.

Keeping the low enrolment in mind, the data as presented seem to indicate that compliance with Tobi Podhaler® in cystic fibrosis patients seems at least comparable to compliance to previous therapy, which is reassuring. No new safety signals were identified.

It is agreed with the MAH that the efficacy and safety data from study CTBM100CFR01 do not warrant an update of the product information of TOBI Podhaler.

3. CHMP overall conclusion and recommendation

☒ **Fulfilled:**

☐ **Not fulfilled:**

4. Additional clarification requested

The compliance in the patients ≥ 18 years of age is lower than the primary endpoint: 48.3% in stead of 60%. Although the numbers are small (n=29), the company should comment whether this compliance in this age group is in line with what can be expected or whether it is a coincidence; if this is in line what can be expected, the company is requested to comment whether this is considered acceptable.

The timetable is a a 30 day response timetable with clock stop.

MAH responses to Request for supplementary information

RSI

The compliance in the patients ≥18 years of age is lower than the primary endpoint: 48.3% instead of 60%. Although the numbers are small (n=29), the company should comment whether this compliance in this age group is in line with what can be expected or whether it is a coincidence; if this is in line what can be expected, the company is requested to comment whether this is considered acceptable.

Summary response of the MAH:

In study CTBM100CFR01 (hereafter referred to as FR01), baseline compliance with previous inhaled anti-pseudomonal treatments for TOBI®, Colimycin® or Cayston® was assessed. In adults ≥18 years, the compliance at baseline was lower than that in children and adolescents. Of 53 adult patients with compliance scores at baseline as assessed by the Morisky questionnaire, 25 (47.2%) were compliant. In children 6-12 years and adolescents 13-17 years, compliance with previous inhaled anti-pseudomonal treatments was recorded in 56.3% (9/16) and 54.5% (6/11), respectively. Compliance with TOBI® Podhaler™ at the 12-month follow up visit was as follows: 48.3% (14/29) in adults, 80.0% (8/10) in children 6-12 years, and 75.0% (6/8) in adolescents 13-17 years. Although the patient numbers were relatively smaller in all age groups at the 12 month follow-up, it appears that compliance increased in the children and adolescent age groups but remain unchanged in the adults.

A search for real-world evidence on compliance and adherence specifically with TOBI Podhaler revealed limited information.

Studies have demonstrated that balancing the demands of CF with those of work, family and other relationships becomes more difficult in adolescence and adult life, with compliance tending to decrease with increasing age (Gudas et al, 1991).

A study evaluated compliance to medications amongst CF patients as assessed by a selfadministered questionnaire. Patients were classified as compliant or non-compliant by medical staff involved in their care. A total of 34 CF patients were enrolled; 11 were between 10 and 20 years, and 9 were older than 20 years. The average time of the evolution of the disease was 12.2 years. Overall, the results of the questionnaire showed a global compliance of 59%. Non-compliant patients were significantly older, had longer time of evolution of their disease and more severe disease. Approximately 24% of patients < than 15 years were non-compliant and approximately 69.2% of adolescent (> 15 years) and adults were noncompliant. (Arias-Llorente et al, 2008).

Conclusions: The data on real-world adherence with TOBI Podhaler is limited. Based on studies evaluating compliance, it has been shown that compliance decreases in adolescence and this continues into adulthood. The results from study FR01 in the adult population seem to be consistent with this trend.

Assessor's comment: Based upon the limited available data it seems that a lower compliance in the adults age group can be expected. The MAH did not answer the question whether the lower compliance in adults is considered acceptable. This is endorsed because the available data are too limited to draw firm conclusions with regard to compliance.

Point resolved.

<Annex. Line listing of all the studies included in the development program>

The studies should be listed by chronological date of completion:

Non clinical studies

Product Name: Active substance:

Study title	Study number	Date of completion	Date of submission of final study report

Clinical studies

Product Name: Active substance:

Study title	Study number	Date of completion	Date of submission of final study report