EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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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/P46/026

Note

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

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1. Introduction

On 7 September, the MAH submitted a completed paediatric study for tobramycin inhalation powder, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that CTBM100CGB01 is a stand alone study.

The MAH stated that this study was not conducted in compliance with an agreed paediatric investigation plan.

2.2. Information on the pharmaceutical formulation used in the study

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. The dose of TOBI Podhaler is the same for all patients within the approved age range, regardless of age or weight. The recommended dose is 112 mg tobramycin (4 x 28 mg capsules), administered twice daily for 28 days. TOBI Podhaler is taken in alternating cycles of 28 days on treatment followed by 28 days off treatment.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study CTBM100CGB01: a combined prospective and retrospective multicentre observational research study to evaluate patient reported and clinical outcomes following initiation of TOBI Podhaler in patients with cystic fibrosis and chronic Pseudomonas infection in UK clinical practice.

2.3.2. Clinical study

- Study CTBM100CGB01: a combined prospective and retrospective multicentre observational research study to evaluate patient reported and clinical outcomes following initiation of TOBI Podhaler in patients with cystic fibrosis and chronic Pseudomonas infection in UK clinical practice.

Description

A combined prospective and retrospective multicentre observational study to evaluate patient reported outcomes and clinical outcomes following initiation of TOBI® Podhaler® in patients with cystic fibrosis and chronic Pseudomonas infection in UK clinical practice. The study was conducted in 5 NHS Trust hospitals known to be using tobramycin inhaled solution (TIS) in the management of patients with CF and with local approval to use the TOBI® Podhaler®.

Methods

Objective(s)

Primary objective

To describe the change in Treatment Burden domain scores of the CF Questionnaire-Revised (CFQ-R) at 1 month and 5 months after initiation of the TOBI® Podhaler®.

Secondary objectives

- To describe the change in the remaining domain scores of the CF Questionnaire-Revised (CFQ-R) at 1 month and 5 months after initiation of the TOBI® Podhaler®. *The domain scores include: physical functioning, role, vitality, emotional functioning, social functioning, body image, eating disturbances, health perceptions, weight, respiratory symptoms and digestive symptoms.*
- To describe the change in treatment satisfaction (Treatment Satisfaction Questionnaire for Medication (TSQM) at 1 month and 5 months after initiation of the TOBI® Podhaler®. The TSQM domain scores include effectiveness, sideeffects, convenience and global satisfaction. (Note the standard fourteen questions of the TSQM were not altered).
- To describe the change in treatment satisfaction using additional TSQM questions as used in the EAGER study, (Konstan 2011) at 1 month and 5 months after initiation of the TOBI® Podhaler®. The additional TSQM questions are on convenience of storage, ease of assembly, use away from home and care of delivery device.
- To describe the impact of the TOBI® Podhaler® on patients' lives at 1 month and 5 months after the initiation of treatment.
- To describe the change in clinical parameters of cystic fibrosis from baseline to 1 month and 5 months after the initiation of the TOBI® Podhaler® (or 6 months pre and post TOBI® Podhaler® initiation, as appropriate to the parameter); lung function, days of new anti Pa antibiotic treatment oral /IV home/hospital.
- To describe the adverse drug reactions associated with TOBI® Podhaler®.

Study design

This is a combined prospective and retrospective multi-center observational research study conducted in five UK secondary care specialist cystic fibrosis.

Patient Questionnaires at Baseline, 1 month and 5 months

Once consent had been given the patient was asked to complete the study questionnaires at baseline and at 1 month (= after 1 cycle of treatment) and 5 months (= after 3 cycles of treatment) after TOBI Podhaler initiation. This was done either at a scheduled clinic appointment or by post.

Retrospective data at 6 months

At 6 months after TOBI Podhaler initiation the clinical parameters of CF [e.g. FEV1% predicted, days of new anti-pseudomonal antibiotic treatment (oral/IV at home/ hospital)] which had been recorded over past 12 months (i.e. 6 months pre- and 6 months post-TOBI Podhaler initiation) as part of routine clinical practice, were collected from patients' medical records by either a member of the clinical team or a researcher from the Trust or pH Associates.

Study population /Sample size

The study population was comprised of males or females aged 14 years or over at baseline with a diagnosis of CF, documented chronic Pseudomonas infection and a first prescription of tobramycin inhaled powder (TIP). Only patients starting treatment within the licensed indications of the TOBI® Podhaler® were included.

The primary endpoint of this study is the mean (SD) change from baseline in Treatment Burden domain CFQ-R scores at 1 month and 5 months of TOBI® Podhaler treatment.

It was decided that a sample of approximately 90 patients would provide a sufficient degree of reliability for this study.

Treatments

All patients were prescribed TOBI® Podhaler treatment.

Outcomes/endpoints

Primary endpoint

- Mean (SD) change from baseline in Treatment Burden domain CFQ-R* scores at 1 month and 5 months after initiation of TOBI® Podhaler treatment

  *Cystic Fibrosis Quality of Life Questionnaire- Revised

Secondary endpoints

- Mean (SD) change from baseline in remaining CFQ-R domain scores at 1 month and 5 months after initiation of TOBI® Podhaler® treatment
- Mean (SD) change from baseline in TSQM* domain scores at 1 month and 5 months after initiation of TOBI® Podhaler® treatment

  * Treatment Satisfaction Questionnaire for Medication
- Mean (SD) change from baseline in additional TSQM questions score on treatment satisfaction at 1 month and 5 months after initiation of TOBI® Podhaler® treatment
- Qualitative summary of themes in patients' comments on how TOBI® Podhaler® has impacted their daily life
- Distribution and summary statistics of anti-pseudomonal antibiotic use (treatment days of oral and IV Pa antibiotics, admissions to hospital for Pa IV antibiotic therapy, length of stay, IV Pa antibiotic treatments carried out at home) over the 6 months observation period pre- and post-TOBI® Podhaler® initiation
- Comparison of % change from 6 months pre-TOBI® to baseline and baseline to 6 months post-TOBI® Podhaler® initiation in:
  - ✓ FEV1% predicted
  - ✓ O2 saturation
  - ✓ BMI

To note with regard to the questionnaires that any blanks and apparently outlying responses were not queried with the patient. All data were accepted as correct.

Statistical Methods

Analyses are descriptive in nature.

The study sample was analysed as a whole and stratified by patients who remained on TOBI® Podhaler® for 3 cycles of treatment and those who stopped treatment prior to competing 3 cycles. There are no between-center comparisons.

Sub-group analyses have been conducted to explore differences in changes in CFQR and TSQM scores and resource use between those patients who remained on TOBI® Podhaler® and those patients who stopped TOBI® Podhaler® prior to completing 3 cycles of treatment.

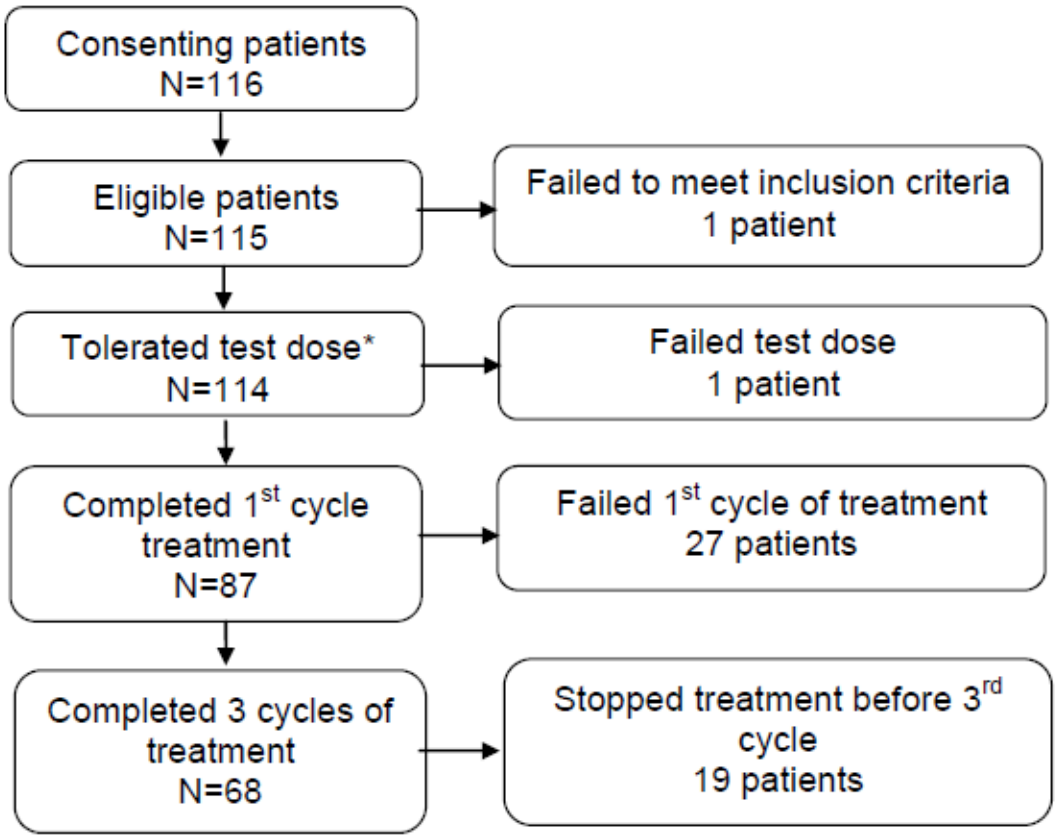
There was no imputation for missing data.

Results

Recruitment/ Number analysed

The first patient enrolled on 18 June 2012 and the last patient completed the study 30 November 2013. The study was conducted at 5 sites in the UK.

Figure 9-1 Recruitment



CHMP comments

There is a substantial loss to follow-up during the study. Approximately a quarter of patients fails the first treatment cycle. Almost 1/3 of remaining patients discontinued before the 3rd cycle. One centre (centre 5) did not any provide information about the number of patients that failed the test dose.

Baseline data

Of the 87 patients enrolled in the study, 48 patients (55.2%) were male. The mean age was 29.4 years. Four patients were between the ages of 14 and 18 years old. 46.5% (40/86) of the patients had diabetes and 62.2% (54/87) were on 2 or more nebulized medications at initiation.

To note: Of the 72 patients with a documented reason for starting TOBI® Podhaler®, 29 (40.3%) started it because they were starting chronic inhaled anti-pseudomonal antibiotic therapy following acute treatment with IV and/or nebulised therapy.

CHMP comments

Baseline data confirm the high treatment burden for these patients.

The risk for selection bias is unclear, because for center 5, including relatively most patients, the data on how many patients were approached for consent were not available.

Efficacy results

Primary outcome

Mean CFQ-R treatment burden domain scores* increased following the initiation of TOBI® Podhaler® with a mean increase of 7.9 points (SD± 19.2) at 1 month and 6.5 points (SD± 20.3) at 5 months (see Table 9-9). Student t testing, using a MID of 1 SE, confirmed a clinically significant improvement at the 99% level after 1 month, but not after 5 months.

*Domains are scored out of 100 with a higher score indicating greater patient satisfaction.

Table 9-9 Change in CFQ-R treatment burden domain scores at 1 month & 5 months

	Change at 1 month	Change at 5 months
N	84	55
Mean	+7.9	+6.5
SD	19.2	20.3
SE	2.1	2.7
Student t test*	p<0.01	NS

**Results were tested against a MID of 1 SE*
Changes in score could only be measured where data was recorded at both time points

To note that the mean (SD) CFQ-R treatment burden domain scores at baseline, 1 month and 5 months were 48.8 (19.5 57.3 (18.5) and 56.0 (18.0), respectively.

CHMP comments

Results are of descriptive nature for this observational study, and should be interpreted as such. No firm conclusions can be drawn. Note that there is a large loss to follow-up during the observational period.

Secondary outcomes

Change in other CFQ-R burden domain scores at 1 month (see Table 9-11)

A mean (SD) increase of 5.8 points (17.5) was seen in the respiratory domain at 1 month (clinically significant at the 95% level).

Table 9-11 Change in other CFQ-R burden domain scores at 1 month

To note that an increase in score signifies an improvement.

Score	N	Mean	SD	SE	Student t test result*
Physical	**84**	**1.5**	**20.9**	**2.28**	**NS**
Vitality	**84**	**4.1**	**18.7**	**2.04**	**NS**
Emotion	**84**	**3.4**	**14.4**	**1.57**	**NS**
Respiratory	**83**	**5.8**	**17.5**	**1.92**	**p<0.05**
Eating	84	-0.1	17.4	1.89	NS
Health perceptions	83	0.4	18.7	2.06	NS
Social	84	0.1	13.9	1.52	NS
Body image	84	0.8	19.2	2.10	NS
Role	81	4.0	16.9	1.87	NS
Weight	83	0.0	26.5	2.91	NS
Digestion	83	4.7	16.0	1.76	NS

**Results were tested against a MID of 1 SE*
Changes in score could only be measured where data was recorded at both time points

Change in other CFQ-R burden domain scores at 5 month (see Table 9-12)

A mean (SD) decrease of 4.2 points (22.9) was seen in the Eating domain at 5 months (clinically significant at the 95% level).

Table 9-12 Change in other CFQ-R burden domain scores at 5 month

To note that an increase in score signifies an improvement.

Score	N	Mean	SD	SE	Student t test result*
Physical	**56**	**-0.9**	**20.5**	**2.74**	**NS**
Vitality	**56**	**1.0**	**18.1**	**2.41**	**NS**
Emotion	**56**	**-1.2**	**18.6**	**2.48**	**NS**
Respiratory	**56**	**3.3**	**19.2**	**2.57**	**NS**
Eating	56	-4.2	22.9	3.06	p<0.05
Health perceptions	55	-0.6	17.0	2.30	NS
Social	55	-0.9	15.8	2.13	NS
Body image	55	-2.2	18.3	2.47	NS
Role	56	2.9	16.5	2.21	NS
Weight	56	0.6	33.9	4.53	NS
Digestion	56	-1.4	17.7	2.37	NS

**Results were tested against a MID of 1 SE*
Changes in score could only be measured where data was recorded at both time points

Change in TSQM domain scores at 1 month & 5 months

Increases were also seen in the scores for all four domains of the TSQM (see Table 9-14) and in the score for the additional TSQM questions (see Table 9-15). Domains are scored out of 100 with a higher score indicating greater patient satisfaction.

Table 9-14 Change in TSQM domain scores at 1 month & 5 months

An increase in score signifies an improvement.

	Effectiveness		Side effects	
	Change at 1 month	**Change at 5 months**	**Change at 1 month**	**Change at 5 months**
N	83	57	82	57
Mean	+5.0	+10.2	+5.2	+5.6
SD	24.1	19.9	18.7	15.9
SE	2.6	2.6	2.1	2.1
Student t test*	NS	p<0.01	NS	NS

**Results were tested against a MID of 1 SE*
Changes in score could only be measured where data was recorded at both time points

	Convenience		Global satisfaction	
	Change at 1 month	**Change at 5 months**	**Change at 1 month**	**Change at 5 months**
N	83	57	83	57
Mean	+25.6	+29.7	+12.9	+19.9
SD	23.5	24.6	23.6	22.9
SE	2.6	3.3	2.6	3.0
Student t test*	p<0.001	p<0.001	p<0.001	p<0.001

**Results were tested against a MID of 1 SE*
Changes in score could only be measured where data was recorded at both time points

Table 9-16 Mean change in additional TSQM question scores at 1 month & 5 months

An increase in score signifies an improvement.

	Additional TSQM question scores	
	Change at 1 month	**Change at 5 months**
N	80	55
Mean	+24.2	+27.1
SD	20.6	20.2
SE	2.3	2.7
Student t test*	p<0.001	p<0.001

**Results were tested against a MID of 1 SE*
Changes in score could only be measured where data was recorded at both time points

Anti-pseudomonal antibiotic treatment and clinical parameters

In the 6 months prior to initiation of TOBI Podhaler treatment, 42.5% of patients had a hospital admission for IV antibiotics administration associated with pulmonary infection vs 34.5% in the 6 months post initiation. Patients spent an average of 7.6 days in hospital for the administration of IV antibiotics for pulmonary infections during the 6 months prior to initiation vs 5.8 days during the 6 months post initiation. Mean number of days of IV antibiotic use was 16.2 during the 6 months prior to initiation and 13.7 during the 6 months post initiation. None of the changes were statistically significant.

FEV1% increased by 1.2% from 6 months pre initiation to baseline and decreased by 0.1% from baseline to 6 months post initiation, statistically not significant.

Stopping treatment

Table 9-27 Reasons for stopping treatment with TOBI® Podhaler® before the end of the study observation period

Nineteen (21.8%) patients stopped their treatment with TOBI® Podhaler® before the end of the study observation period (ie before completing 3 cycles).

Reason	No. of patients (n=19)
Chest tightness	4
Commenced IV antibiotics	3
Not tolerated	3
May be causing a reduction in lung function	2
Hospital admissions for pulmonary exacerbations	1
Preferred nebulizer	1
Became unwell	1
Achromobacter isolates identified in sputum	1
Not documented	3
Total	19

To note that patients remaining on treatment for 3 cycles had a lower mean age than those stopping treatment before completing 3 cycles (28.5 years v 32.5 years) and a higher mean FEV1% (64.3 v 52.6).

Safety results

A total of 51 adverse events (see Table 9-42) were reported in respect of 43 patients recruited to this study. Forty-two of these related to study patients and 9 to patients who failed to complete their test dose or first cycle of treatment and consequently were not included in the study. Of the 42 adverse events reported for study patients 12 resulted in patients stopping their treatment with TOBI Podhaler before the end of the study period.

Table 9-42 Adverse events

Type of event	No. of episodes (n=51)
Chest tightness	4
Decline in lung function	4
Chest tightness & cough	3
Cough	3
Bronchoconstriction	2
Hearing and balance problems	2
Blood in sputum	1
Bronchospasm	1
Chest heaviness	1
Cold, cough & chest tightness	1
Cough & hoarse voice	1
Cough and sore throat	1
Cough wheeze and short of breath	1
Cough, chest infection	1
Cough, chest pain	1
Coughing blood, chest tightness	1
Diarrhoea, bad taste	1
Dry cough	1
Dry cough, lost voice	1
Dry lips	1

Type of event	No. of episodes (n=51)
Dry mouth	1
Fatigue	1
Haemoptysis	1
Increase in cough	1
Increased breathlessness/palpitations	1
Increased cough, chest tightness, wheeze	1
Increased cough, infected exacerbation	1
Increased SOB, chest tightness	1
Increased SOB, increased sputum	1
Irritable cough	1
Migraine, chest tightness	1
Pulmonary exacerbations	1
Reduced exercise tolerance, chest tightness	1
Shards of plastic in mouth after medicating	1
Shortness of breath, increased cough	1
Smell/taste deteriorated, rash, wheeziness	1
SOB on exertion	1
Tinnitus	1
Wheeze bronchospasm	1

2.3.3. Discussion on clinical aspects

The MAH's main conclusion is that the overall patient satisfaction is higher for TOBI Podhaler than previous treatment with tobramycin inhaled solution. The Mean CFQ-R treatment burden domain scores increased following the initiation of TOBI Podhaler with a mean increase of 7.9 points (SD± 19.2) at 1 month and 6.5 points (SD± 20.3) at 5 months. Increases were also seen in the scores for all four domains of the TSQM and the score for the additional TSQM questions. Results are purely of a descriptive nature for this observational study, and should be seen as such. No firm conclusions can be drawn.

The CHMP agrees on that the study results suggest that the overall patient satisfaction might be higher for TOBI Podhaler than previous treatment with tobramycin inhaled solution. At this stage, the data from study CTBM100CGB01 do not warrant an update of the product information of TOBI Podhaler.

3. CHMP's overall conclusion and recommendation

The CHMP agrees on that the study results suggest that the overall patient satisfaction might be higher for TOBI Podhaler than previous treatment with tobramycin inhaled solution. At this stage, the data from study CTBM100CGB01 do not warrant an update of the product information of TOBI Podhaler.

☒ **Fulfilled:**

No regulatory action required.

4. Additional clarification requested

n.a.