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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/P46/028

Note

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

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1. Introduction

On 10 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 CTBM100DDE03 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 CTBM100DDE03*, An observational study to assess Treatment Satisfaction of patients with Cystic Fibrosis applying TOBI Podhaler, with particular reference to Time saving, Improved Hygiene, and Portability (EASE)*, 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 CTBM100DDE03: An observational study to assess Treatment Satisfaction of patients with Cystic Fibrosis applying TOBI Podhaler, with particular reference to Time saving, Improved Hygiene, and Portability (EASE)

2.3.2. Clinical study

Study CTBM100DDE03: An observational study to assess Treatment Satisfaction of patients with Cystic Fibrosis applying TOBI Podhaler, with particular reference to Time saving, Improved Hygiene, and Portability (EASE)

Description

The EASE study is a prospective, non-interventional study – aimed to evaluate therapy satisfaction, changes in compliance, and efficacy of TOBI Podhaler® and to gather specific characteristics (anamnesis, antibiotic pretreatment, accompanying diseases, concomitant medication) of patients suffering from CF and was conducted in 30 specialized CF centers in Germany.

Out of the 16 patients that were enrolled in the study, 3 patients were paediatric patients.

Methods

Objective(s)

- Assessment of therapy satisfaction of patients treated with the new TOBI Podhaler®
- Evaluation of specific characteristics of patients suffering from CF combined with P. aeruginosa infection, their medical history, antibiotic pretreatments, accompanying

diseases, concomitant medication, as well as safety and tolerability of the therapy in daily life

- Assessment of the efficacy of the TOBI Podhaler® in daily life
- Evaluation of the compliance and its change during the use of the TOBI Podhaler® in comparison to the prior, traditionally used nebulizer

CHMP comment

The objectives seem appropriate to evaluate treatment satisfaction.

Study design

This was a non-interventional, multicenter, observational study according to the definition of non-interventional studies (under daily clinical routine care). The examination of the questions specified under "objectives" allowed an assessment with a relative high number of patients as close as possible to the daily medical treatment.

The purpose of this study was the assessment of the newly introduced TOBI Podhaler® in a broad patient collective in the everyday routine. At the beginning of the observational study, each participating physician received one physician questionnaire per patient. A special patient-related questionnaire was handed out to every partaking patient.

The analysis of therapy satisfaction and compliance was carried out by means of the special patient-related questionnaire and the analogous parts of the physician questionnaire after completion of the treatment. For the evaluation of effectiveness the value of the forced expiratory volume in one second (FEV1) were used.

Study population

Any patient with a diagnosis of CF and at a minimum age of 6 who was prescribed the TOBI Podhaler® for the first time was suitable for this study.

Aside from the signed consent form the exclusion criteria were limited to contraindications of TOBI Podhaler® described in the SmPC.

Sample size

It was intended to document prospectively the treatment course of at least 120 patients in total, all characterized by the minimum age of 6 and suffering from CF.

CHMP comment

No rationale for the planned sample size of 120 patients was provided.

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. The observation period was 12 months.

During the observation period of 12 months, visits should take place approximately every 3 months according to standard treatment routine. Time point of visits was not specified relating to on / off phase.

Table 2-2: Assessment schedule

	Visit				
Assessment	**1**	**2**	**3**	**4**	**5**
Obtain informed consent	x				
Demographic data	x	x	x	x	x
Height/weight	x	x	x	x	x
Lung function (spirometry)	x	x	x	x	x
Medical history	x				
Assessment of antibiotics therapy	x	x	x	x	x
Evaluation of compliance	x				x
Evaluation of quality of life	x				x
AEs/SAEs	x	x	x	x	x
Patients questionnaire	x	x			

Outcomes / endpoints

Parameters of special interest were:

- Therapy satisfaction and factors for therapy satisfaction
- Therapy compliance
- Effectiveness of therapy
- Evaluation of specific characteristics of patients suffering from CF
- Collection of adverse events (AEs) containing information on intensity, seriousness, outcome and causality.

Statistical Methods

This NIS was analyzed with epidemiological methods using descriptive, statistical procedures. Analyses were conducted using Microsoft Office Excel, 2013.

According to confidentiality guidelines, no data that could be directly assigned to patients were recorded.

Results

Recruitment / Number analysed

A total of 16 patients were enrolled from May 2012 to January 2013. As is obvious from Table 3-1 the obtained data was incomplete. Complete data sets were obtained for three patients, only. For two patients no physician data were available and for one patient the data from the patient questionnaire were lacking.

Table 3-1: Obtained data
This table gives an overview about obtained data (x) and missing data (-).

	Physician Questionnaire					Patient Questionnaire	
Patient	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 1	Visit 2
Code 9/1	x	x	x	-	-	x	x
Code 9/2	x	x	-	x	x	x	x
Code 9/3	x	x	x	x	x	x	x
Code 9/4	-	-	-	x	x	x	x
Code 9/5	x	x	x	x	-	x	x
Code 12/1	x	x	x	-	-	x	x
Code 12/2	x	x	x	x	x	x	x
Code 36/1	x	-	x	x	x	x	x
Code 36/2	x	x	-	-	-	-	-
Code 36/3	x	x	x	x	x	x	x
Code 48/1	-	-	-	-	-	x	-
Code 52/1	-	-	-	-	-	x	x
Code 61/1	x	x	-	x	x	x	x
Code 61/2	x	x	-	x	x	x	x
Code 64/1	x	x	-	x	x	x	x
Code 64/2	x	x	-	x	x	x	x

CHMP comment:

Patients were enrolled between April 2012 and January 2013, in August 2013, the study was cancelled due to low recruitment. As there were very little patients enrolled (N=16), and the collected data is incomplete for the far majority of these patients, the result can only be descriptive.

Baseline data

Demographic data of 14 patients collected at the first visit are shown in Table 3-2.

64% of patients were male (N=9/14) and 36% female (N=5/14). The mean age ± standard deviation (SDM) was 25.6 ± 8.6 years (median: 26.5 years). The youngest patient was 13 years old and the oldest patient 42 years of age. The average height of patients was 168.9 ± 7.8 cm (median: 168.5 cm). The average weight of patients was 58.0 ± 11.9 kg (median: 62.0 kg).

Table 3-2: Patients demographics at Visit 1, N=14

Patient	Sex	Age [years]	Height [cm]	Weight [kg]
Code 9/1	m	27	181	67
Code 9/2	f	31	168	46
Code 9/3	f	23	165	45
Code 9/4	m	19	169	59
Code 9/5	m	32	179	62
Code 12/1	f	27	173	63
Code 12/2	m	37	164	64
Code 36/1	f	13	162	54
Code 36/2	m	17	161	62
Code 36/3	m	13	154	28
Code 48/1	-	-	-	-
Code 52/1	-	-	-	-
Code 61/1	f	26	163	54
Code 61/2	m	42	176	72
Code 64/1	m	21	174	71
Code 64/2	m	31	175	65

Efficacy results

- Assessment of therapy satisfaction of patients treated with the new TOBI Podhaler®

At Visit 1 the patients (N=15) were asked to rate five distinct features of the TOBI Podhaler® that may contribute to therapy contentment (Table 3-8). Features valuated with scores of 2 or greater were considered to be important.

Table 3-8: Rating of desirable attributes of TOBI Podhaler® by users (Visit 1, N=15).
Evaluation of desirable attributes by using scores from not important (1) to very important (10).

Scale	Small / compact device	Shorter inhalation time	Simple in use	Simple cleaning	No refrigera-tion needed
1 (not important)	1 (7%)	1 (7%)	-	-	-
2	-	-	-	-	-
3	-	-	-	-	1 (7%)
4	1 (7%)	-	1 (7%)	-	-
5	-	-	-	-	-
6	-	-	-	-	3 (20%)
7	5 (33%)	-	3 (20%)	-	2 (13%)
8	4 (27%)	1 (7%)	3 (20%)	3 (20%)	1 (7%)
9	-	3 (20%)	4 (27%)	6 (40%)	2 (13%)
10 (very important)	4 (27%)	10 (67%)	4 (27%)	6 (40%)	6 (40%)
important (≥ 2)	14 (93%)	14 (93%)	15 (100%)	15 (100%)	15 (100%)

Patients evaluated nearly all suggested features of TOBI Podhaler® – 93% (N=14/15) the small size, 93% (N=14/15) the shorter inhalation time, 100% (N=15/15) the simple usage, 100% (N=15/15) the simple cleaning, and 100% (N=15/15) no requirement for cooling – as essential. The comparison of the mean scores of the distinct features points out, that a simple cleaning (9.2 ± 0.8) and a short inhalation time (9.1 ± 2.3) are most important for the asked patients. Also very important are the simple usage (8.3 ± 1.6) and no cooling needed (8.1 ± 2.2), followed by the small size of the device (7.5 ± 2.4).

The patients were asked to mark the advantages of the TOBI Podhaler® in respect to common nebulizers at Visit 1 (N=15) and Visit 2 (N=14). The results of this survey are summarized in Table 3-9.

Table 3-9: Overview of advantages at Visit 1 (N=15) and Visit 2 (N=14).

	Visit 1		Visit 2	
Advantages	Number of Patients/ total	Portion	Number of Patients/ total	Portion
On trips/away from home	13	87%	9	69%
Discretion	-	0%	1	8%
More flexible in everyday life	9	60%	NA	NA
Less time needed	13	87%	11	85%
Simple to use	9	60%	6	46%
Simple to clean	14	93%	12	92%
others	-	0%	1	8%

CHMP comment:

The main positive attributes of TOBI Podhaler® reported by the patients included in this study were shorter inhalation times compared with nebulizers, fast and easy cleaning of the device, and no refrigerator needed. No separate analysis was performed for paediatric vs adult patients.

- Evaluation of specific characteristics of patients suffering from CF combined with P. aeruginosa infection, their medical history, antibiotic pretreatments, accompanying diseases, concomitant medication, as well as safety and tolerability of the therapy in daily life

An overview of medical history and previous antibiotic treatment is shown in Table 3-3.

Table 3-3: Overview about medical history and previous antibiotic treatment, N=14

		Number of patients	Portion
Infection with *P. aeruginosa*	yes	13	93%
	no	1	7%
Type of infection	intermittent	2	14%
	chronic	9	64%
	not specified	3	22%
Previous treatment with inhaled antibiotics		14	100%
Which active compound?	Tobramycin	12	86%
	Colistin	5	36%
	Aztreonam	1	7%
Type of inhalation	continuous	3	21%
	in cycles	10	71%
	not specified	1	7%

For 93% of all patients (N=13/14) an infection with P. aeruginosa was recorded at Visit 1. An intermittent infection was present in 14% of patients (N=2/14), whereas 64% of patients (N=9/14) suffered from a chronic infection with P. aeruginosa. For 22% of patients (N=3/14) the type of infection could not be specified. All included patients (N=14/14) had been previously treated with inhaled antibiotics. In this respect, 86% of patients (N=12/14) had been treated with Tobramycin, 36% (N=5/14) with Colistin, and 7% (N=1/14) with Aztreonam. The different types of inhalation

were continuous treatment for 21% of patients (N=3/14), an application in cycles for 71% of patients (N=10/14), or not specified for 7% of patients (N=1/14), respectively.

CHMP comment:

As TOBI Podhaler is indicated for "the suppressive therapy of chronic pulmonary infection due to *Pseudomonas aeruginosa* in adults and children aged 6 years and older with cystic fibrosis", it is noted that 1 patient does not seem to have an infection with *P. aeruginosa*. The reason for TOBI Podhaler prescription in this patient is not reported in the clinical study report.

- Assessment of the efficacy of the TOBI Podhaler® in daily life

Therapy effectiveness in daily life of TOBI Podhaler® was assessed by determination of lung function (spirometry), e. g. forced expiratory volume in one second (FEV1), vital capacity (VC) and peak expiratory flow (PEF). The time point of spirometric assessments, regarding Tobramycin treatment cycle, was not specified. Thus, lung function data can derive from the 4 week treatment phase and the 4 week inhalation break, respectively.

Table 3-4 shows an overview of the development of mean FEV1, VC and PEF from Visit 1-5 as percentage of predicted and as percentage of Baseline. Values for predicted FEV1, VC and PEF were determined according to C.–P. Criée (Criée et al., 2006) for patients 18 years and older and according to Polgar (Polgar and Weng, 1979) for adolescents.

Lung function at Baseline varied heavily between single patients, e. g. ranging from 27% to 109% of predicted FEV1 at Visit 1. Within these broad interindividual differences, mean lung function of patients remained relatively constant throughout the study.

Table 3-4: Overview of lung function from Visit 1 - Visit 5.

Parameter		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
FEV1	[% of predicted]	63 ± 24	53 ± 20	61 ± 28	54 ± 20	54 ± 19
	[% of Baseline]	100 ± 0	92 ± 20	101 ± 29	95 ± 22	91 ± 23
VC	[% of predicted]	80 ± 21	72 ± 23	70 ± 15	71 ± 17	69 ± 12
	[% of Baseline]	100 ± 0	96 ± 22	93 ± 19	96 ± 17	91 ± 17
PEF	[% of predicted]	95 ± 47	73 ± 25	73 ± 18	79 ± 17	76 ± 21
	[% of Baseline]	100 ± 0	86 ± 27	90 ± 25	105 ± 16	94 ± 29

Mean FEV1 of predicted was 63 ± 24% at Visit 1 (N=14) and changed to 54 ± 19% at the end of the study (N=10), representing 91 ± 23% of Baseline FEV1. Mean VC was 80 ± 21% of predicted at study start (N=14) and changed to 69 ± 12% at Visit 5 (N=10), representing 91 ± 17% of Baseline VC. Mean PEF changed from 95 ± 47% of predicted at Visit 1 (N=12) to 76 ± 21% at Visit 5 (N=8).

CHMP comment:

No conclusions should be drawn based on the limited number of patients included, but overall lung function suggests to be relatively stable throughout the 12 months observation period.

- Evaluation of the compliance and its change during the use of the TOBI Podhaler® in comparison to the prior, traditionally used nebulizer

Current compliance vs. expected compliance with TOBI Podhaler®

The current inhalation and cleaning compliance with previous used devices as well as the expected inhalation compliance with the TOBI Podhaler® were assessed and rated by the physicians for each patient at Visit 1. Patients rated with a score of 6 or greater were considered to have a good compliance. The results of the assessments are summarized in Table 3-10.

Table 3-10: Current and expected inhalation compliance and cleaning compliance of patients at Visit 1 (N=12).

The current inhalation and cleaning compliance as well as the expected inhalation compliance were assessed by using scores from very poor (1) to very good (10).

	Current inhalation Compliance		Current Cleaning Compliance		Expected inhalation compliance with TOBI Podhaler®	
Scale	Number of Patients	Portion	Number of Patients	Portion	Number of Patients	Portion
1 (very poor)	-	-	-	-	-	-
2	-	-	1	8%	-	-
3	1	8%	-	-	-	-
4	1	8%	-	-	-	-
5	1	8%	1	8%	-	-
6	2	17%	-	-	-	-
7	2	17%	-	-	1	8%
8	4	33%	5	42%	2	17%
9	1	8%	1	8%	6	50%
10 (very good)	-	-	4	33%	3	25%
good (≥ 6)	9	75%	10	83%	12	100%

75% (N=9/12) of patients were considered to have a good current inhalation compliance. 83% (N=10/12) of patients were considered to have a good current cleaning compliance. The expected inhalation compliance with the TOBI Podhaler® was rated to be good for 100% (N=12/12) of patients.

Change in compliance with the TOBI Podhaler®

The inhalation compliance of the participating patients (N=10) was again evaluated by the physicians at the end of the study. At Visit 5 physicians were asked to rate the changes in inhalation compliance of their patients. These changes in compliance are depicted as bar chart in Figure 3-1.

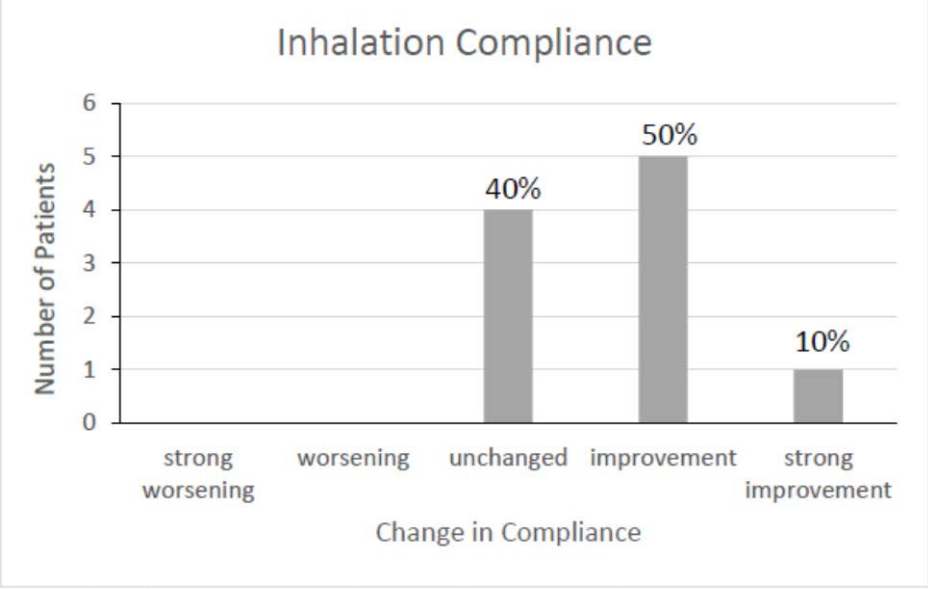

Figure 3-1: Change in compliance at Visit 5, N=10

The use of the TOBI Podhaler® has not caused a worsening in the inhalation compliance of any patient (N=0/10). In 40% (N=4/10) of patients the treatment with the TOBI Podhaler® had no effect on the inhalation compliance, whereas in 50% (N=5/10) of patients use of the new device

induced a significant improvement. A strong improvement was stated for 10% (N=1/10) of patients.

Self-assessment of compliance

At Visit 2 the patients (N=14) were requested to perform a self-assessment of compliance based on answering yes/no questions and on their inhalation data of 4 weeks. Positive answers were counted and are summarized in Table 3-11. Mean values of the inhalation data can be found in Table 3-12.

Table 3-11: Patients Compliance at Visit 2, N=14

	Number of Patients/ total	Portion
Has your doctor shown you how to correctly use your new inhalation device?	14/14	100%
Have you experienced any difficulties using your new inhalation device?	1/14	7%
Do you inhale more often according to your doctor´s recommendations using the TOBI Podhaler® than before?	14/14	100%

The correct usage of the TOBI Podhaler® was shown to all (N=14/14) patients. 7% (N=1/14) of patients had difficulties in using the new inhalation device. 100% of patients stated that they do inhale more often according to the doctor's recommendations using the TOBI Podhaler® than before.

Table 3-12: Inhalation data and inhalation compliance at Visit 2, N=12-14

During the last 4 weeks of your TOBI-Podhaler® Prescription, ...	Mean	SDM
on how many days have you Not inhaled [days]	0.8	1.5
on how many days have you inhaled a reduced dose [days]	0.8	1.7
How many breaths do you need per capsule?	1.8	0.9
How many time do you need between inhalation of two capsules [min]?	1.0	0.8

During the first 4 weeks of using the TOBI Podhaler® the patients (N=12-14) did not inhale on 0.8 ± 1.5 days and inhaled a reduced dose on 0.8 ± 1.7 days. In average, patients needed 1.8 ± 0.9 breaths per capsule and 1.0 ± 0.8 minutes between inhalation of two capsules.

CHMP comment:

Compliance suggested to remain stable or improved compared to the prior nebulizer.

Safety results

For the safety population, 16 patients were analysed. A total of 17 adverse events was reported in 7 patients (41.2%). The incidence of non serious not related AE's was 41.2%. Non serious ADRs occurred in 5.9% of patients. No SAEs or SADR were reported.

Table 3-13: Adverse events (patient based)

	N	(%)
Total AEs	17	100
Patients with adverse events	7	44
Patients with non serious adverse events not related (nsAEnr)	7	44
Patients with non serious adverse drug reactions (nsADR)	1	6
Patients with serious adverse events not related (SAEnr)	0	-
Patients with serious adverse drug reactions (SADR)	0	-

A listing of all occurred AEs is shown in Table 4-14. Of 17 AEs, 16 were considered not drug related. In one patient, occurring nausea with moderate intensity was classified as possibly drug related (nsADR).

Table 3-14: Listing of AEs

Patient/ Code	Kind of AE	Intensity	Causality	Outcome	Serious	Duration [d]
Code 12/2	Exacerbation of Aspergillosis	2	5	1	0	21
Code 36/1	Acute Gastroenterits	2	4	2	0	18
	Infection	2	4	2	0	28
	Pulmonary infection	2	4	1	0	15
	Allergic cough	3	4	2	0	-
Code 36/3	Nausea	2	3	1	0	30
	Nausea/Vomiting	3	4	1	0	11
Code 61/1	Bronchopulmonary infection	1	4	1	0	21
Code 61/2	Chronic P(S)A infection	1	5	1	0	14
Code 64/1	Chronic infection with *S. aureus* and *Burkholderia*	1	5	1	0	14
	Bronchopulmonary infection	1	5	1	0	20
	Bronchopulmonary infection	2	5	1	0	20
Code 64/2	Chronic infection with *P. aeroginosa*	1	5	1	0	14
	Depression	2	5	2	0	-
	PEF decreased	3	5	1	0	37
	Chronic infection with *P. aeroginosa*	1	5	1	0	14
	Chronic infection with *P. aeroginosa*	1	5	1	0	14

Intensity: 1=mild, 2=moderate, 3=severe. Causality: 1=assured, 2=probable, 3=possible, 4=no causality, 5=not assessable. Outcome: 1=recovered, 2=recovering, 3=fatal, 4=life-threatening, 5=requiring an unplanned and unforeseen hospitalization or prolonged hospitalization, 6=resulting in persistent or significant disability/incapacity or impairment, 7=resulting in congenital anomalies or birth defects, 8=unknown. Serious: 1=yes, 0=no.

CHMP comment

Based upon the safety results of the 16 patients enrolled, no new safety signals are identified. The reported AEs were most often of moderate severity and considered either not related or causality could not be assessed.

2.3.3. Discussion on clinical aspects

The aim of this observational study was the assessment of TOBI Podhaler® in a broad patient collective in the everyday routine. This aim could however not be realized as only 16 out of the planned 120 patients were enrolled. As no conclusions can be drawn based on such low enrolment, it is agreed with the MAH that the product information of TOBI Podhaler does not warrant an update based on the results from study CTBM100DDE03.

3. CHMP overall conclusion and recommendation

☒ **Fulfilled:**

☐ **Not fulfilled:**

4. Additional clarification requested

Not applicable