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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/P46/034

Note

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

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

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1. Introduction

On 16 September 2022, the MAH submitted the final results of the study CTMBM100C2407 (2407), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

No proposals for amendments to the Product Information were submitted as part of this procedure.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study CTBM100C2407 is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

The medications used were TOBI Podhaler (tobramycin inhalation powder) and comparator agents, e.g., TOBI solution (tobramycin inhalation solution), Bethkis (tobramycin inhalation solution) and Cayston (aztreonam inhalation solution).

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- CTMBM100C2407 (2407), a prospective observational study in cystic fibrosis patients with chronic respiratory Pseudomonas aeruginosa infection treated with TOBI Podhaler (tobramycin inhalation powder) or other FDA-approved inhaled antipseudomonal antibacterial drugs.

The study was requested as increased resistance to tobramycin and other antibiotics, as well as emergence of other pathogens, was observed during therapy.

2.3.2. Clinical study CTMBM100C2407 (2407)

Description

This was a multicenter, prospective, observational cohort study conducted over a 5-year period in a subset of CF patients with chronic *P. aeruginosa* infection enrolled in the Cystic Fibrosis Foundation Patient Registry Database (PortCF). Based on physician discretion, enrolled patients were either treated with TOBI Podhaler (tobramycin inhalation powder) or other FDA-approved inhaled antipseudomonal antibacterial drugs.

The purpose of the study was: 1) To determine if decreased susceptibility to tobramycin is increasing in *P. aeruginosa* from CF patients. 2) To monitor resistance to meropenem, imipenem, ceftazidime, aztreonam and ciprofloxacin. 3) Evaluate the emergence of the following treatment-emergent pathogens: *Staphylococcus aureus, Stenotrophomonas maltophilia, Achromobacter xylosoxidans*, and B*urkholderia spp*. 4) Evaluate clinical outcomes in the first year (change in lung function, respiratory and non-respiratory hospitalisations, mortality and use of new antipseudomonal antibiotics) in patients using TOBI Podhaler compared to a cohort using other FDA-approved inhaled anti-pseudomonal antibiotics.

The design of the study is presented in Figure 1. Patients were screened consecutively (i.e., as they presented in the clinic) and, if eligible, enrolled either into the TOBI Podhaler cohort or the non-TOBI Podhaler cohort (other FDA-approved inhaled antipseudomonal treatments). Patients could be enrolled at any time, i.e., during an on-cycle or off-cycle treatment period. Treatment cohorts were defined by the inhaled antibiotic – TOBI Podhaler or non-TOBI Podhaler (other FDA-approved inhaled antipseudomonal treatments) – used by the patients at baseline (Figure 1). For patients enrolled during an off-cycle treatment period, cohort assignment was defined by the inhaled antibiotic used during the on-cycle treatment period immediately preceding enrolment.

The design seems adequate to evaluate whether susceptibility to tobramycin is decreasing and which treatment-emergent pathogens occur in CF patients chronically treated with TOBI Podhaler or other FDA-approved inhaled anti-pseudomonal antibiotics in a real-world setting. An observational study with no randomisation reflects normal prescribing procedures and the real-world situation. However, the lack of randomisation could potentially lead to patient selection, treatment biases and disbalances in baseline characteristics.

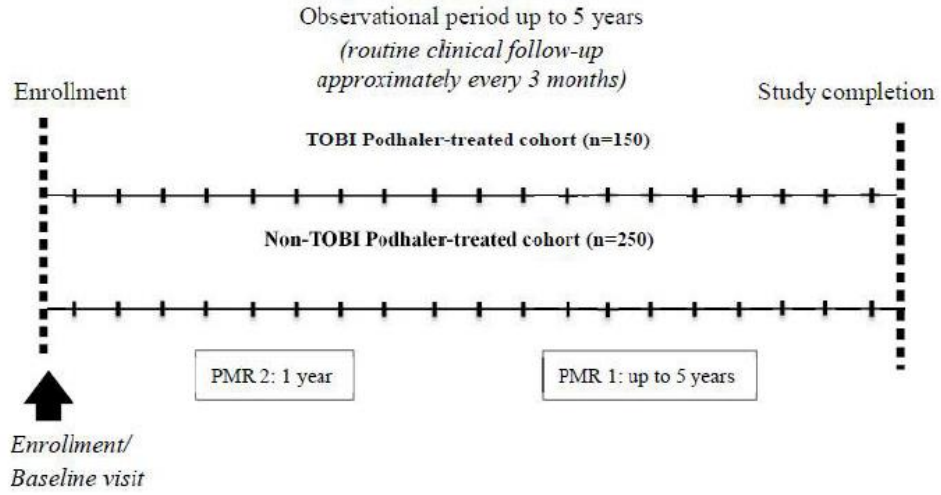

Figure 1: Study design.

Methods

Study participants

This study included CF patients with chronic *P. aeruginosa* infection enrolled in the PortCF registry and using TOBI Podhaler (TOBI Podhaler cohort) or other FDA-approved inhaled antipseudomonal antibiotics (non-TOBI Podhaler cohort). To be eligible for the study, male and female patients ≥6 years of age (including adults) were required to have at least two positive *P. aeruginosa* cultures and adequate lung function (FEV1 ≥ 25% predicted documented in the previous year). In addition, they needed to be prescribed, and initiated chronic treatment with FDA-approved inhaled antipseudomonal antibiotics for chronic P. aeruginosa infection (e.g., TOBI Podhaler, TOBI solution (tobramycin inhalation solution), Bethkis (tobramycin inhalation solution), or Cayston (aztreonam inhalation solution)).

Patients were excluded from the study if they met the following criteria: 1) they had a documented FEV1 < 25% predicted in the previous year; 2) were participating in an interventional clinical study with an inhaled antibiotic treatment; 3) were on treatment with compounded tobramycin (e.g., tobramycin intravenous solution adapted for use by inhalation) or treatment with inhaled

antipseudomonal antibacterial drug(s) that were not FDA-approved; or 4) if they were undergoing an early eradication regimen for CF (first line therapy).

The population is representative of the real-world CF population with chronic *P. aeruginosa* infection. Prescribers were free to choose treatment regimens for their patients. However, it is noted that the upper limit of FEV1% of 80% was removed from the protocol. It is stated in the FDA label that "Safety and efficacy have not been demonstrated in patients under the age of 6 years, patients with forced expiratory volume in 1 second (FEV1) <25% or >80%, or patients colonised with *Burkholderia cepacian*" (EMA SmPC states <25% or >75%). As the limit was removed, participants could have higher FEV1%. This indicates that participants with better lung function could be included in the study if they were diagnosed with CF and had *P. aeruginosa* infection.

Treatments

The medications of interest were TOBI Podhaler (tobramycin inhalation powder) and comparator agents, e.g., TOBI solution (tobramycin inhalation solution), Bethkis (tobramycin inhalation solution) and Cayston (aztreonam inhalation solution). The choice of treatment, as well as the decision to discontinue treatment, were at the sole discretion of the prescribing physician and the patients/parents or legal guardians and was independent from participation in this study.

Enrolled patients were followed for up to 5 years whether or not they continued on the TOBI Podhaler or non-TOBI Podhaler options they were using at baseline visit. In particular, patients switching from TOBI Podhaler to alternative inhaled antibiotics or vice versa for any reason during the study continued to be followed up to 5 years post enrolment unless they voluntarily withdrew from the study. This is understood from a prescriber's perspective; however, this could hamper conclusions being drawn from this study.

Objective(s)

Primary objective:

The primary objective was:

- To monitor minimum inhibitory concentration (MIC) of tobramycin and the following antipseudomonal antibacterial drugs (meropenem, imipenem, ceftazidime, aztreonam and ciprofloxacin) for *P. aeruginosa* sputum isolates annually and cumulatively over a 5-year period in both treatment cohorts.
- To evaluate the frequency of the following treatment-emergent pathogens in sputum: *S. aureus* (methicillin-resistant *Staphylococcus aureus* [MRSA] and methicillin-susceptible *Staphylococcus aureus* [MSSA]), *S. maltophilia, A. xylosoxidans,* and *Burkholderia spp.* annually and cumulatively over a 5-year period in both treatment cohorts.

Secondary objectives:

The secondary objective was to

- To evaluate the frequency of SAEs in patients treated with TOBI Podhaler or other FDA-approved inhaled antipseudomonal treatments for *P. aeruginosa* infection.

Outcomes/endpoints

Microbiological assessment

For microbiological assessments during the course of the study, sputum collected as part of routine care, including at baseline, from patients able to spontaneously produce sputum was used. If a patient was unable to spontaneously expectorate, a deep-throat cough swab specimen was collected instead (the protocol was amended in October 2017 to allow for the use of deep-throat cough swab specimens when patients are unable to spontaneously produce sputum).

Sputum was collected in sterile containers and cultured for the presence of *P. aeruginosa* (quantitative test), the following pathogens (*S. aureus* [MRSA and MSSA], *S. maltophilia, A. xylosoxidans*, *Burkholderia spp*.) and other typical CF respiratory pathogens (qualitative tests). MIC values for *P. aeruginosa* were determined for specimens obtained to assess change in pathogen susceptibility to tobramycin. Meropenem, imipenem, ceftazidime, aztreonam and ciprofloxacin MIC values were also determined.

The number of *P. aeruginosa* CFUs in sputum was also assessed quantitatively. A central laboratory (ICON plc) was used for quantitative and qualitative microbiology assessments and susceptibility testing. Details on the collection, shipment of samples, generation of data and reporting of results by the central laboratory was provided to participating sites in a separate laboratory manual.

Safety assessments

Information on all AEs and SAEs occurring during the course of this study were collected and reported.

Sample size

No formal sample size estimation was performed. The revised sample size of 400 patients (150 TOBI Podhaler-treated patients and 250 patients on other inhaled antipseudomonal antibiotics) was anticipated to provide sufficient data for the study's objectives. As this was a non-randomised, observational study, the fact that no sample size calculation was performed can be accepted

Randomisation and blinding (masking)

Not applicable.

Statistical Methods

The baseline demographic and clinical outcomes of the study population were described for overall population and stratified by initial treatment cohort. All categorical data were summarised by frequencies and percentages. Continuous data were summarised by number of patients, mean, standard deviation, median, quartiles, minimum and maximum.

Descriptive statistics were used to summarise the microbiology assessments and safety in this final report.

Study populations

A total of 409 patients were enrolled and 408 were included in the full analysis set (FAS), as 1 patient in the TOBI Podhaler cohort did not receive any inhaled antipseudomonal antibiotic during the study. The safety set consisted of 408 patients who took at least one dose of TOBI Podhaler or another FDA - approved inhaled antipseudomonal antibiotic. The propensity score matching (PSM) analysis set was defined as the patients that were successfully matched between the two treatment cohorts using the PSM method.

Microbiological analyses were done in patients who provided sputum samples and for whom microbiology data was available.

Five patients sets were defined for analysis purpose:

1. The Full Analysis Set: included 408 eligible CF patients who enrolled in the study and were chronically colonised with *P. aeruginosa* infection: 149 of whom were using TOBI Podhaler and 259 patients were using another FDA-approved inhaled antipseudomonal antibiotic (non-TOBI Podhaler cohort) at baseline.
2. The Safety Analysis Set: consisted of all patients in the FAS who took at least 1 dose of TOBI Podhaler or non-TOBI Podhaler agent.
3. PK set: included 51 (34.0%) patients out of 149 TOBI Podhaler patients who were able to spontaneously produce at least one sputum sample, including 5 (3.3%) patients using TOBI Podhaler who provided the informed consent to participate in the optional TOBI Podhaler PK sub-study.
4. Optional sputum microbiology sub-set: included 6 (4.0%) patients in the TOBI Podhaler cohort and 7 (2.7%) patients in the non-TOBI Podhaler cohort who were able to spontaneously produce sputum.
5. Propensity score matched (PSM) analysis set: included 262 (64.1%) patients who were successfully matched between the two treatment cohorts using the propensity score matching method, including 131 (87.3%) patients in the TOBI Podhaler cohort and 131 (50.6%) patients in the non-TOBI Podhaler cohort.

Microbiological assessment and MIC

The MIC data for tobramycin and the antipseudomonal antibacterial drugs (meropenem, imipenem, ceftazidime, aztreonam and ciprofloxacin) for *P. aeruginosa* were summarised.

The distribution of tobramycin and other antibiotic MIC with respect to *P. aeruginosa* at baseline and for the last assessment within each post-baseline time interval (> baseline to 1 year, > 1-2 years, > 2-3 years, > 3-4 years, and > 4-5 years) was summarised by biotype, all biotypes and maximum of biotypes. This summary was based on the total number of isolates during a time interval, not the number of patients, a patient with more than one biotype is included with as many biotypes as isolated.

Shifts of MIC with respect to *P. aeruginosa* at the last assessment within each post-baseline time interval, as compared to baseline were summarised by biotype, maximum MIC of all biotypes and all biotypes according to the following categories:

- MIC > 8 µg/mL (baseline must be ≤ 8 µg/mL).
- MIC > 128 µg/mL (baseline must be < 64 µg/mL).
- ≥ 2, 4, and 8-fold increase from baseline.
- Change within 2-fold from baseline (increase or decrease).
- ≥ 4-fold increase and MIC > 8 µg/mL.

A graphical display of the MIC distribution was provided for all *P. aeruginosa* biotypes per time point and cohort.

As an exploratory analysis, statistical comparison of MIC between two treatment cohorts was explored using the PSM set with a repeated measure logistic regression analysis on the incidence of a 2-fold (4-fold, 8-fold) MIC increase compared to the baseline value for the maximum of biotypes. The model included x-fold MIC increase (yes, no) as dependent variable, and treatment cohort, log10(baseline value of MIC), time interval and treatment cohort by time interval interaction as exploratory variables. Analyses were carried out with SAS PROC GENMOD using patients within matched pairs as subject for

the repeat statement and type=CS (compound symmetry) correlation structure. Odds ratios (ORs), including 95% CI, were presented.

Treatment-emergent pathogens in sputum

Sputum specimens for microbiology were analysed by a central laboratory to assess pathogens present and *P. aeruginosa* CFUs in sputum. The frequency of the following treatment-emergent pathogens in sputum: *S. aureus* (MRSA and MSSA), *S. maltophilia, A. xylosoxidans*, and *Burkholderia spp*. were summarised per year in study and cumulatively as the number of patients and percentage for overall population and by treatment cohorts.

Serious adverse events and adverse events of special interest

AEs and SAEs were summarised by primary system organ class (SOC) and preferred term (PT) for each treatment cohort and overall for the population. Additionally, the number and incidence rates (IRs) of SAEs, together with the 95% confidence interval (CI) for the IRs were provided. AEs were coded using the MedDRA Version 24.1 terminology.

Missing values

All attempts were made by the treating physician and/or site personnel to limit the amount of missing data. No imputation was made on the CRFs for missing data and no imputation was made in the analysis in this report. All summaries were done based on the available observed values unless otherwise specified.

Sensitivity analyses

Sensitivity analyses were conducted to assess any effect of enrolling patients during an on-cycle or off-cycle treatment period on select treatment comparisons.

Amendments to the statistical analysis plan

Statistical analysis plan was amended twice (dated 09 February 2017 and 07 March 2018) to align with changes introduced by protocol amendments 3 (dated 10 August 2016) and 4 (dated 13 October 2017). The changes addressed FDA recommendations to conduct sensitivity analyses to assess any influence of allowing patients to be enrolled on- or off-cycle on treatment comparisons.

Additional changes were implemented to include analyses based on microbiology samples collected with throat swabs. The plan was amended two additional times (dated 07 June 2019 and 10 July 2019) to address the change in sponsorship and implement slight modifications of the mixed model and multiple imputation specifications. The plan was further amended (dated 02 April 2020) to revise the PK analysis due to the limited number of PK samples collected. The final amendment (dated 03 March 2022) was made to clarify the exploratory analysis of MIC concentration data.

Results

Participant flow

A total of 409 patients were enrolled. Out of the 408 (99.8%) patients who received at least one dose of any inhaled antipseudomonal antibiotic, 149 patients were in the TOBI Podhaler cohort, and 259 patients were in the non-TOBI Podhaler cohort.

Overall, 279 (68.2%) patients completed the 5-year follow-up: 96 (64.0%) patients in the TOBI Podhaler cohort and 183 (70.7%) patients in the non-TOBI Podhaler cohort completed the 5-year follow-up. A total of 130 (31.8%) patients discontinued from the study including 54 (36.0%) patients in the TOBI Podhaler cohort and 76 (29.3%) patients in the non-TOBI Podhaler cohort. Reasons

underlying the study discontinuation were administrative problems (11.2%), patient/guardian's decision (7.6%), lost to follow-up (5.4%), death (3.7%), physician's decision (3.7%), and protocol deviation (0.2%).

The participant flow is, in general, comparable in both treatment groups. However, a slightly higher percentage of participants discontinued in the TOBI Podhaler group, 36.0%, compared to the non-TOBI Podhaler group, 29.3%, mainly driven by more patients being lost-to-follow up (13 patients (8.7%) in the TOBI Podhaler group vs 9 (3.5%) in the non-TOBI Podhaler group).

Recruitment/Number analysed

The first patient enrolled on 05 May 2015 and the final patient visit date was 31 December 2021.

The study was conducted at 50 sites in the USA.

Number analysed

The disposition of all enrolled patients in different analysis sets is presented in Table 1.

Table 1 Analysis sets

Analysis Set	TOBI Podhaler (N=150) n (%)	non-TOBI Podhaler (N=259) n (%)	Total (N=409) n (%)
Full analysis set	149 (99.3)	259 (100)	408 (99.8)
Safety set	149 (99.3)	259 (100)	408 (99.8)
Pharmacokinetic set	51 (34.0)	0	51 (12.5)
TOBI Podhaler PK sub-study set	5 (3.3)	0	5 (1.2)
Sputum microbiology sub-study set	6 (4.0)	7 (2.7)	13 (3.2)
Propensity score matched (PSM) set	131 (87.3)	131 (50.6)	262 (64.1)

- PK: pharmacokinetics; TOBI: Tobramycin Inhalation Powder.
- Refer to Statistical Analysis Plan for definition of the analysis sets.
- Source: Table 14.1-2.1.

Baseline data

At the time of enrollment, the majority of the patients were more than 18 years old (n=283, 69.4%). Overall, the mean age was 26.4 years (standard deviation (SD)=12.35); patients in the TOBI Podhaler cohort had a mean age of 24.4 years (SD=10.71) and that of the non-TOBI Podhaler cohort was 27.5 years (SD=13.09). A total of 45 (11.0%) patients were of 6 to 12 years of age, including 12 (8.1%) patients in the TOBI Podhaler cohort and 33 (12.7%) patients in the non-TOBI Podhaler cohort. The majority of the patients were Caucasian (n=376, 92.2%). More than half of the participants were male, overall (n=220, 53.9%) and in the TOBI Podhaler cohort (n=91, 61.1%), respectively.

A total of 407 patients (99.8%) were diagnosed with CF; one patient had missing CF diagnosis data (non-TOBI Podhaler cohort) due to data issues in PortCF registry (source of CF diagnosis data). A quantitative pilocarpine iontophoresis sweat test was performed for 358 patients out of the 407 patients, of whom 16 (4.5%) patients had sweat test values of ≤ 60 mmol/L. Overall, 407 patients (99.8%) were genotyped.

At baseline, a total of 396 (97.1%) patients had spirometry assessments. Patients in the TOBI Podhaler cohort on average had a FEV1 % predicted of 75.7% (SD=23.96) as compared to that of 64.9% (SD=22.80) among patients in the non-TOBI Podhaler cohort.

The mean time since chronic *P. aeruginosa* infection established was 7.1 years (SD=5.36) in the TOBI Podhaler cohort comparing to 6.5 years (SD=5.67) in the non-TOBI Podhaler cohort.

A total of 186 patients provided sputum samples at baseline for microbiology assessments. Sputum culture results were available for 68 patients in the TOBI Podhaler cohort (of which 51 patients had *P. aeruginosa* isolated) and 118 patients in the non-TOBI Podhaler cohort (of which 110 patients had *P. aeruginosa* isolated). The mean sputum densities for sum of all biotypes of *P. aeruginosa* at baseline tended to be similar between the TOBI Podhaler cohort (6.5 log10 CFU, SD=1.80) and the non-TOBI Podhaler cohort (6.3 log10 CFU, SD=1.81). The majority of patients with baseline microbiology data (73.8%) had *P. aeruginosa* isolates with MIC ≤ 8 µg/mL (74.1% in the TOBI Podhaler cohort, 73.6% in the non-TOBI Podhaler cohort). None of the patients analysed for *Burkholderia cepacia* had presence of *Burkholderia cepacia* in their baseline sputum sample.

Microbiological results

For microbiological assessments, sputum collected as part of routine care, including at baseline, from patients able to spontaneously produce sputum was used. If a patient was unable to spontaneously expectorate, a deep-throat cough swab specimen was collected instead (the protocol was amended in October 2017 to allow for the use of deep-throat cough swab specimens when patients are unable to spontaneously produce sputum).

MIC

The MIC distribution for all biotypes of *P. aeruginosa* at baseline and the end of each year in the study for FAS were presented. The trend in changes in MIC distribution over time was similar between the TOBI Podhaler and non-TOBI Podhaler cohorts after baseline.

The categorical change in MIC for *P. aeruginosa* from baseline for the FAS was presented. The proportions of patients with an increased shift in MIC were 34.0% (n=16), 28.9% (n=13), 45.7% (n=16), 55.6% (n=15), and 40.0% (n=4) in the TOBI Podhaler cohort from baseline to the 1 year, 1 to 2 years, 2 to 3 years, 3 to 4 years, and 4 to 5 years follow-up, respectively; and 34.0% (n=32), 37.7% (n=29), 45.0% (n=36), 49.1% (n=26), and 39.4% (n=13) of patients in the non-TOBI Podhaler cohort had increased shift in MIC during the follow-up visits/intervals, respectively.

The categorical change in MIC for *P. aeruginosa* from baseline for the PSM set was presented. In total, 35.7% (n=15) of patients in the TOBI Podhaler cohort vs. 34.2% (n=13) of patients in the non-TOBI Podhaler cohort had ≥ 2-fold increase in MIC from baseline to the 1-year follow-up. Additionally, 29.3% (n=12) vs. 42.4% (n=14), 46.9% (n=15) vs. 51.5% (n=17), 58.3% (n=14) vs. 57.1% (n=12), and 44.4% (n=4) vs. 30.0% (n=3) of patients had ≥ 2-fold increase in MIC during the 1 to 2 years, 2 to 3 years, 3 to 4 years, and 4 to 5 years follow-up period, respectively.

In total, 16.7% (n=7) of patients in the TOBI Podhaler cohort vs. 13.2% (n=5) of patients in the non-TOBI Podhaler cohort had ≥ 4-fold increase in MIC from baseline to the 1-year follow-up. Additionally, 17.1% (n=7) vs. 27.3% (n=9), 18.8% (n=6) vs. 36.4% (n=12), 25.0% (n=6) vs. 28.6% (n=6), and 11.1% (n=1) vs. 20.0% (n=2) of patients had ≥ 4-fold increase in MIC during the 1 to 2 years, 2 to 3 years, 3 to 4 years, and 4 to 5 years follow-up period, respectively.

The MIC analyses were also done by baseline medication which is defined as the inhaled antibiotic a patient was using at enrollment: TOBI Podhaler, Cayston, or tobramycin solution. The trend in changes in MIC distribution for P. aeruginosa for all biotypes during the follow-up was similar between participants who used TOBI Podhaler, Cayston, and tobramycin solution at baseline.

Treatment-emergent pathogens in sputum

The treatment-emergent pathogens up to end of 5-years are summarised cumulatively below:

- Stenotrophomonas maltophilia: 31 patients (31.0%) in the TOBI Podhaler cohort, 60 patients (34.5%) in the non-TOBI Podhaler cohort
- Staphylococcus aureus: 56 patients (56.0%) in the TOBI Podhaler cohort, 88 patients (50.6%) in the non-TOBI Podhaler cohort
- Methicillin-resistant Staphylococcus aureus: 21 patients (21.0%) in the TOBI Podhaler cohort, 48 patients (27.6%) in the non-TOBI Podhaler cohort
- Achromobacter xylosoxidans: 3 patients (3.0%) in the TOBI Podhaler cohort, 12 patients (6.9%) in the non-TOBI Podhaler cohort
- Burkholderia spp.: 2 patients (2.0%) in the TOBI Podhaler cohort, 2 patients (1.1%) in the non-TOBI Podhaler cohort

Based on the data presented, no clear impact of the prescribed treatment on MIC distribution was observed. The percentage of patients with a categorical increase in MIC was largely comparable between the 2 cohorts over time. However, as 81 patients in the TOBI Podhaler group and 61 in the non-TOBI Podhaler group were exposed to the medication in the other cohort, the observed results cannot be directly attributed to the treatment, and the conclusions that can be drawn are limited, especially as it is unclear when this happened. The MAH was asked to present the data on MIC distribution based on the treatment received in patients who did not receive treatment from the other cohort (i.e., treated with a single treatment) as a sensitivity analysis. In case a patient used medication included in the other cohort, the data of that patient should be censored from time of use. The MAH provided this sensitivity analysis and the results were largely in line with the primary analysis. No clear trends on MIC distribution could be observed in either group. It is acknowledged that this sensitivity analysis could potentially be biased, as switching to or concomitant use of the medication from the other cohort could be due to efficacy/resistance development.

The results from the propensity score matched set indicate that differences in baseline characteristics, due to fact that no randomisation occurred in this observational study, did not impact the outcome on MIC distribution. However, as stated before, the criteria for matching were not clearly presented.

No impact of the prescribed treatment on treatment-emergent pathogens was seen.

Safety results

Exposure

A total of 408 patients contributed 1712.1 patient-years of follow-up over the course of the study (TOBI Podhaler cohort: 581.5 patient-years; non-TOBI Podhaler cohort: 1130.6 patient-years). The duration of initial exposure to baseline inhaled antipseudomonal antibiotic medications is defined as the number of days in the study when patients were taking baseline medications (from the date of the first dose to the last dose) before switching to another medication excluding interruptions. The duration of the overall exposure to inhaled antipseudomonal antibiotics refers to the total number of days that a patient used TOBI Podhaler or non-TOBI Podhaler antibiotics throughout the study excluding treatment interruptions. Changes from initial cohort treatment included adding a new inhaled antipseudomonal antibiotic to the drug regimen at the time of enrolment or switching to a new inhaled antipseudomonal antibiotic.

It is worth noting that 81 patients in the TOBI Podhaler cohort were exposed to an inhaled antipseudomonal antibiotic other than TOBI Podhaler and 61 patients in the non-TOBI Podhaler cohort were exposed to TOBI Podhaler. This includes patients on continuous therapy (alternating TOBI Podhaler with another FDA-approved antipseudomonal antibiotic) and patients who had changes in their inhaled antibiotic used at enrolment.

Adverse Events

A total of 133 (89.3%) patients in the TOBI Podhaler cohort experienced at least one AE compared to 250 (96.5%) patients in the non-TOBI Podhaler cohort. The most common AEs (≥ 10%) by SOC reported in both cohorts were infections and infestations (TOBI Podhaler: n=131, 87.9%; non-TOBI Podhaler: n=238, 91.9%), followed by respiratory, thoracic, and mediastinal disorders (TOBI Podhaler: n=62, 41.6%; non-TOBI Podhaler: n=124, 47.9%), gastrointestinal disorders (TOBI Podhaler: n=32, 21.5%; non-TOBI Podhaler: n=83, 32.0%), investigations (TOBI Podhaler: n=30, 20.1%; non-TOBI Podhaler: n=65, 25.1%), general disorders and administration site conditions (TOBI Podhaler: n=26, 17.4%; non-TOBI Podhaler: n=76, 29.3%), psychiatric disorders (TOBI Podhaler: n=26, 17.4%; non-TOBI Podhaler: n=40, 15.4%), nervous system disorders (TOBI Podhaler: n=21, 14.1%; non-TOBI Podhaler: n=37, 14.3%), musculoskeletal and connective tissue disorders (TOBI Podhaler: n=18, 12.1%; non-TOBI Podhaler: n=35, 13.5%), and metabolism and nutrition disorders (TOBI Podhaler: n=15, 10.1%; non-TOBI Podhaler: n=34, 13.1%).

The most common AE by PT reported in both treatment cohorts was infective pulmonary exacerbation of CF (TOBI Podhaler cohort: n=124, 83.2%; non-TOBI Podhaler cohort: n=230, 88.8%). Other frequently reported (≥ 10% in any cohort) AEs were cough (TOBI Podhaler: n=34, 22.8%; non-TOBI Podhaler: n=57, 22.0%), sinusitis (TOBI Podhaler: n=19, 12.8%; non-TOBI Podhaler: n=33, 12.7%), hemoptysis (TOBI Podhaler: n=19, 12.8%; non-TOBI Podhaler: n=40, 15.4%), upper respiratory tract infection (TOBI Podhaler: n=17, 11.4%; non-TOBI Podhaler: n=26, 10.0%), and influenza (TOBI Podhaler: n=15, 10.1%; non-TOBI Podhaler: n=24, 9.3%).

The majority of AEs were either moderate or severe in intensity. Overall, by maximum intensity, 49 patients (12.0%) had mild, 116 patients (28.4%) had moderate, and 218 patients (53.4%) had severe AEs. Specifically, the proportion of patients with mild AEs was 14.8% (n=22) for patients in TOBI Podhaler cohort vs. 10.4% (n=27) in non-TOBI Podhaler cohort. The proportion of patients with moderate AEs was 30.9% (n=46) in TOBI Podhaler cohort vs. 27.0% (n=70) in non-TOBI Podhaler cohort. The proportion of patients with severe AEs was 43.6% (n=65) in the TOBI Podhaler cohort and 59.1% (n=153) in the non-TOBI Podhaler cohort.

Twenty-eight patients had AEs which were suspected to be related to study drug, 10 (6.7%) in the TOBI Podhaler cohort and 18 (6.9%) in the non-TOBI Podhaler cohort

Deaths and SAEs

Overall, 15 patients died during study, 3 patients (2.0%) in the TOBI Podhaler cohort and 12 patients (4.6%) in the non-TOBI Podhaler cohort. None of the deaths were considered to be related to the study medications by investigators.

A total of 256 patients experienced an SAE during study, 81 patients (54.4%) in the TOBI Podhaler cohort and 175 patients (67.6%) in the non-TOBI Podhaler cohort. The most common SAE by PT reported in both treatment cohorts was infective pulmonary exacerbation of CF (TOBI Podhaler cohort: n=72, 48.3%; non-TOBI Podhaler cohort: n=152, 58.7%). Five SAEs (2 in TOBI Podhaler and 3 in non-TOBI Podhaler treatment cohort) were suspected to be related to study medication: two SAEs of infective pulmonary exacerbations of CF in the TOBI Podhaler cohort, and one SAE of hemoptysis and two SAEs of infective pulmonary exacerbations of CF in the non-TOBI Podhaler cohort.

Sixteen patients discontinued study drug due to AEs: 5 patients (3.4%) in the TOBI Podhaler cohort and 11 patients (4.2%) in the non-TOBI Podhaler cohort. Most of these AEs were of mild to moderate intensity, except one AE of respiratory failure in the non-TOBI Podhaler cohort and were suspected to be related to study drug for 3 patients (2.0%) in the TOBI Podhaler cohort and 7 patients (2.7%) in the non-TOBI Podhaler cohort.

The presentation of exposure was considered very confusing; as for example, the percentage of participants with a duration of follow-up of ≥90 days is substantially lower compared to the percentage of participants with a duration of overall exposure of ≥90 days. The MAH was also asked to explain the increase in the percentage of participants that had a duration of follow-up ≥1620 days (32.0%) and ≥ 1800 days (45.2%) over ≥1440 days (18.1%) in the non-TOBI Podhaler group. The MAH agreed and provided an updated table where these values were included, but this did not impact overall duration of follow-up or summary of exposure presented.

The MAH confirmed there is an overlap in the 81 patients in the TOBI Podhaler cohort that were exposed to an inhaled antipseudomonal antibiotic other than TOBI Podhaler and the 38 patients who had at least one change from the initial cohort treatment. In addition, information on when switching occurred for the 81 patients was provided. Switching occurred at different time points after start of the study. The same information was provided for the 61 patients in the non-TOBI Podhaler cohort who were exposed to TOBI Podhaler and the 93 patients who had at least one change from the initial cohort treatment.

The MAH was asked to present the reason for the physician's decision to switch medication in both TOBI Podhaler and non-TOBI Podhaler cohort, and in case resistance development is a part of the reason, to switch to present the MIC value prior to switching. The MAH stated that the reason for physician’s decision was not collected.

Based on the presented data, 81 patients in the TOBI Podhaler cohort were exposed to an inhaled antipseudomonal antibiotic other than TOBI Podhaler, and 61 patients in the non-TOBI Podhaler cohort were exposed to TOBI Podhaler. This limits any conclusions on the safety profile that can be drawn from this study.The safety profiles in both TOBI Podhaler and non-TOBI Podhaler cohorts were similar. The percentage of participants experiencing AEs suspected to be related to the study treatment was similar. No new safety signals were observed.

Overall, 5 SAEs were suspected to be related to the study medications, 4 of which were cases of infective pulmonary exacerbation of CF. Considering the fact that infective pulmonary exacerbations are frequently encountered in patients with CF, it is unclear why these 4 cases were considered related to the study medication. The MAH provided the narratives and no clear link between study medication and exacerbation of CF was observed. It is most likely that the patients presented with infections and exacerbations in the natural course of the disease.

None of the deaths reported were considered related to the study drug, which is deemed plausible as most deaths were related to the underlying disease of cystic fibrosis. However, one death in the non-TOBI Podhaler group was classified as unknown. As the cause of death is unknown, it cannot be concluded that this death is unrelated to the study drug.

2.3.3. Discussion on clinical aspects

Due to its observational nature, the study has several limitations:

- Lack of randomisation led to differences in baseline characteristics of the disease.
- During the course of the study, patients could cycle or switch antibiotics; however, they continued to be included in the cohort to which they were originally assigned, which limits any conclusions based on a comparison between the groups.

Based on the information presented, no clear impact of the prescribed treatment on MIC distribution or treatment of emergent pathogens was observed. The MAH was asked to present the data on MIC distribution based on the treatment received in patients who did not receive treatment from the other cohort (i.e., treated with a single treatment) as a sensitivity analysis. In case a patient switched

medication to the one used in the other cohort, the data of that patient should be censored from time of switch. The sensitivity analysis was provided and the results were largely in line with the primary analysis. No clear trends on MIC distribution could be observed in either group. It is acknowledged that this sensitivity analysis could potentially be biased, as switching to or concomitant use of the medication from the other cohort could be due to efficacy/resistance development.

No new safety signals were observed.

Based on the information presented, it can be agreed with the MAH that an amendment of the SmPC is not required.

3. Overall conclusion and recommendation

Based on the data presented, no clear impact of the prescribed treatment on MIC distribution was observed. The percentage of patients with a categorical increase in MIC was largely comparable between the 2 cohorts over time.

No impact of the prescribed treatment on treatment-emergent pathogens was seen.

The safety profiles in both TOBI Podhaler and non-TOBI Podhaler cohorts were similar. The percentage of participants experiencing AEs suspected to be related to the study treatment was similar. No new safety signals were observed. Based on the information presented, it was agreed that an amendment to the Product information is not required.

☒ **Fulfilled:**

No regulatory action required.