18 August 2016
EMA/220887/2023
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/P46/030

Note

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

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1. Introduction

On 17 May 2016, the MAH submitted a completed paediatric study for tobramycin inhalation powder, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

The MAH states that the efficacy and safety data from study CTBM100C2409 do not warrant an update of the product information of TOBI Podhaler.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study CTBM100C2409, *a 6 month observational cohort study to assess compliance in cystic fibrosis patients chronically infected with P. aeruginosa and treated with TOBI Podhaler*, 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 CTBM100C2409 A 6 months observational cohort study to assess the compliance in cystic FibRosis patients chronically infected with psEudomonas aEruginosa and treated with Tobi Podhaler® (FREE study).

A total of 82 patients were enrolled of which there were 22 paediatric patients.

2.3.2. Clinical study

Study CTBM100C2409 A 6 months observational cohort study to assess the compliance in cystic FibRosis patients chronically infected with psEudomonas aEruginosa and treated with Tobi Podhaler® (FREE study).

Description

This non-interventional phase IV study was a 6 month observational cohort study to assess compliance in cystic fibrosis patients chronically infected with P. aeruginosa and treated with TOBI Podhaler. The study was conducted in 17 Italian centers and enrolled 82 patients, including 22 paediatric patients.

Methods

Objective(s)

Primary objective

To evaluate in real-life setting the compliance to Tobi Podhaler at the end of the third cycle of therapy or after 6 months from enrollment (whichever comes first) as measured by item 8 of the Italian Treatment Adherence Cystic Fibrosis Questionnaire (ITA-CFq).

Other objectives

1. To describe the compliance to overall therapies (i.e. physiotherapy, exercise, enzymes, vitamins and antibiotics), and the compliance to each single component of the therapeutic scheme, by means of ITA-CFq, at the end of the third cycle of Tobi Podhaler treatment or after 6 months of observation, whichever comes first.
2. To describe the factors implied in poor or non-compliance to each treatment of the therapeutic scheme (i.e. physiotherapy, exercise, enzymes, vitamins and antibiotics) during Tobi Podhaler® treatment as reported in ITA-CFq.
3. To describe the changes in the compliance to overall therapies (as measured by ITA-CFq) as well as to each component of the therapeutic scheme (i.e. physiotherapy, exercise, enzymes, vitamins and antibiotics) at the end of the third cycle of Tobi Podhaler treatment or after 6 months (whichever comes first) compared to previous antibiotic treatment.
4. To describe the following clinical outcomes during Tobi Podhaler treatment:

   a. body weight

   b. FEV1% predicted

   c. microbiology (sputum/deep-throat cough swab).
5. To describe the compliance during Tobi Podhaler treatment in terms of the following factors assessed by a patient diary:

   a. number of missing doses per week

   b. number of inhaled capsules per dose

   c. reasons of missing doses

   d. timing of inhalations

   e. method of use (i.e. critical errors of use, duration of the inhalation) of Podhaler® inhaler, including the interest of the dose visual control.
6. To evaluate the treatment patients satisfaction at the end of the third cycle of Tobi Podhaler® treatment or after 6 months (whichever occurred first) in comparison with the previous inhaled antibiotic treatment assessed by the TSQM questionnaire.
7. To describe changes in quality of life assessed by the CFQ-R questionnaire at the end of the third cycle of Tobi Podhaler treatment or after 6 months (whichever occurred first) compared to the start of treatment.
8. To describe the safety and tolerability of Tobi Podhaler in terms of:

   a. frequency of AEs and SAE during the period of treatment;

   b. reasons for treatment discontinuation.

FREE - ITA-CFq validation study

Main objectives

To conduct the psychometric validation of the Italian Treatment Adherence Cystic Fibrosis Questionnaire (ITA-CFq) by testing convergent validity, internal consistency and test-retest reliability.

Other objectives:

- To evaluate ITA-CFq comprehensibility.
- To estimate the weights of score compliance to each therapy used in the overall score.

CHMP comment

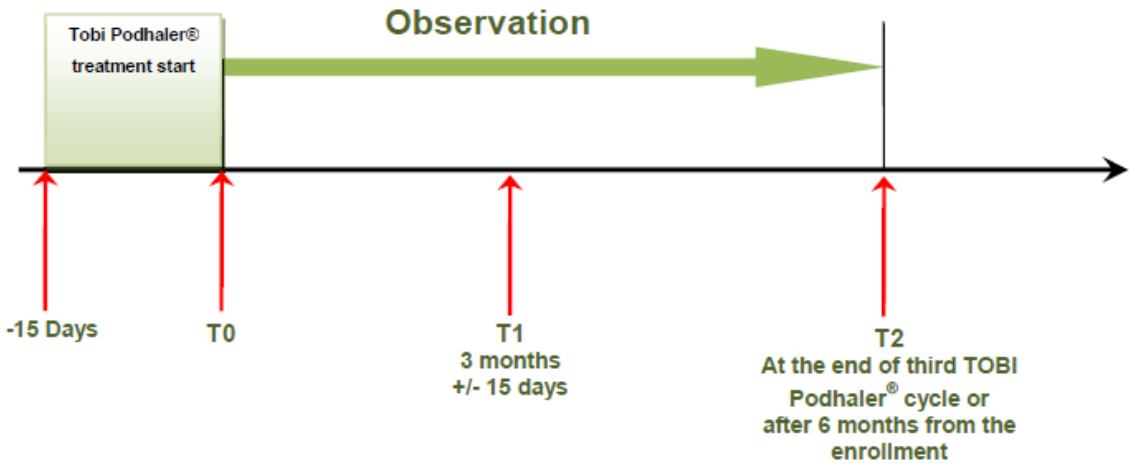
As the objectives are based on a self-administered questionnaire, developed in Italian language by the sponsor (in collaboration with a multidisciplinary advisory board), the relevance of the outcome of this small study for the overall CF population worldwide is questionable.

Study design

FREE was an observational longitudinal multicenter cohort study involving 17 Italian centers.

According to routine medical practice, the observational period consisted of 2 follow-up visits. The first follow-up was performed at 3 months (+/- 15) days from baseline, and the second at the end of third Tobi Podhaler cycle or after 6 months from the enrollment, whichever occurred first.

Figure 4-1 Study design



The FREE – ITA-CFq psychometric validation, a substudy of the main FREE study, was an observational, longitudinal, multicenter study aimed to assess comprehensibility and psychometric properties of ITA-CFq (internal consistency, test-retest reliability, and convergent validity). The entire psychometric validation process lasted 15 months (12 months for enrollment + 3 months follow-up + 2-7 days for retest).

A qualitative comprehensibility test had been conducted before starting the core FREE study, and the psychometric validation substudy and had been performed on a group of patients different from the one involved in the main study.

Study population

The FREE core study and the substudy population consisted of patients diagnosed with cystic fibrosis chronically infected with *Pseudomonas Aeruginosa* who started Tobi Podhaler treatment as per clinical practice within 15 days before the enrollment visit.

All patients referred to the participating sites that met eligibility criteria were consecutively enrolled.

Patients who met the following criteria were considered eligible for the study:

1. Male and female patients ≥12 and ≤35 years of age at enrollment.
2. Written informed consent and privacy disclosure given by patients or by the parent/legal guardian on behalf of the subject if <18 years old.
3. Patients with a proven cystic fibrosis diagnosis.
4. Patients chronically infected with P. aeruginosa confirmed by microbiological/ molecular test within 6 months prior to enrollment.
5. Patients who started TOBI Podhaler treatment as per clinical practice within 15 days before the enrollment visit.
6. Patients receiving at least one cycle of inhaled antibiotic treatment 2 months before starting TOBI Podhaler treatment.

Patients who meet the following criteria were not considered eligible for the study:

1. Patients unable to complete the patient questionnaires.
2. Patients participating to any clinical trial.
3. Patients with any contraindications to aminoglycosides

Sample size

The primary objective of the core study was to evaluate the compliance to treatment with Tobi Podhaler at the end of the third cycle of therapy or after 6 months from enrollment in reallife setting, by means of a newly developed questionnaire. Given no literature data were available to this regard at the time of the sample size evaluation, a sample size of 120 evaluable subjects was deemed as appropriate, on the basis of simulations aimed at determining precision of the estimate and feasibility. Hypothesizing a maximum of 10% of drop-out rate, including not-evaluable patients, 108 evaluable patients were foreseen for the primary end-point.

During the study, mainly for feasibility reasons as the unexpectedly slow recruitment rate made study timelines unrealistic, and in alignment with the descriptive intent of the study, the final sample size was reduced to 82 patients, provided adequate communication to each participating site. The final sample size was considered to be acceptable for statistical analysis since CF is a rare disease and no a priori statistical hypothesis was drawn.

For the primary objective of the substudy, i.e. the evaluation of the psychometric properties of ITA-CFq, a sample size of 40 patients was calculated on the basis of simulations of achievable precision of the estimates.

CHMP comment

The planned sample size was reduced from 120 to 82 patients during the study for feasibility reasons, further limiting the value of the results.

Treatments

This was a non-interventional study and did not impose a therapy protocol, diagnostic/therapeutic procedure, or a visit schedule. Patients were treated according to the local prescribing information, and routine medical practice in terms of visit frequency and types of assessments performed and only these data were collected as part of the study.

Outcomes/endpoints

Compliance to treatment were recorded at each time point by means of the Italian Treatment Adherence Cystic Fibrosis Questionnaire (ITA-CFq).

This questionnaire, developed in Italian language by Novartis in collaboration with a multidisciplinary Italian Advisory Board, was self-administered to the patient. It referred to the last 4 weeks of antibiotic treatment prescription period and its main aim was to measure an overall degree of compliance to the whole therapeutic scheme (i.e. physiotherapy, exercise, pancreatic enzymes, vitamins and antibiotics) as perceived by the patient.

ITA-CFq consists in 5 sections, one for each therapeutic scheme, to evaluate the following issue:

1. Compliance to treatment: evaluated by means of a numerical rating scale ranging from 0 to 10, where 0 is no compliance and 10 is fully compliance;
2. Reasons for non-compliance: evaluated by means of a multiple choice;
3. Patient's perception of prescribed therapy: measured as poor, adequate, excessive, unknown.

The patient answered the questionnaire in a quiet room and could ask parents/physician support in case of any doubts related to therapy under review.

Safety related measurements included physical examination, vital signs and lab evaluation, weight and FEV1% predicted, and other safety assessments (Pulmonary exacerbations. The Revised Cystic Fibrosis Quality of Life Questionnaire (CFQ-R) was used to assess the Quality of Life. Patient's self-reported satisfaction or dissatisfaction with study drug were measured using the validated Treatment Satisfaction Questionnaire for Medication (TSQM). A diary captured the following information: number of missing doses per week, number of inhaled capsules per dose, reasons of missing doses, timing of inhalations and method of use (i.e. critical errors of use, duration of the inhalation) of Tobi Podhaler® inhaler, including the interest of the dose visual control.

Statistical Methods

For the main objective, appropriate descriptive statistics and 95% CI of the mean value of the compliance to inhaled capsules at second follow-up visit were provided.

Quantitative variables were described by mean, standard deviation, median, first and third quartile, minimum and maximum, while qualitative variables by absolute and relative frequency. Bilateral 95% confidence intervals were given where relevant.

Results

Recruitment/ Number analysed

Eighty-two (82) patients were enrolled, 56 (68.3%) patients completed the study.

Table 10.1.1-1 Patient disposition (Enrolled patients)

Enrolled	82 (100.0%)
Completed patients	56 (68.3%)
Discontinued patients	26 (31.7%)
Reason for premature discontinuation	
Voluntary discontinuation (withdrawal of patients consent to collect or use their data)	4 (15.4%)
Lost to follow-up	5 (19.2%)
Tobi Podhaler® treatment discontinuation	15 (57.7%)
Not Recorded	2 (7.7%)

Note 1. For completed and discontinued patients, percentages are computed out of the total number of enrolled patients.

Note 2. For the reason for premature discontinuation, percentages are computed out of the total number of discontinued patients.

Note3. Discontinued patients and their respective reasons for premature discontinuation include also not evaluable patients. In particular those with reason for premature discontinuation not recorded were two not evaluable patients.

Source: Table 14.1.1.1.1 – FREE Observational Statistical Report v. 1.2 26/02/2016

Twenty-two (22) paediatric patients (i.e. <18 years old) were enrolled, of whom 17 completed the observation.

Table 10.1.1-2 Patient disposition – pediatric patients (Enrolled patients)

Enrolled	22 (100.0%)
Completed patients	17 (77.3%)
Discontinued patients	5 (22.7%)
Reason for premature discontinuation	
Lost to follow-up	2 (40.0%)
Tobi Podhaler® treatment discontinuation	2 (40.0%)
Not Recorded	1 (20.0%)

Note 1. For completed and discontinued patients, percentages are computed out of the total number of enrolled patients - pediatric patients.

Note 2. For the reason for premature discontinuation, percentages are computed out of the total number of discontinued patients - pediatric patients.

Note3. Discontinued patients and their respective reasons for premature discontinuation include also not evaluable patients. In particular that with reason for premature discontinuation not recorded was a not evaluable patient.

Source: Table 14.1.1.1.2 – FREE Observational Statistical Report v. 1.2 26/02/2016

At enrollment, 72 patients (87.8% of enrolled patients) were considered evaluable and therefore included in the Full Analysis Set (FAS) for the core study, and 28 patients were considerable evaluable for the validation substudy.

Baseline data

The overall evaluable patients were well balanced regarding the distribution by sex (little prevalence of female subjects, 51.4%), while the majority of them were Caucasian/white (98.6%), and mean age at enrollment was 24.8 ± 7.9 years. Cystic fibrosis duration was 21.7 ± 8.2 years on average, and patient's age at diagnosis was 3.3 ± 6.1 years on average.

Efficacy results

ITA-CFq was not fully answered in most of the cases (N=38, N=42 and N=41 patients included in the FAS provided compliance scores for all treatments at enrollment, first and second follow-up visit, respectively). In order to maximise available information, compliance at single timepoints has also been evaluated.

The primary objective, compliance to antibiotic treatment, is depicted below (Table 10.4.1-1), paediatric data is depicted in Table 4-6.

Table 10.4.1-1 Compliance to antibiotic – aerosol at enrollment and inhaled capsules at follow-up visits (ITA-CFq) and changes (FULL ANALYSIS SET)

	Enrollment	1st follow-up	2nd follow-up	Change from enrollment to 1st follow-up	Change from enrollment to 2nd follow-up
N	51	52	48	35	32
Mean	7.8	9.4	9.5	1.3	1.6
95% CI of the mean – lower limit	6.9	9.0	9.1	0.3	0.4
95% CI of the mean – upper limit	8.7	9.7	9.8	2.3	2.8
SD	3.2	1.2	1.2	2.9	3.3
25th percentile	7.0	9.0	9.0	0.0	0.0
Median	9.0	10.0	10.0	0.0	0.0
75th percentile	10.0	10.0	10.0	2.0	2.0
Min	0.0	4.0	3.0	-3.0	-2.0
Max	10.0	10.0	10.0	10.0	10.0

Source: Table 14.2.1.2.1 – FREE: Observational Statistical Report v. 1.2 26/02/2016

Table 4-6 **Compliance to antibiotics-aerosol at enrolment and inhaled capsules at follow-up visit- paediatric patients (FAS)**

	Enrolment	1st follow-up	2nd follow-up	Change from enrolment to 1st follow-up	Change from enrolment to 2nd follow-up
N	11	14	13	8	7
Mean	7.5	9.4	9.8	1.1	3.0
95% CI of the mean – lower limit	5.0	8.8	9.4	-2.0	-1.6
95% CI of the mean – upper limit	10.1	10.1	10.1	4.3	7.6

Source: Table 14.2.1.2.2 – FREE Observational Statistical Report v. 1.2

CHMP comment

The number of evaluable subjects to answer the study's main question(s), was limited. This, together with the nature of the questionnaire (sponsor developed, single country, non-validated) makes that the data can only be regarded descriptive. No conclusions should be drawn based on these results.

- Compliance to other treatments and overall compliance score (ITACFq) (secondary objectives #1 and #3)

Table 10.4.2.1-11 shows values of overall compliance score at each time point and relative changes for the overall population, Table 4-5 shows data for paediatric patients.

Table 10.4.2.1-11 Overall score of compliance to treatment (ITA-CFq) at each time point and changes (FULL ANALYSIS SET)

	ITA-CFq overall compliance score at enrollment	ITA-CFq overall compliance score at 1st follow-up	ITA-CFq overall compliance score at 2nd follow-up	Change from enrollment to 1st follow-up	Change from enrollment to 2nd follow-up
N	38	42	41	24	23
Mean	77.7	87.2	85.0	6.2	4.8
95% CI of the mean – lower limit	71.5	83.0	80.6	1.3	-2.5
95% CI of the mean – upper limit	84.0	91.4	89.4	11.0	12.1
SD	19.1	13.5	13.9	11.5	16.8
25th percentile	68.5	82.0	76.0	0.0	-3.0
Median	80.5	89.5	89.0	3.3	0.0
75th percentile	90.0	98.0	96.0	12.8	16.5
Min	20.0	42.0	43.5	-12.0	-27.0
Max	100.0	100.0	100.0	35.0	50.0

Note 1. See 'Computed Variables' for algorithms.

Source: Table 14.2.1.1.1 – FREE: Observational Statistical Report v. 1.2 26/02/2016

Table 4-5 Overall score of compliance to treatment (ITA-CFq) at each time point and changes for paediatric patients (FAS)

	ITA-CFq overall compliance score at enrolment	ITA-CFq overall compliance score at 1st follow-up	ITA-CFq overall compliance score at 2nd follow-up	Change from enrolment to 1st follow-up	Change from enrolment to 2nd follow-up
N	10	13	12	7	6
Mean	78.2	89.2	88.8	5.5	5.8
95% CI of the mean – lower limit	70.5	81.7	82.2	-9.8	-17.5
95% CI of the mean – upper limit	85.9	96.7	95.3	20.8	29.0

Source: Table 14.2.1.1.2 – FREE Observational Statistical Report v. 1.2

The most commonly reported factor of poor or non-compliance to treatment with aerosol antibiotic at enrollment was forgetfulness (15.7%), followed by lack of time (9.8%) and treatment assumption only when the patient does not feel good (7.8%). The most frequently reported factor of poor or non - compliance at first and second follow-up visits was forgetfulness (19.2% and 16.7%, respectively), while others were negligible.

- Description of body weight, FEV1% predicted, and microbiology (secondary objective #4)

Patient's average weight was 56.8 ± 10.5 kg at enrolment (n=69), 57.4 ± 9.9 kg at first follow-up visit (n=54), and 57.2 ± 10.1 kg at second follow-up visit (n=52).

Patient's average FEV1% predicted was 73.8 ± 23.9 % at enrolment (n=43), 78.1 ± 20.7 % at first follow-up visit (n=26), and 77.2 ± 17.9 % at second follow-up visit (n=24).

Patient's average Tobramycin MIC value was 2.8 ± 1.2 µg/ml at enrollment (n=18) and 6.3 ± 11.5 µg/ml at second follow-up visit (n=16).

- Compliance during Tobi Podhaler treatment (patient diary) (secondary objective #5)

According to patient diary, the average number of missed antibiotic dose per patient during the past week was 0.5 ± 0.7 at first cycle (n=46), 0.4 ± 0.5 at second cycle (n=36), and 0.4 ± 0.8 at third cycle (n=28).

- Patient's treatment satisfaction (TSQM) (secondary objective #6)

With respect to efficacy domain, a mean value of 63.6 ± 19.8 was observed at enrollment that increased to 67.5 ± 15.1 at second follow-up with a change of 1.8 ± 22.4 (with a 95% CI of [- 4.6 ; 8.2]).

Regarding the convenience domain, the mean score was74.2 ± 17.1 at enrollment and 77.8 ± 15.9 at second follow-up with a mean increase of 2.8 ± 17.9 (with a 95% CI of [-2.4 ; 8.0]).

Regarding the global satisfaction domain, the mean score was:62.4 ± 19.3 at enrollment and 63.9 ± 16.9 at second follow-up with a change of -0.2 ± 22.1 (with a 95% CI of [-6.6 ; 6.3]).

Regarding the adverse events domain, the mean score was:94.0 ± 12.1 at enrollment and 95.3 ± 12.4 at second follow-up with a negative change of -1.2 ± 14.6 (with a 95% CI of [-5.5 ; 3.1]).

- Changes in quality of life (CFQ-R) (secondary objective #7)

No substantial impact of Tobi Podhaler was observed in terms of QoL, as assessed by the CFQ-R. All domains remained roughly unchanged from baseline to study end.

Safety results

There were 12 patients (16.7%) that discontinued the treatment with Tobi Podhaler, one of which was a paediatric patient. Among those subjects, 3 patients (25.0%) discontinued the treatment due to lack of breath, and 2 (16.7%) because of bronchospasm and cough.

The safety profile is in line with previously reported findings. 26 patients (31.7%) experienced at least one AE, and at least one serious AE (SAE) was reported in 7 (8.5%).

Among AEs, the most represented clusters were N=9 infections, with main incidence of infective pulmonary exacerbations CF related (8.5%), and N=14 respiratory, thoracic and mediastinal disorders, with main incidence of cough (N=3), dyspnea (N=3) and respiratory failure (N=2). Tobi Podhaler®-related AEs occurred in 10 (12.2%) patients, and SAEs related to Tobi Podhaler® use occurred in 2 patients (2.4%). All safety findings described in the study are aligned with the known safety profile of the drug and in line with current SmPC reported findings, with the single exception of one lip oedema case described as not related to study medication and completely recovered.

Among paediatric patients, 4 (18.2%) had experienced at least one adverse event and 2 (9.1%) at least one serious adverse event. The SAEs experienced by paediatric patients were:

- a serious haemoptysis event of severe intensity in a female patient aged 15 years. It occurred 15 days after the first dose of TOBI Podhaler, the relationship was considered to be suspected and the study drug was permanently discontinued. The event was completely recovered. This

event was also the only suspected drug related adverse event occurring in the paediatric population.

- a serious moderate pulmonary exacerbation with upper respiratory tract infection as primary precipitating factor (reported in in a female patient aged 15 years). The event occurred 78 days after the start of treatment with TOBI Podhaler, and resulted in a prolonged hospitalization which resolved after 13 days. The relation with TOBI Podhaler was not suspected, but the dosage was adjusted/temporarily interrupted.

CHMP comment

Based upon the reported safety results, no new safety signals are identified.

2.3.3. Discussion on clinical aspects

The main objective of the FREE study was to evaluate the compliance to Tobi Podhaler treatment in the real-life setting at the end of the third cycle of therapy, or after 6 months from enrollment. Compliance was assessed by ITA-CFq, a specific questionnaire that was developed by the sponsor to evaluate patient's compliance to therapy.

The small sample size and patients' low responsiveness to the questionnaire, together with the nature of the questionnaire (sponsor developed, single country, non-validated) makes that the data can only be regarded descriptive. No conclusions should be drawn based on these results.

The reported safety findings did not give rise to new concerns.

3. Rapporteur's overall conclusion and recommendation

It is agreed with the MAH that the product information of TOBI Podhaler does not warrant an update based on the results from study CTBM100C2409.

Fulfilled:

No regulatory action required.

4. Additional clarification requested

N.A.

MAH responses to Request for supplementary information

N.A.