TBM100C / Tobramycin Inhalation Powder

Clinical Trial Protocol CTBM100C2419

A multicenter, human factors validation study in cystic fibrosis patients aged 6 years and older to evaluate the user interface of TOBI® Podhaler™ (tobramycin inhalation powder) using placebo capsules

On Aug 31, 2018, Mylan purchased from Novartis the worldwide rights to commercialize their global cystic fibrosis products TOBI Podhaler® and TOBI® solution.

All responsibilities for this study will be continued in comparable manner by Mylan, following Mylan's operational procedures

Mylan Specialty L.P.
781 Chestnut Ridge Road
Morgantown, WV 26505

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List of Abbreviations

AE	Adverse Event
CF	Cystic Fibrosis
CFR	US Code of Federal Regulations
cGMP	Current Good Manufacturing Practice
CRA	Clinical Research Associate
CRF	Case Report/Record Form (paper or electronic)
CPO	Country Pharma Organization
CRO	Contract Research Organization
CTRD	Clinical Trial Results Database
DSPC	1, 2-distearoyl-sn-glycero-3-phosphocholine
eCRF	Electronic Case Report Forms
EDC	Electronic Data Capture
FDA	Food and Drug Administration
FEV_1	Forced expiatory volume in one second
GCP	Good Clinical Practice
HCP	Health Care Professional
HF	Human Factors
HFE	Human Factors Engineering
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFU	Instructions for use
IRB	Institutional Review Board
IRT	Interactive Response Technology
MedDRA	Medical dictionary for regulatory activities
NDA	New drug application
PI	Prescribing Information
PIL	Patient Information Leaflet
PMR	Post-marketing Requirement
PSRM	Product Safety & Risk Management
REALM-SF	Rapid Estimate of Adult Literacy in Medicine-Short Form
SAE	Serious Adverse Event
SAF	Safety Set
SOC	System Organ Class
TIP	Tobramycin Inhalation Powder
TIS	Tobramycin Inhalation Solution
US	United States
WHO	World Health Organization
WoC	Withdrawal of Consent

Glossary of Terms

Close calls	Instances in which a user has difficulty or makes a use error that could result in harm, but the user takes an action to "recover" and prevents the harm from occurring.
Critical tasks	Critical tasks are defined as "the tasks that, if performed incorrectly or not performed at all, would or could cause serious harm".
Dosage	Dose of the study treatment given to the patient in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (e.g. prior to starting any of the procedures described in the protocol)
Human factors study	Is the study of designing equipment and devices that fit the human body and its cognitive abilities
Instructions for use	Is a set of written and illustrated steps describing how to use TOBI Podhaler. The instructions for use are included in each weekly pack.
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug" or "investigational medicinal product."
HF Interviewer	A qualified person will conduct the HF assessment sessions (assessment of TOBI Podhaler use and post-use interview).
HF Observer	A person will be required to capture study data and help monitor the HF sessions for subject safety.
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Subject	The terms "subject" and "patient" were used interchangeably in this protocol
Subject ID	A unique number assigned to each patient upon signing the informed consent
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), placebo/comparator active drug run-ins or background therapy
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of study consent (WoC)	Withdrawal of consent from the study is defined as when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

Amendment 01

Amendment rationale

The protocol was amended in response to feedback from the Food and Drug Administration (FDA) prior to the start of the study.

Changes to the protocol

- Removed the inclusion criteria regarding minimum score on REALM-SF literacy test (Section 4.1, Section 13.9)
- Added footnote to clarify that the urine pregnancy test will only be recorded as source documentation and that only subjects ≥14 years of age will take the REALM-SF Health Literacy Test (Section 6)
- Added clarification on how revisions to the IFU general notes and warnings will be assessed (Section 13.4.5)
- Added and clarified comprehension questions in the post-use discussion (Section 16)
- Clarified that comprehension of dosing task will be assessed post use, if comprehension of dosing is not reflected during the task (Section 17)

An opportunity was also taken to clarify language regarding the electronic data capturing system and its corresponding CRFs.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

Protocol summary

Protocol number	CTBM100C2419
Full Title	A multicenter, human factors validation study in cystic fibrosis patients aged 6 years and older to evaluate the user interface of TOBI Podhaler (tobramycin inhalation powder) using placebo capsules
Brief title	Human factors study to validate the user interface of TOBI Podhaler using placebo capsules
Sponsor and Clinical Phase	Mylan, Clinical Phase IV
Investigation type	Human factor assessment for inhalation device
Study type	Interventional (placebo-Podhaler device combination)
Purpose and rationale	The purpose of this study is to validate the user interface of TOBI Podhaler by establishing that the product can support safe and effective use for the intended users
Primary Objective(s)	The primary objective of this study is to evaluate whether the user interface of TOBI Podhaler can support safe and effective use for patients with CF by assessing use errors and close calls associated with the simulated inhalation of one dose using TOBI Podhaler
Secondary Objectives	None
Study design	open-label, non-randomized, single arm, placebo, single visit study (1 day)
Population	Males and females aged 6 years and older with a diagnosis of CF and with a FEV1 of at least 25% of normal predicted values for age, sex, and height are eligible for inclusion into this study. It is estimated that about 50 subjects will be enrolled with the aim of having 45 CF subjects completing the study. These completers will be divided among three age groups: 6-10, 11-17 and ≥ 18 years (approximately 15 subjects per age group). Subjects and caregivers should have no previous experience with the use of the Podhaler device.
Key Inclusion criteria	• Written informed consent or, parent/guardian consent and where applicable pediatric assent, must be obtained before any assessment is performed. • Male and female subjects aged 6 years and older. • Confirmed diagnosis of CF • FEV_1 value must be at least 25% of normal predicted values for age, sex, and height as documented in the patient's medical history (historical values within 3 months can be used for this criterion). • Able to comply with all protocol requirements. • Clinically stable in the opinion of the investigator.
Key Exclusion criteria	• Subjects currently enrolled in studies that are not considered as observational non-investigational studies. • If the subject or caregiver has used the Podhaler device previously. • Hemoptysis more than approximately 60 mL at any time within 30 days prior to enrollment. • History of hypersensitivity to the inhaled placebo dry powder (DSPC and/or calcium chloride powder). • Signs and symptoms of acute pulmonary disease, e.g. pneumonia, pneumothorax. • Clinically significant conditions or findings at enrollment that might interfere with the accurate and valid assessment of this study.

	• Subjects or caregivers who are considered potentially unreliable or considered unlikely to be compliant within the trial. • Pregnant women.
Study treatment	Placebo
Efficacy assessments	None
Key safety assessments	• Adverse event monitoring • Physical examinations and vital signs
Other assessments	• Human factor assessments, including: • The full Prescribing Information and the Patient Information Leaflet which contains the Instruction for Use will be part of the monthly TOBI Podhaler study pack provided. • An interview guide will provide a script for the HF Interviewer. • HF assessment checklist will be a paper form completed both by a qualified trained HF Interviewer and by the trained HF Observer. The checklist is used to collect all of the information required for data analysis on observed performance of use steps and response to comprehension questions. Demographic variables include but are not limited to subject age, gender, previous inhalation device experience, dominant hand, vision and dexterity challenges, health literacy (US school reading grade equivalent), educational attainment, and assistance provided to minors by caregivers during the study. Observed data collected for subject performance of use steps will be marked as pass or fail. Evident close calls will also be noted down. Key points from HF Interviewer-led discussion will be noted down on the HF Assessment checklists (e.g. observations, opinions of the subject etc.) – with the objective of capturing root cause of use errors and/or subject misunderstandings. • HF Assessment sessions will be digitally recorded in audio and video for future reference, and to allow independent checking of study data. • The used capsules (including photos) and Podhaler device(s) (if device(s) seem to be defective) will be subject to post-use inspection by the HF Interviewer in order to inform discussion on errors and their root cause.
Data analysis	All safety data, including AEs, SAEs, vital signs and concomitant medications will be summarized descriptively. Safety analysis will be based on descriptive statistics for subjects who have inhaled the contents of at least one capsule of placebo. Data collected from HF assessments will be summarized descriptively and analyzed using qualitative methods. The assessment against the study objectives will be based on: • Recording all use errors and close calls associated with the critical tasks of inhalation of one dose of TOBI Podhaler (i.e., inhaling the contents of four placebo capsules via the Podhaler device) by subjects (CF patients and/or their caregivers). • Assessing the root cause of use errors and close calls and establishing those which can be attributed to an element of the user interface. • Assessing the potential consequences of any errors or close calls, in particular, those which are 'critical' - could result in significant harm to the subject or other use. In addition, subjects' and caregivers' subjective feedback on the TOBI Podhaler system will be recorded and assessed.
Key words	Inhaled tobramycin, tobramycin inhalation powder, TOBI podhaler, human factors, user interface

1 Introduction

1.1 Background

TOBI® Podhaler™ (tobramycin inhalation powder) was approved by the United States (US) Food and Drug Administration (FDA) on March 22, 2013. It is indicated for the management of Cystic Fibrosis (CF) patients (aged 6 years and older) with *Pseudomonas aeruginosa* (*P. aeruginosa*). Tobramycin Inhalation Powder (TIP) is administered in repeated cycles of 28 days on-drug, inhaling the contents of 4 capsules using the Podhaler device (T-326 dry powder inhaler) twice daily, followed by 28 days off-drug period. The product required for the 28 day on-treatment period is provided to the subject in a monthly pack which contains 4 weekly packs, a reserve inhaler in a case, and the full Prescribing Information (PI). Each weekly pack contains one inhaler in a case, 7 blister cards, each blister card containing 8 capsules (the daily dose), and the Patient Information Leaflet (PIL) which contains the Instructions for Use (IFU).

The Podhaler device is a low-to-medium resistance, passive, capsule-based, dry powder inhaler. Capsules are manually loaded into the device and then pierced within the device by the user pressing a button that drives two sharp metal pins through the capsule shell. Inhalation through the device provides the energy required to aerosolize the powder and the airflow required to transport it out of the capsule and into the lung. The airflow resistance of the Podhaler device allows it to be used by patients with limited inspiratory capacity and young children.

This study is being conducted to fulfill US FDA post-marketing requirement (PMR) 1928-5:

Conduct a human factors validation study to demonstrate that the user interface of the product can support safe and effective use for the intended users. The human factors validation study should be conducted in patients aged 6 years and older under simulated yet representative of realistic use conditions and include all the critical tasks identified from your updated use-related risk analysis.

The study will enroll 50 CF subjects with the aim of having 45 subjects completing the study across three age groups of approximately 15 subjects each (6-10 years, 11-17 years, and ≥ 18 years). Only CF patients who are naïve to the use of the Podhaler device will be enrolled. These subjects will not be trained prior to using TOBI Podhaler and will be observed during the dosing procedure and interviewed afterwards to establish root cause of any errors during the inhalation process. The study will also require that any caregiver is also naïve to the use of the Podhaler device.

The study is a simulated use study conducted under realistic settings, in that subjects will inhale the content of placebo capsules through the TOBI Podhaler device. It involves Human Factor (HF) observational assessments conducted within a clinical study.

1.2 Purpose

The purpose of this HF study is to validate the user interface of TOBI Podhaler by establishing that the product can support safe and effective use for the intended users.

2 Study objectives and endpoints

2.1 Objectives and related endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective(s)	**Endpoint(s) for primary objective(s)**
• To evaluate whether the user interface of TOBI Podhaler can support safe and effective use for patients with CF	• Use errors and close calls associated with the simulated inhalation of one dose using TOBI Podhaler
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**
• Not applicable	• Not applicable
Exploratory Objective(s)	**Endpoint(s) for exploratory objective(s)**
• Not applicable	• Not applicable

3 Investigational plan

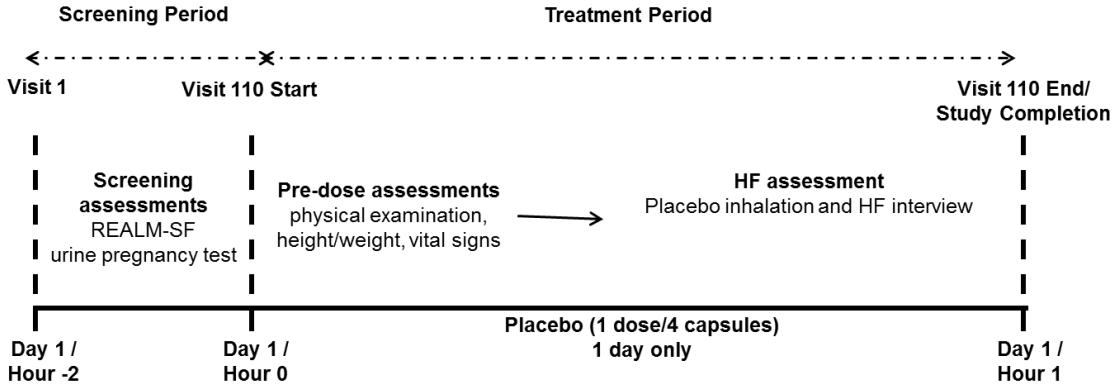
3.1 Study design

This is an open-label, non-randomized, single arm, single visit study (Figure 3-1) which will be conducted at CF centers to make sure the centers are adequately equipped and have trained personnel who are experienced in caring for CF patients.

Subjects (and caregivers, if applicable: all subjects aged under 18 will be accompanied throughout the study by a parent or guardian acting as a caregiver) will be consented into the study and asked to confirm that they have had no previous experience with using TOBI Podhaler or the Podhaler device. Subjects who meet the entry criteria will be enrolled in the study. Subjects (or subject and caregiver pairs) that are eligible will participate in a HF assessment to determine whether or not a subject (or subject/caregiver pair) can demonstrate safe and effective use of the Podhaler device. Only one subject or subject/caregiver pair will be assessed at a time.

A specialist HF engineering vendor will provide an Interviewer (HF Interviewer) to conduct the HF assessment session. A second person, an HF Observer (site personnel or provided by the vendor), will also be present and will be required to capture study data and support in monitoring the sessions for subject safety. The subject or subject and caregiver pair will be given the opportunity to familiarize themselves with the study materials and then demonstrate taking a four-capsule dose from the Podhaler device using placebo capsules (powder-filled). No training will be given. Subsequently, after all tasks are completed, the HF Interviewer will conduct a discussion with the subject or subject/caregiver pair to establish root cause of any misunderstanding (i.e. errors or close calls), in order to establish whether they can be attributed to the product user interface. The end of this interview denotes the end of the HF assessment and the end of the study. Each HF assessment session is expected to last approximately 60 minutes.

Figure 3-1 Study design



3.2 Human factors study assessment

Informed consent/assent will be obtained from subjects at enrollment. The informed consent form will include permission to record the HF assessment session on digital audio/video files

and store these recordings at the investigational site. Backup audio/video files will be taken and held by the specialist vendor performing the HF evaluation of this study in order to allow further analysis if required; these files will be stored securely and for a period of time as permitted by the applicable data protection laws. Assent will be sought from subjects who are younger than 18 years old, as required by the Institutional Review Board (IRB). Subjects 18 years and older and caregivers of younger subjects will be consented. Failure to attain the adult/caregiver's informed consent and younger subject's assent (as appropriate) to participate shall mean the subject is not eligible for enrollment in the study. Subject may discontinue their participation in the trial at any time and for any reason without prejudice. If premature withdrawal occurs for any reason, the HF Interviewer must make the effort to determine the reasons for premature withdrawal and record this information in the HF Assessment Checklist (See Section 6.5).

Prior to the commencement of the HF assessment session, the HF Interviewer will re-inform subjects and caregivers of the nature, content and purpose of the session, including what will be expected of a subject during participation. The use scenario is that of first use where no training has been received and the subjects and caregivers are asked to take a dose using the contents of the standard monthly pack. Although subjects will not be told how to use TOBI Podhaler, they will be given the minimum information that would be provided with a prescription: that TOBI Podhaler allows a subject to take TIP by using an inhaler, that they will be provided with a standard monthly pack containing all the materials required, and that caregivers should provide assistance to subjects using TOBI Podhaler (including preparing the dose for inhalation) particularly for those aged 10 years or younger. Caregivers of subjects aged 11 and over will be asked to give whatever support they would in reality provide to the subject in preparing and administering a new medication.

Before the HF assessment begins, the subject (and caregiver if appropriate) will be asked to sit in the interview room in a position which allows the HF Interviewer and HF Observer to have a clear view of the simulated TOBI Podhaler use. The HF Interviewer will outline the use scenario to the subject at time of handing over the monthly pack to ensure that the subject understands the context of use of TOBI Podhaler (Appendix 4).

3.2.1 Study materials and assessment process

A monthly pack will be provided that is matching the commercial configuration and presentation as approved by FDA, containing four weekly packs, full PI and a reserve Podhaler device in a case. Each weekly pack contains a Podhaler device, seven daily blister cards and the PIL which contains the IFU. Although only one dose is to be used by each subject, a monthly pack is provided in order to simulate the package that patients would receive when their prescription is filled; the HF assessment includes consideration of whether the subject can access and use the device and capsules when they are provided in a representative commercial configuration and presentation. Subjects will be given the opportunity to familiarize themselves with the study materials and labeling in advance of the first TOBI Podhaler use, and at any point during the dosing procedure, just as they would if using the product for the first time in reality. During the subject's (or subject and caregiver's) preparation and usage of placebo capsules and the Podhaler device, the HF Interviewer and HF Observer will independently complete a HF Assessment Checklist to capture data on use errors and close calls on all tasks as listed in Appendix 5. Both the HF Interviewer and HF Observer will watch closely and intervene should

the subject or caregiver be acting in a way which may endanger the subject's health or well-being. Furthermore, a member of the investigational site staff qualified for performing clinical trials, including assessment for medical safety, will be present during the study assessments to support monitoring of the subject's health or well-being from a clinical perspective (could be the HF Observer).

Used capsules will be collected by the HF Interviewer, double checked for remaining amount of powder and placed in order of use into a custom photo fixture to create a digital photographic image. This visual assessment will be done before the post-dose discussion in order that any failure to empty the capsules can subsequently be addressed and root cause established. The images will be stored at the investigational site. Backup copies of the image files will be labelled with the subject identification number, taken and held at a specialist vendor performing the HF evaluation in order to allow further analysis if required; these images will be destroyed after a period of time as permitted by local and study guidelines.

After the completion of the Podhaler device use, there will be a discussion session in which the HF Interviewer will ask about use errors and close calls to establish root cause. As it may not be possible for the HF Interviewer to note down all errors during the demonstration of use, he/she will consult the HF Observer before the post-dose discussion to compare notes and ensure that the list of discussion points is complete and properly recorded/captured in the Assessment Checklist. The HF Interviewer will also ask the subject (and caregiver as appropriate) open-ended questions to elicit feedback on any element of the user interface which was confusing or difficult.

Video recording of all assessment sessions will facilitate the resolution of any difference in assessments between the HF Interviewer and HF Observer.

3.2.2 HF Data

The HF data will comprise all successfully completed task steps, observed use errors and close calls and a record of the discussion investigating root cause of errors, close calls and difficulties.

Study analysis and reporting will primarily be qualitative. It will include discussion of the nature of any use errors and close calls that might reflect that the product interface has not been optimized. HF validation will include all critical tasks identified in preliminary analyses and evaluations.

Opportunities for use error have been identified via a detailed use-related risk assessment (TBM100C_HFA_314-TIP System FMECA_15) and their potential for causing harm assessed. The potential for harm to the user of the TOBI Podhaler is known to relate to two hazardous scenarios: clinically significant under- dosing and choking. With regard to the clinical significance of under-dosing: in the case of TOBI Podhaler, the therapeutic effect depends on adequate adherence to the dosing regimen (twice a day for 28 days). The clinical impact of an occasional missed or inadequately delivered dose is low. Adherence estimates from the pivotal registration trials for TOBI Podhaler ranged from approximately 90-95%, and the known clinical efficacy and safety data related to TOBI Podhaler are based on these trials. Furthermore, as each dose consists of the powder from 4 capsules, a use error that affects a single capsule has very low clinical impact. Therefore, in the case of TOBI Podhaler, a use error relating to dosing can only be "critical" if it is routinely repeated by the user.

The critical use errors associated with use of TOBI Podhaler that have the potential, however remote, to result in choking or clinically significant under-dosing are:

a. Placing capsule into the top of the mouthpiece rather than into the inhaler (potential for choking if capsule is inhaled)
b. Failure to adequately attach the mouthpiece before inhalation (potential for choking)
c. Routine failure to adequately pierce capsules (powder cannot be inhaled)
d. Routine failure to release blue (piercing) button before inhalation (powder cannot be inhaled).
e. Routine multiple piercing of capsules (powder may not be inhaled).
f. Routine instances of exhalation into the mouthpiece after loading and before inhalation (may lead to exhaled water vapor condensation in the capsule chamber resulting in powder agglomeration and reducing the available inspirable dose).
g. Routine instances of inadequate seal of mouth around mouthpiece.
h. Routine failure to inhale deeply (inadequate inhalation technique).
i. Routine blocking of inspiratory airflow with tongue/lips.
j. Routine failure to administer four capsules per dose.
k. Routine instances of swallowing capsules, as opposed to inhalation of capsule contents.
l. Failure to identify malfunctioning Podhaler device and use reserve inhaler
m. Routine failure to administer two doses per day.
n. Sustained failure to dispose of a Podhaler device after it has been used for one week.
o. Washing Podhaler (if the Podhaler is damp, it may reduce the available inspirable dose)

In this single assessment, it may not be possible to assess whether errors would be routinely repeated. Therefore all errors and close calls related to items a-l above will be investigated in post-dose discussion with the subjects (or subjects and caregivers), together with any failure to empty the capsules of powder (only a fine coating of powder should remain). In the post-dose discussion the HF Interviewer will seek to establish the root cause of errors and therefore whether the error is likely to reoccur (e.g. the subject fails to understand how to assess whether a capsule is emptied of powder) or unlikely (e.g. the subject fails initially to pierce a capsule because of a physical slip, but recognizes and corrects the error). Moreover, in all cases the HF Interviewer will seek to establish whether errors can be attributed to the design of the TOBI Podhaler user interface.

Items m, n and o above cannot be assessed in a single HF assessment session. However, comprehension of the IFU related to these three items was tested in a previous IFU validation study (CTBM100C2412) and data indicated that users could find and understand the relevant information. This will therefore not be tested in this study.

3.3 Rationale for study design

The study design follows the FDA recommendations on simulated use validation study design as described in the FDA guidance 'Applying Human Factors and Usability Engineering to Medical Devices' (FDA 2016). As per FDA guidance, this HF study intends to enroll sufficient patients to have a total of 45 subjects completing the study, with approximately 15 subjects in each of the three age groups: 6-10 years, 11-17 years, and ≥ 18 years. In order to minimize bias,

only CF patients and caregivers naïve to the use of the Podhaler device will be enrolled. These subjects will not be trained prior to using TOBI Podhaler. Placebo capsules instead of active drug will be used to mimic the real life self-administration of the active drug. Subjects will be observed during dosing and will be subsequently interviewed after completing the dose.

3.4 Rationale for dose/regimen, route of administration and duration of treatment

The use of placebo capsules instead of active TIP capsules should shorten the recruitment period by allowing enrollment of a broader range of TOBI Podhaler-naïve CF patients, including those who may be currently taking other inhalational treatments, or those who do not have a positive culture for *P. aeruginosa*. Also it allows for a flexible scheduling of subject's study visit day, independent of the subject's treatment. This is important as it will allow having a HF specialist at the site to observe the use, conduct post-dose discussions including root cause analysis of errors and collect subjective feedback. Involvement of this HF specialist in all study assessment sessions will ensure consistency.

3.5 Rationale for choice of comparator

Not applicable.

3.6 Purpose and timing of interim analyses/design adaptations

Not applicable.

3.7 Risks and benefits

Besides contributing to the assessment of the user interface that could be of benefit to patients, this trial may not offer a direct benefit to the subjects. Any risk to subjects in this trial will be minimized by compliance with the inclusion/exclusion criteria. No active drug is being administered but there is a potential risk of an allergic reaction from unrecognized sensitization to the placebo content (i.e. DSPC (1, 2-distearoyl-sn-glycero-3-phosphocholine) and/or calcium chloride).

As with all inhaled medications, cough and bronchospasm (asymptomatic or reported as wheeze) may occur; especially in subjects with known or suspected bronchial hyper-responsiveness.

Patients who experience any of these symptoms after dosing should be managed as per standard of care and the events should be recorded as Adverse Events (AEs).

Subjects will also be asked not to continue with any activity that they find painful. If bodily fluid is drawn or expelled, the HF Interviewer and Investigator/designated staff will quarantine the Podhaler device and anything that could have come into contact with the bodily fluid. The room will be sanitized and the subject will be treated as per the investigator decision. All AEs must be recorded on the appropriate CRF capturing AEs.

3.7.1 Low risks

- It is possible that the subjects may attempt to swallow a capsule.

Mitigation: the HF Interviewer and HF Observer will be trained to prevent subjects from swallowing capsules as far as possible along with any other potentially hazardous activity involving their interaction with the Podhaler device. Any attempts to swallow a capsule will be appropriately recorded by the HF Interviewer and HF Observer.

- It is possible that small fragments of the capsule can get into the user's mouth or throat after inhalation – this may disconcert the subject but is not harmful as the capsule material is pharmaceutical grade, manufactured under Current Good Manufacturing Practice (cGMP) and the capsule material is otherwise used for oral ingestion.

Mitigation: Subjects who express any concern after inhalation will be informed that they may feel a slight sensation of capsule fragments in the back of their throat and that these small pieces will not hurt them if swallowed or inhaled (per PIL).

3.7.2 Medium risks:

- It is important to keep CF patients away from one another to avoid cross-contamination and shared infections.

Mitigation: where subjects are seen in a clinical/research facility, assessment sessions will be arranged so that individuals are not waiting in a room together. The interview room tabletops and chairs will be sanitized as per the site's hygiene protocols. The HF Interviewer and HF Observer will sanitize his/her hands between sessions. CF patients will only be allowed to touch the materials that they will be using in the study. Other monthly packs will be stored outside the interview room and in a place where subjects will not enter.

- It is possible that the subject will put the capsule into the device without removing the mouthpiece first, and could inhale the whole capsule; it is also possible that the subject will put the capsule into the device and neglect to replace the mouthpiece before inhaling, and could inhale the whole capsule.

Mitigation: the HF Interviewer and/or HF Observer will be instructed to intervene immediately if they see that subjects have placed the capsule into the device without removing or replacing the mouthpiece and are about to inhale a capsule. This will be appropriately recorded by the HF Interviewer and HF Observer if it occurs.

4 Population

Males and females aged 6 years and older with a diagnosis of CF and with a forced expiratory volume in one second (FEV_1) of at least 25% of normal predicted values for age, sex, and height are eligible for inclusion into this study. It is estimated that about 50 subjects will be enrolled with the aim of having 45 CF subjects completing the study. These completers will be divided among three age groups: 6-10, 11-17 and ≥ 18 years (approximately 15 subjects per age group). Subjects and caregivers should have no previous experience with the use of the Podhaler device.

4.1 Inclusion criteria

Subjects eligible for inclusion in this study must fulfill all of the following criteria:

1. Written informed consent or, parent/guardian consent and where applicable pediatric assent, must be obtained before any assessment is performed.
2. Male and female subjects aged 6 years and older.
3. Confirmed diagnosis of CF by one or more of the following tests for CF as documented in the patient's medical history :
   - quantitative pilocarpine iontophoresis sweat chloride test of > 60 mmol/L or 60 mEq/L
   - genotype with identifiable CF-causing mutations on both chromosomes,
   - an abnormal nasal transepithelial potential difference characteristic of CF
4. FEV_1 value must be at least 25% of normal predicted values for age, sex, and height as documented in the patient's medical history (historical values within 3 months can be used for this criterion).
5. Able to comply with all protocol requirements.
6. Clinically stable in the opinion of the investigator.

4.2 Exclusion criteria

Subjects fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible subjects.

1. Subjects currently enrolled in studies that are not considered as observational non-investigational studies.
2. If the subject or caregiver has used the Podhaler device previously.
3. Hemoptysis more than approximately 60 mL at any time within 30 days prior to enrollment.
4. History of hypersensitivity to the inhaled placebo dry powder (DSPC and/or calcium chloride powder).
5. Signs and symptoms of acute pulmonary disease, e.g. pneumonia, pneumothorax, bronchospasm, acute respiratory infection.
6. Clinically significant conditions or findings at enrollment that might interfere with the accurate and valid assessment of this study.
7. Subjects or caregivers who are considered potentially unreliable or considered unlikely to be compliant within the trial.
8. Pregnant women.

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

All subjects will receive a placebo drug-device combination product. The placebo is provided in hard capsules containing 20 mg of placebo particles consisting of DSPC and calcium chloride. Each subject will receive a monthly pack containing:

- One reserve Podhaler device in its case
- One full PI (with the IFU incorporated)
- Four weekly packs, each containing
  - One Podhaler device in its case
  - Seven blister cards, each blister card containing eight placebo capsules
  - One PIL, which contains the IFU

Although only one dose is to be used by each subject, a monthly pack is provided in order to simulate the package that patients would receive when a prescription is filled. The following changes to the artwork and graphics will be made to comply with clinical study labeling requirements:

- a label will be attached to the monthly pack, each weekly pack, blister card and inhaler case indicating clinical trial number and caution statement
- the statement "28 mg per capsule" on the monthly pack, weekly pack and blister card will be replaced with "placebo capsule"

5.1.2 Additional treatment

No additional treatment beyond placebo is included in this study.

5.2 Treatment arms

This is a single arm study and all subjects will be assigned to placebo. The dose regimen for the test product is the contents of four capsules of placebo (i.e. one dose) inhaled via the Podhaler device.

5.3 Treatment assignment

At enrollment, all eligible subjects will be registered via Interactive Response Technology (IRT). The investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. In case a subject does not qualify, he/she can be re-screened at a later time point.

It is estimated that approximately 50 subjects will be enrolled with the aim of having 45 subjects completing the study including approximately 15 in each age group as follows: 6-10, 11-17 and ≥ 18 years. Recruitment will be controlled by IRT taking subject age into account.

5.4 Treatment blinding

Not applicable.

5.5 Treating the patient

Sponsor qualified medical personnel will be readily available to advise on study related medical questions or problems.

5.5.1 Patient numbering

Each patient is uniquely identified by a Subject Number assigned by the Sponsor. The Subject Number is composed of a site number and a sequential number. Once assigned to a patient, the Subject Number will not be reused.

Upon signing the informed consent form or, parent/guardian consent and where applicable pediatric assent, the patient is assigned the next sequential number available in electronic data capture (EDC) system. The investigator or his/her staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. The site must select the CRF book with a matching Subject Number in the EDC system to enter data. If the patient fails to start the inhalation of the study medication for any reason, the IRT must be notified within 2 days that the patient was not started. The reason for not being enrolled will be entered on the appropriate CRFs capturing screening and demography information.

5.5.2 Dispensing the study drug

Each study site will be supplied with study drug in packaging of identical appearance.

Each subject will receive the same study drug. The study drug packaging will have one label with the medication number.

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective the Sponsor's Quality Assurance department.

Medication labels will be in English and comply with the legal requirements of the US. They will include storage conditions for the study treatment but no information about the patient except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Subjects will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Sponsor's monitor or to the Sponsor's address provided in the investigator folder at each site.

5.5.3.2 Handling of additional treatment

Not applicable.

5.5.4 Instructions for prescribing and taking study treatment

The TOBI Podhaler with placebo drug will be dispensed by the investigator during the HF assessment session. Each subject will receive a full monthly pack matching the commercial monthly pack with the exception that placebo capsules instead of active capsules will be used (See Section 5.1). The site will NOT assist the subject with this inhalation at the site during this visit. Subjects will be given the opportunity to familiarize themselves with the study materials before performing the inhalation. Caregivers will be given the information – as provided in the PI and PIL – that they should help children who are 10 years of age and younger to use TOBI Podhaler and should keep watching them use their TOBI Podhaler until they are able to use it the right way without help. Caregivers of subjects aged 11 and over will be asked to give whatever support they would in reality provide to the subject in preparing and administering a new medication.

The capsule containing the placebo inhalation powder has to be released from the blister card, inserted into the Podhaler device, actuated and the placebo inhalation powder inhaled. Upon completion of this process, the next hard capsule (four in total) shall be removed from the blister card.

Administration of any other inhaled medications should be taken, and any chest physiotherapeutic measures should be completed prior to administration of study treatment. Also, the examinations which should be performed before study drug inhalation (Figure 3-1) need to be completed prior to study drug administration.

All study medication prescribed and dispensed to the subject must be recorded on the CRF.

The subject should be instructed to inform the investigator and HF Interviewer if he/she is unable for any reason to take the study drug as prescribed.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Dose adjustments and/or interruptions are not permitted. Study drug can only be dispensed and administered on the same day so interruptions for 1 day or more are not permitted.

5.5.6 Rescue medication

Since no active drug is planned to be administered, no rescue medication is needed in this study.

5.5.7 Concomitant medication

This study is a single visit study and it is expected that all study procedures will be completed in few hours. In the event a subject needs to take any medication at the site after enrollment

and/or during the study assessments (for e.g. for treatment of an emerging AE), the patient must notify the study site. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient is enrolled into the study must be recorded in the appropriate CRF.

5.5.8 Prohibited medication

All concomitant treatments are allowed at the investigator's discretion.

Subjects and caregivers with previous experience with the Podhaler device are not eligible for participation in this study.

5.5.9 Emergency breaking of assigned treatment code

Not applicable. This is an open-label study.

5.6 Study completion and discontinuation

5.6.1 Study completion and post-study treatment

The study will be considered completed for an individual subject when the subject completes the HF assessments.

Enrollment will be stopped when sufficient subjects have been recruited to achieve the intended population of 45 completed subjects in total (target of 15 subjects in each of the three age groups). Screened subjects will not be enrolled when the enrolled estimates have been reached to reach the target of 45 completed subjects.

The investigator will make sure appropriate medical care is being provided for all subjects who are prematurely withdrawn from the study.

5.6.2 Discontinuation of study treatment

Discontinuation of study treatment for a patient occurs when study drug is stopped earlier than the protocol planned duration, and can be initiated by either the patient or the investigator. In this single visit study, discontinuation will occur if the subject does not complete the inhalation of the 4 placebo capsules and/or the HF interview.

The investigator must discontinue study treatment for a given patient if, on balance, he/she believes that continuation would negatively impact the risk/benefit of trial participation.Study treatment must be discontinued under the following circumstances:

- Patient wish
- Any situation in which study participation might result in a safety risk to the patient
- Non-compliance of the subject with study procedures or investigator instructions, as per the investigator's judgment
- Emergence of Adverse Events (AE) when worsened from study entry or any newly occurring development of AEs
- Any other protocol deviation that results in a significant risk to the subject's safety

Subjects who are prematurely withdrawn from the study will be replaced by an equal number of newly enrolled subjects to meet the intended target of 15 subjects in each of the three age categories i.e., 45 completed subjects. However, premature withdrawal does not necessarily mean that the subject has failed to complete the HF assessment. It is possible in certain circumstances that subjects could demonstrate the ability to use TOBI Podhaler and carry out the dosing task without using all four capsules; for example, a 6 year-old child may not demonstrate sufficient attention or patience for the entire dose to be taken.

5.6.3 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent from the study is defined as when a patient:

- Does not want to participate in the study anymore

and

- Does not want any further assessments

and

- Does not want any further study related contacts

In this situation, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for the patient's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued, and no further assessments conducted, and the data that would have been collected will be considered missing.

Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal.

5.6.4 Loss to follow-up

Not applicable in this single visit, one day study.

5.6.5 Early study termination by the Sponsor

The study can be terminated by the Sponsor at any time for any reason. This may include reasons related to the benefit risk assessment of participating in the study, practical reasons, or for regulatory or medical reasons (including slow enrolment). The investigator will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

6 Visit schedule and assessments

All the assessments are listed in Table 6-1. In this table "x" indicates clinical assessments and "x^{HF}" indicates HF assessments.

Table 6-1 Assessment schedule

Period	**Screening**	**Treatment**
Visit Name	**Screening**	**Treatment**
Visit Number	**1**	**110**
Day/Hour	**1 / Hour -2**	**1 / Hour 0-1**
Obtain informed consent/assent	X	
Inclusion/Exclusion	X	
Demographics	X	
Height, Weight		X
Date of CF diagnosis		X
Physical examination		X[a]
Vital signs		X
Urine dipstick pregnancy test		X[a]
Medical history		X
Prior/Concomitant medication review		X
Adverse events/ Serious adverse events review		X
REALM-SF health literacy test	X[b]	
Audio/Video/ photo fixture equipment setup by interviewer		X^{HF}
Dispense monthly study drug package		X
Audio/Videotaping starting from opening monthly study drug package		X^{HF}
HF assessment - Subject performs inhalation, post-use inspection of inhaler/capsules		X^{HF}
HF discussion and root cause analysis of use errors		X^{HF}
Collect and record used/ unused capsules (plus Podhaler if required)		X^{HF}
Collect video/audio/picture data and HF assessment material (checklists, etc.)		X^{HF}
Study Completion disposition form		X

[a] Assessment to be recorded on source documents

[b] Level of health literacy for subjects (if ≥ 14 years of age) or caregivers (Source data)

[HF] Human Factors assessments

6.1 Information to be collected on screening failures

Subjects who are screened but are recognized to have not met all inclusion and exclusion criteria will be considered as screening failures. The study completion page for the screening period will be completed and data on demographics, inclusion/exclusion, and serious adverse event (SAE) will be collected for these patients. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

6.2 Patient demographics/other baseline characteristics

Subject demographic and baseline characteristic data to be collected on all subjects include: age, sex, race and ethnicity. Relevant medical history/current medical condition data includes data until the start of study treatment administration. Where possible, diagnoses and not symptoms will be recorded.

Conditions associated with CF disease and signs/symptoms but not limited to pancreatic insufficiency, sinusitis, diabetes mellitus, and clubbing, will be captured on the CRF capturing medical history.

6.3 Treatment exposure and compliance

No active treatment is being administered. Subjects are expected to complete one dose comprising of 4 capsules of placebo inhalation powder to demonstrate their comprehension of the labeling.

6.4 Efficacy

Not applicable for this open-label, placebo, one day study.

6.5 Human factors assessment

The HF assessment is summarized in Section 3.2 and detailed in Appendix 1 and includes the following:

- An interview guide will provide a script for the HF Interviewer (Appendix 4).
- HF assessment checklist will be a paper form completed both by a qualified trained Interviewer from a specialized HF vendor and by the trained HF Observer. Data capture by two independent assessors will help to ensure accurate and unbiased recording. The checklist is used to collect all of the information required for data analysis on observed performance of use steps and response to comprehension questions. Demographic variables include but are not limited to subject age, gender, previous inhalation device experience, dominant hand, vision and dexterity challenges, health literacy (US school reading grade equivalent), educational attainment, and assistance provided to minors by caregivers during the study. Observed data collected for subject performance of use steps will be marked as pass or fail. Evident close calls will also be noted down. Key points from Interviewer-led discussion will be noted down on the HF Assessment checklists (e.g. observations, opinions of the subject etc.) – with the objective of capturing root cause of use errors and/or subject misunderstandings.
    - HF Assessment sessions will be digitally recorded in audio and video for future reference, and to allow independent checking of study data.
    - The used capsules (including photos) and Podhaler device(s) (if device(s) seem to be defective) will be subject to post-use inspection by the HF Interviewer in order to inform discussion on errors and their root cause.

6.5.1 Appropriateness of Human Factors assessment

The HF assessment described in this protocol is in accordance with FDA guidance and current standards for HF validation of medical devices.

6.6 Safety

6.6.1 Physical examination

A short physical examination will be performed and will include the examination of general appearance and vital signs. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent or, parent/guardian consent and where applicable pediatric assent, must be included in the CRF capturing medical history. Significant findings made after first administration of investigational drug which meet the definition of an Adverse Event (AE) must be recorded on the appropriate CRF capturing AEs.

6.6.2 Vital signs

Vital signs, including systolic and diastolic blood pressure, radial pulse rate (over a 30-second interval), respiratory rate, and body temperature will be recorded. Single measurements will be performed. All blood pressure, radial pulse rate, and respiratory rate measurements should be taken after the subject has rested in the sitting position for at least 10 minutes.

6.6.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured.

6.6.4 Laboratory evaluations

Not applicable.

6.6.5 REALM-Short Form health literacy test

The REALM-SF test is a 7-item word recognition test to provide investigational sites with a valid quick assessment of subject health literacy. The REALM-SF has been validated and field tested in diverse research setting, and has excellent agreement with the 66-item REALM instrument in terms of grade-level assignments (Appendix 2).

This reading level test will be performed on Visit 1 to assess subjects (if ≥ 14 years of age) or caregiver's level of health literacy. The evaluation will be performed by the investigational sites and this form will be kept as source data. Scores and Grade Equivalents will be collected on the HF assessment checklist as they may assist the HF Interviewer when assessing a subject's and/or caregiver's response to the IFU/labelling.

6.6.6 Electrocardiogram (ECG)

Not applicable as the subject is administrated placebo on one day.

6.6.7 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have a urine pregnancy test before starting the inhalation process. The urine dipstick pregnancy test will be performed locally and will be captured ONLY in the source.

6.6.8 Appropriateness of safety measurements

Safety assessments selected are deemed relevant for the indication of CF and this patient population participating in this HF assessment within a clinical trial setting.

6.7 Other assessments

6.7.1 Clinical Outcome Assessments (COAs)

Not applicable.

6.7.1.1 Clinician Reported Outcomes (ClinRO)

Not applicable.

6.7.1.2 Patient Reported Outcomes (PRO)

Not applicable.

6.7.1.3 Performance Outcomes (PerfO)

Not applicable.

6.7.1.4 Observer Reported Outcomes (ObsRO)

Not applicable.

6.7.1.5 Proxy Reported Outcomes

Not applicable.

6.7.2 Resource utilization

Not applicable.

6.7.3 Pharmacokinetics

Not applicable.

6.7.4 DNA sampling

Not applicable.

6.7.5 Other biomarkers

Not applicable.

7 Safety monitoring

7.1 Adverse events

An AE is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject *after providing written informed consent* for participation in the study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The occurrence of adverse events must be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events.

Adverse events must be recorded in the appropriate CRF capturing AEs under the signs, symptoms or diagnosis associated with them, accompanied by the following information:

- the severity grade
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities
- its relationship to the study treatment
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
- whether it constitutes a serious adverse event (SAE - See Section 7.2 for definition of SAE) and which seriousness criteria have been met.
- action taken regarding study treatment

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- [investigational] treatment dose not changed (e.g. further observation only)
- [investigational] treatment dose increased/reduced
- [investigational] treatment interrupted/withdrawn
- concomitant medication or additional therapy given

- patient hospitalized/patient's hospitalization prolonged (see Section 7.2 for definition of SAE)
- its outcome (not recovered/not resolved; recovered/resolved; recovered/resolved with sequelae; fatal; or unknown)

Once an AE is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common risks with inhalation of placebo powder will be included in the informed consent and should be discussed with the patient during the study as needed.

Patients who experience any of the symptoms of the risks associated with placebo (see Section 3.7) after dosing should be managed as per standard of care and the events should be recorded as Adverse Events (AEs).

The investigator must also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to the Sponsor.

7.2 Serious adverse events

7.2.1 Definition of SAE

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, e.g. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to Annex IV, ICH-E2D Guideline).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to Annex IV, ICH-E2D Guideline).

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days after the last study visit must be reported to the Sponsor's safety department within 24 hours of learning of its occurrence. Any SAEs experienced after the 30-day period after the last study visit should only be reported to the Sponsor's safety if the investigator suspects a causal relationship to study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess the relationship of each SAE to study treatment, complete the SAE Report Form in English, and submit the completed form within 24 hours to the Sponsor. Detailed instructions regarding the submission process and requirements for signature are to be found in the investigator folder provided to each site.

Follow-up information is submitted as instructed in the investigator folder. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

Information about common risks with inhalation of placebo powder will be included in the informed consent and should be discussed with the patient during the study as needed.

7.3 Liver safety monitoring

Not applicable as the subject is administrated placebo on one day.

7.4 Renal safety monitoring

Not applicable as the subject is administrated placebo on one day.

7.5 Reporting of study treatment errors including misuse/abuse

The assessment of use errors with TOBI Podhaler is the objective of this study (please refer to Section 3.2 for a description of HF assessments).

7.6 Pregnancy reporting

To ensure patient safety, each pregnancy occurring after signing the informed consent must be reported to the Sponsor within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the Sponsor's Product Safety & Risk Management Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment. Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

7.7 Prospective suicidality assessment

Not applicable as the subject is administrated placebo on one day.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Sponsor's representative will review the protocol and data capture requirements (i.e. eCRFs) with the investigators and their staff. During the study, the Sponsor employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a Sponsor's designated CRO organization. Additionally, the Sponsor's or designee's organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Sponsor's Clinical Teams to assist with trial oversight.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. Data required for the HF assessment will be recorded on the HF assessment checklist only. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. The Sponsor's monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients/subjects will be disclosed.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRFs) using fully validated secure web-enabled software that conforms to US CFR 21 Part 11 requirements. Designated investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The Investigator must certify that the data entered into the electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

HF assessment data collection

HF assessment data will be recorded on paper HF Assessment Checklist forms, interview sessions will be digitally recorded on audio/video and digital photo images of used capsules will be created.

The paper Assessment Checklist forms will be completed for each subject by the HF Interviewer and the HF Observer independently in ink (hardcopies). These are original documents and will be handled, maintained and archived by the specialist HF vendor and copies retained at the investigator site. Any amendments will also be dated and initialled and rationale provided in the HF study report.

Original digital recorded interview sessions and digital photo images will be kept securely at the investigational site. Backups will be made and securely managed and archived by the HFE specialist vendor. All information managed by the HF specialists must be traceable to these source documents.

8.3 Database management and quality control

The Sponsor's personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff is required to respond promptly to queries and to make any necessary changes to the data.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Data from the HF assessment checklist are entered into a database held by the HF specialist vendor staff following their own internal standard operating procedures that have been reviewed and approved by the Sponsor. These data will be written up and provided as a report. Collected data may be transferred to the Sponsor, if required.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time can only be made after written agreement by Sponsor's Clinical Operations Department.

8.4 Data Monitoring Committee

Not required.

8.5 Adjudication Committee

Not required.

9 Data analysis

The analysis will be conducted on all subject data at the time the trial ends. Any data analysis carried out independently by the investigator should be submitted to the Sponsor before publication or presentation.

Data collected from clinical and human factor assessments will be presented. All safety data, including AEs, SAEs, vital signs and concomitant medications will be summarized descriptively. Safety analysis will be based on descriptive statistics for subjects who have inhaled the contents of at least one capsule of placebo.

Unless otherwise specified, clinical data will be summarized as follows. Categorical variables will be presented as the number and percentage of subjects in each category. Continuous variables will be summarized using descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum).

For each item of the HF Assessment Checklist the number and percentage of subjects with each response will be summarized descriptively. Where relevant: number, percentage, average, standard deviation, minimum and maximum shall be presented per age group. A bar chart illustrating each response will also be displayed. A comprehensive data table will also be provided which gives details of all errors related to each task step listed by participant.

A report from the HF vendor will be prepared summarizing both objective performance data and subjective data collected. The results attained, the difficulties, deviations and/or complaints observed/reported will be reported and analyzed following completion of the study. Analysis and discussion of observations and qualitative assessment will also be presented.

9.1 Analysis sets

The screen Failure Set: The Screen Failure Set included all patients who signed the informed consent and failed the screening.

The Safety set (SAF) will consist of all subjects that enter the study and who have inhaled the contents of at least one capsule of placebo regardless of whether the related HF assessment is completed.

9.2 Patient demographics and other baseline characteristics

Appropriate descriptive statistics for demographics (age, sex, race and ethnicity), disease history, CF signs and symptoms - and previous medications will be presented to describe the study population overall and by the three age categories.

9.3 Treatments

Not applicable. Subjects are expected to complete one dose comprising of 4 capsules of placebo powder to demonstrate their comprehension of the instructions.

9.4 Analysis of the primary variable(s)

Data collected from HF assessments will be summarized descriptively. The assessment against the study objectives will be based on:

- recording all use errors and close calls associated with the critical tasks of inhalation of one dose of TOBI Podhaler (i.e., inhaling the contents of four placebo capsules via the Podhaler device) by subjects (CF patients and/or their caregivers). The critical tasks associated with inhalation of one dose of TOBI podhaler are detailed in Section 13.6.
- assessing the root cause of use errors and close calls and establishing those which can be attributed to an element of the user interface
- assessing the potential consequences of any errors or close calls, in particular, those which are 'critical' - could result in significant harm to the subject or other use

In addition, subjects' and caregivers' subjective feedback on the TOBI Podhaler system will be recorded and assessed.

Study analysis and reporting will primarily be qualitative with the aim to establish either that the TOBI Podhaler user interface is safe and effective for its intended users, or that risk remains to the user. If any risk remains; potential mitigations will be discussed based on the root cause of errors observed in the study. Please refer to Appendix 1 for a detailed description study data collection and analysis.

9.4.1 Primary Variable(s)

The primary variables of this study include the use errors and close calls associated with the inhalation of one dose using TOBI Podhaler.

9.4.2 Statistical model, hypothesis, and method of analysis

Data analysis does not include statistical testing of any hypothesis. Since all subjects receive placebo in this single arm design, there will be no formal statistical testing performed in the study. Data will be summarized descriptively.

9.4.3 Handling of missing values/censoring/discontinuations

There will be no imputation for missing data.

9.4.4 Sensitivity analyses

Not applicable.

9.5 Analysis of secondary variables

Not applicable.

9.5.1 Efficacy variables

Not applicable.

9.5.2 Safety variables

Adverse events and SAEs will be coded according to the MedDRA coding system and summarized by system organ class (SOC) and preferred term by onset date within the study population overall and within each age group. For this purpose, the same event, as defined by preferred term, will be counted only once for each subject. AEs will also be summarized by

SOC, preferred term, and maximum severity within the study population overall and within each age group. AEs resulting in withdrawal of treatment will be summarized by SOC, preferred term.

Appropriate summary statistics will be provided for vital signs.

9.5.3 Resource utilization

Not applicable.

9.5.4 Pharmacokinetics

Not applicable.

9.5.5 DNA

Not applicable.

9.5.6 Biomarkers

Not applicable.

9.5.7 PK/PD

Not applicable.

9.6 Analysis of exploratory variables

Not applicable.

9.7 Interim analyses

Not applicable.

9.8 Sample size calculation

The FDA guidance document 'Applying Human Factors and Usability Engineering to Medical Devices' (FDA 2016) suggests a minimum of 15 subjects per distinct user group is required for validation testing; as described in "Appendix B - Considerations for Determining Sample Sizes for Human Factors Validation Testing". Per the guidance, "The FDA views populations as distinct when their abilities or the nature of their device interactions are expected to be different". In the case of CF, age is the only characteristic which is likely to contribute to variation in abilities and/or device interaction. Therefore, the study will include 45 subjects with approximately 15 subjects in each of the three age groups (6-10 years, 11-17 years, and ≥ 18 years).

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible patients/subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if applicable after such consent has been provided by a legally acceptable representative(s) of the patient. In cases where the patient's representative gives consent, the patient must be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she must indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

The Sponsor will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by the Sponsor before submission to the IRB/IEC, and a copy of the approved version must be provided to the Sponsor's or designated CRO's monitor after IRB/IEC approval.

10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to patients/subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Sponsor's monitors, auditors, Sponsor's Quality Assurance representatives, designated agents of the Sponsor, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform the Sponsor immediately that this request has been made.

10.4 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the

results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

10.5 Quality Control and Quality Assurance

The Sponsor maintains a robust Quality Management system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Sponsor's systems are performed by Sponsor's Inspection Readiness and Clinical Oversight department. The clinical audit process uses a knowledge/risk-based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to the Sponsor's written processes.

11 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients/subjects should be administered as deemed necessary on a case by case basis. Under no circumstances is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by the Sponsor and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

11.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by the Sponsor, health authorities where required, and the IRB/IEC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients/subjects may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 Safety Monitoring must be followed.

12 References

Arozullah AM, Yarnold PR, Bennett CL et al. (2007). Development and validation of a short-form, rapid estimate of adult literacy in medicine. Med Care; 45(11):1026-33.

Miller MR, Hankinson J, Brusasco V, Burgos F, et al, ATS/ERS Task Force (2005) Standardisation of spirometry. Eur Respir J; 26(2):319-38.

Molimard M, Raherison C, et al, (2003) Assessment of Handling of Inhaler Devices in Real Life: An Observational Study in 3811 Patients in Primary Care J Aerosol Med.;16:249–54.

Newman SP. (2005) Inhaler treatment options in COPD. Eur Respir Rev.;14:102–8.

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13 Appendix 1

Discussion of Human Factors Study Design

13.1 Important Note

The usability of the TOBI Podhaler system was validated in observational simulated use studies conducted in the US and the EU in 2011, in which subjects were assessed, after receiving representative training, as they simulated dosing using empty capsules. A human factors engineering/ usability engineering summary report was subsequently submitted as part of the New Drug Application (NDA) to the FDA (TBM100_HANDR_Human factors engineering report_01).

The FDA-approved TOBI Podhaler IFU was tested in an actual-use IFU validation study (CTBM100C2412) in which subjects used placebo-filled capsules to demonstrate the dosing procedure after reading the IFU. This study was conducted to meet a post-marketing requirement (PMR 1928-3), following which a number of IFU amendments were implemented in agreement with FDA.

The study defined in this protocol is being conducted to fulfill the following PMR 1928-5:

Conduct a human factors validation study to demonstrate that the user interface of the product can support safe and effective use for the intended users. The human factors validation study should be conducted in patients aged 6 years and older under simulated yet representative of realistic use conditions and include all the critical tasks identified from your updated use-related risk analysis.

Background information is included here for the convenience of the reader/reviewer of the human factors engineering (HFE) context of the study and of the HF elements of the study design.

13.2 Discussion of Terminology

The application of HFE to medical devices is fundamentally a risk control process. The focus is on "critical aspects of device use potentially resulting in hazards to users and subjects". These critical aspects of device use are labeled "critical tasks" and they are defined and prioritized on the basis of the hazard associated with them. It is the severity of the potential harm resulting from failure at a task that is the key factor in defining task criticality.

As part of the HFE activities during the development of TOBI Podhaler, a detailed use-related risk assessment has been completed. Opportunities for use error have been identified and their potential for causing harm assessed. As a result, it has been possible to define "critical use errors", based on the severity of the potential harm resulting from the use error.

In this document the following hierarchical risk-based terminology is used:

Critical	a task, task step, use-error or miscomprehension of an instruction is labelled 'critical' if potential for significant harm is associated with it.

Essential	a task or task step that must be completed in order that tobramycin powder is delivered to the lung is labelled 'essential'. Failure to complete an essential task step does not necessarily constitute a critical use error.
Desirable	a task step or instructed technique is labelled 'desirable' if it has been included either as a helpful suggestion to make a task easier to complete or as a description of optimal technique which has a risk mitigation function or has limited impact on task outcome. No hazardous consequences follow inevitably from failure to complete a desirable task step or follow a desirable instructed technique.

In particular:

- A critical task is one that has one or more specific critical use error(s) associated with it.
- A critical use error is a failure to complete, or sub-optimal performance of, a critical task that results in potential for significant harm.

13.3 Introduction

TOBI® Podhaler™ (tobramycin inhalation powder) was approved by the United States (US) Food and Drug Administration (FDA) on March 22, 2013. It is indicated for the management of Cystic Fibrosis (CF) patients (aged 6 years and older) with *Pseudomonas aeruginosa* (*P. aeruginosa*). Tobramycin Inhalation Powder (TIP) is administered in repeated cycles of 28 days on-drug, inhaling the contents of 4 capsules using the Podhaler device (T-326 dry powder inhaler) twice daily, followed by 28 days off-drug period. The product required for the 28 day on-treatment period is provided to the subject in a monthly pack which contains 4 weekly packs, a reserve inhaler in a case, and the full Prescribing Information (PI). Each weekly pack contains one inhaler in a case, 7 blister cards, each blister card containing 8 capsules (the daily dose), and the Patient Information Leaflet (PIL) which contains the Instructions for Use (IFU).

The Podhaler device is a low-to-medium resistance, passive, capsule-based, dry powder inhaler. Capsules are manually loaded into the device and then pierced within the device by the user pressing a button that drives two sharp metal pins through the capsule shell. Inhalation through the device provides the energy required to aerosolize the powder and the airflow required to transport it out of the capsule and into the lung. The airflow resistance of the Podhaler device allows it to be used by patients with limited inspiratory capacity and young children.

Capsule based dry powder inhalers of this "load, pierce, inhale" type have been in use for many decades and examples are currently on the market in the US (e.g. Handihaler® for delivery of Spiriva®, Neohaler® for delivery of Arcapta®).

13.4 Intended Users, Use, Use Environments and Training

13.4.1 Intended Users

TOBI Podhaler is indicated for the management of CF patients with *P. aeruginosa* of age 6 years and older.

Caregivers are advised in the PIL to provide assistance to children starting treatment with TOBI Podhaler, particularly to children aged 10 years or younger, and should continue to supervise them until children are able to use the TOBI Podhaler system correctly without help.

Typical CF patients have experienced a range of inhalation delivery systems, are familiar with orally inhaled therapies, are highly engaged in the treatment of their condition and are interested in new advances in treatment technology.

13.4.2 Intended Use

The single intended function of the TOBI Podhaler system is the delivery of doses of tobramycin inhalation powder (TIP) to the lung.

A dose of TOBI Podhaler for adults and pediatric patients (6 years of age and older) is the inhalation of the contents of four 28 mg capsules, taken twice daily for 28 days.

13.4.3 Environments of Use

The use of TOBI Podhaler is not limited to any specific environments, nor is it the case that TOBI Podhaler must be usable in certain specific environments. The user is free to choose where they use the system.

13.4.4 Training

It is usual for all CF patients and their caregivers to be trained by a healthcare professional (HCP) on the use of any new inhalation product upon first prescription and to discuss it during their regular visits. A survey of relevantly experienced HCP's conducted by the Sponsor supported this view.

This study is a test of the user interface and, therefore, study subjects will not be trained in order that the user interface can be assessed and validated as per FDA request.

13.4.5 Description of Device Use and User Interface

The TOBI Podhaler system consists of:

- One reserve Podhaler device in its case
- One full PI (with IFU incorporated)
- Four weekly packs, each containing
  - One Podhaler device in its case
  - Seven blister cards, each blister card containing eight placebo capsules
  - One PIL, which includes the IFU

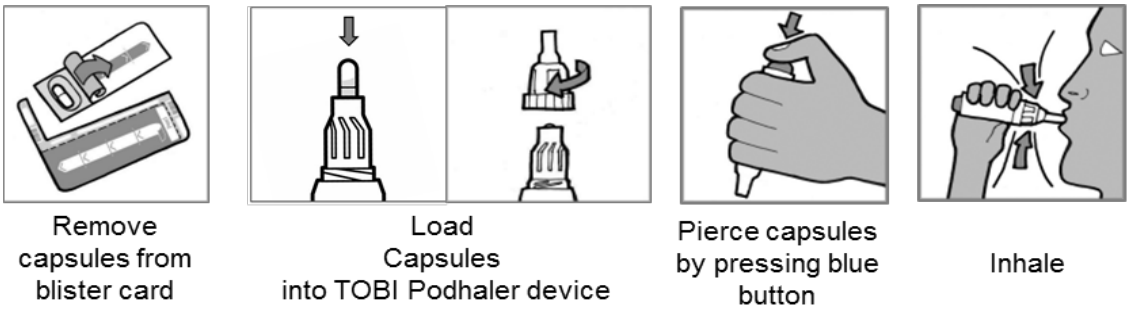
The IFU describes all aspects of user interaction with the product, including routine dosing procedure (numbered steps 1 to 23) with checks and error correction, general notes and warnings, and storage instructions. The approved IFU is included in Appendix 3.

The single primary function of the system is the delivery of doses of TIP to the lung. To successfully complete this task the user must understand the dosage regimen (28 days on treatment, 2 doses per day, 4 capsules per dose; 28 days off treatment) and complete the following essential task steps for each capsule used:

- remove capsules from the blister card
- load capsules into the Podhaler device
- pierce capsules by fully depressing the blue button
- inhale adequately through the Podhaler device

These core task steps are illustrated in Figure 13-1.

Figure 13-1 Task steps for preparation and inhalation of each capsule



The IFU explain in detail how to complete the essential elements of these task steps, i.e. how to achieve the task objective. For example, in order to load capsules into the Podhaler device the user must unscrew the mouthpiece (step 3), place a capsule into the capsule-chamber (step 7) and put the mouthpiece back on his/her Podhaler device (step 8).

Some elements of the instructions are helpful suggestions provided to make the task easier for the user to complete. For example, instruction step 2 suggests standing the Podhaler device in the base of the case during capsule loading. This may be helpful, and is therefore desirable, but it is not essential with regard to dose accuracy.

Some elements of the instructions are descriptions of optimal technique. For example, step 10 instructs the user to breathe out (exhale) all the way. This is desirable for optimal drug delivery to the lung, but a failure to fully exhale has only a minor impact on drug delivery.

Several of the instructions are techniques or procedures that are included as mitigations of known use-related risks. These include:

- instruction to inhale twice with each capsule. Most users will have sufficient inspiratory capability to empty a capsule with a single inhalation. The instruction to inhale twice mitigates the risk of incomplete powder clearance.
- instruction to inspect the capsule after use (step 17). This mitigates the risk of incomplete clearance of powder from a capsule that could be caused by omitted or inadequate piercing, inadequate inhalation or failure of device performance.

These are desirable actions, but not essential to dosing accuracy.

The instructions also contain general notes and warnings, and instructions on storage of the TOBI Podhaler. The revisions that were made to the IFU following the completion of CTBM100C2412 will be validated in this study. Revisions to the IFU general notes and warnings section which describe task steps will be assessed via observation of subjects' task performance, with any errors, difficulties or close calls addressed in post-use discussion to

establish root cause. Subjects will also be asked to review and comment on the clarity of the IFU, including revisions. Revisions which are not related to task steps will be assessed via comprehension questions.

13.5 Summary of HF validation studies and postmarketing complaints data

13.5.1 Summary of TOBI Podhaler HF Validation Study, completed 2011

An HF validation study of TOBI Podhaler, using empty capsules, was successfully completed; the findings formed part of the NDA to the FDA (TBM100_HANDR_Human factors engineering report_01). This study confirmed the understanding of the use and usability of the system that had been developed in earlier formative studies.

The TOBI Podhaler validation study was conducted with a total sample of 62 subjects or subject/caregiver pairs in the US in 2011. All subjects had a clinical diagnosis of either CF (n=12) or another respiratory disease requiring use of inhaled medications (n=50). At least 15 subjects completed the study in each age category: 6-8 years; 9-12 years; 13-17 years and ≥ 18 years.

All subjects were given a brief training before the assessment in accordance with a representative training approach defined in a study with 5 US specialist HCPs. 35 subjects also took part in a 'take-home' study involving home use for 5 days after which subjects returned for a second assessment (the post-1-week assessment) and submitted their home-use capsules and a home dosing diary for assessment and discussion.

The interview after the take-home study allowed the assessment of likely performance in steady state use. No critical errors, i.e. a failure to complete a critical task that results in potential for significant harm, were seen. With regard to the known use errors with capsule inhalers reported in the literature (Molimard et al 2003, Newman 2005), this 2011 validation study found a similar pattern of non-critical use error occurrence to the known use errors reported in the literature:

- difficulty inserting capsule – error rate 1.4% of capsules in post-1-week use (2 subjects each dropped one capsule while loading)
- failure to pierce effectively – error rate 1.5% of capsules in post-1-week use (2 subjects each failed to pierce one capsule)
- failure to breathe out before actuation – error is device-independent. High error rate (65%/n=22 participants at post-1-week use) in study, despite training, suggests a study artifact due to the use of empty capsules/lack of realistic simulation.
- failure to exhale away from mouthpiece – error rate was reduced from 13%/n=8 participants on first use to zero in post-1-week use
- failure to inhale through the mouthpiece – error rate was reduced from 6%/n=4 participants on first use to zero in post-1-week use
- failure to hold breath for a few seconds after inhalation – error rate was reduced from 11%/n=7 of participants on first use to zero in post-1-week use

In addition data was collected on five other use errors specific to TOBI Podhaler's HF study:

- difficulty in opening blister and removing capsule – error rate 2.2% of capsules in post-1-week use as n=3 subjects dropped one capsule each

- failure to invert inhaler during piercing – error rate increased from 32.3% (20/62) to 43% (15/35) study participants between first use and post-1-week. This suggests non-compliance or perhaps a study artifact.
- failure to inhale twice – error rate 11.8% (4/34) of participants in post-1-week use. This may have been a study artifact – the study capsules were empty, so there was no real need to inhale twice.
- failure to check capsules after use - error rate increased from 32.3% (20/62) failing to check at least one capsule to 50% (17/34) of study participants between first use and post-1-week. This suggests non-compliance, probably a study artifact (study capsules were empty, so there was no real need to check).
- failure to use 4 capsules per dose - zero errors on post-1-week use.

The most common difficulty experienced by participants in the validation study was that of opening the blister cards to retrieve capsules. The blister cards are child resistant and intentionally robust, in order to provide necessary protection of the capsules from moisture. This results in physical and cognitive demands on users. Despite experiencing difficulties, success rate at accessing and retaining control over accessed capsules was very high: 98% at post-1-week assessment.

No critical use errors (a failure to complete a critical task that results in potential for significant harm) were observed in the post-1-week assessment sessions. The validation study established that TOBI Podhaler can readily be used safely and effectively by trained users.

13.5.2 Summary of TOBI Podhaler IFU validation study CTBM100C2412

The IFU validation study was conducted in 2014-2015 in the US with 45 CF patients, accompanied by caregivers where the patient was aged 17 years or less. The study was conducted to meet the following PMR 1928-3: “An actual use human factors study to validate the approved IFU. The study will enroll 45 subjects in total with three age groups of approximately 15 subjects each: 6- 10 years, 11-17 years, and > 18 years. Only CF patients naïve to use of the Podhaler device will be enrolled. These subjects will not be trained prior to reading the IFU and will be observed during the study.”

The study showed that the majority of CF patients and/or their caregivers can understand and follow the approved IFU without prior training. All patients understood the basic sequence of operation of the Podhaler device: load, pierce and inhale.

Patients were asked to take one dose. Of the 45 patients, 31 patients emptied the powder from all 4 capsules completely. Of the 14 patients who did not completely empty the powder from all 4 capsules, 4 patients cleared more than ¾ of the total powder and 6/14 patients cleared approximately ¾; 4/14 patients cleared less than ¾ of the total powder.

Six of the 14 patients who did not empty the capsules failed for reasons which are not attributable to the IFU, such as failure to engage with the IFU or failure of the caregiver to understand that a child was not inhaling.

However, 8 of the 14 patients who did not empty the capsules failed because, following incorrect inhalation technique or piercing error, they did not understand the checking procedure outlined in IFU step 17 – in particular, what a correctly emptied capsule should look like.

Moreover, from observation some patients found this step difficult to navigate and understand and 10/45 patients mentioned confusion or difficulty around checking capsules in post-use discussion.

Misunderstanding the recommendation to inhale twice from each capsule was a contributory cause of failure in 4 cases, although it is evidently possible for some patients to empty the capsules with only one inhalation. 8/45 mentioned confusion or difficulty with the repeat inhalation step.

Some IFU changes were recommended following the study, in particular to clarify the capsule check step and the requirement to inhale twice from each capsule. Changes were agreed with the FDA and are shown in the updated IFU in Appendix 3.

13.5.3 Postmarketing complaints

TOBI Podhaler was first launched in Canada in May 2011. Since then it has been launched in more than 38 countries.

A cumulative review conducted in TOBI Podhaler Periodic Safety Update Report (Aug 2016) revealed 64 cases of medical device issues with the majority of the complaints being related to clogging of the device or inability to inhale the entire dose from the device. The review of these cases did not reveal any new relevant safety concern or any trend of specific safety concern.

13.6 User Task Selection / Use Error Criticality Definition for IFU Validation

In the FDA guidance it is suggested that 'critical tasks' should be identified and selected for assessment in a simulated use validation study.

Empirical and analytical data have been used to determine use errors associated with critical tasks; these errors have potential to result in significant harm during TOBI Podhaler use, and the HF assessment will focus on these 'critical use errors'.

The potential for harm to the user of the TOBI Podhaler relates to two primary hazardous scenarios, choking and clinically significant under-dosing:

13.6.1 Critical use error - Choking

There are two critical use errors that have the potential to result in choking, listed in Table 13-1. Both related to the capsule loading procedure.

Table 13-1 Critical use errors relating to choking hazards

Aspect of Use	Description of critical use error	Potential hazardous consequences	IFU content
Capsule Loading	Placing the capsule into the top of the mouthpiece, as opposed to placing it into the capsule-chamber.	Potential for user to choke on capsule.	Step 7
	Failure to adequately attach the mouthpiece before inhalation.	Potential for user to choke on capsule.	Step 8

These are treated as critical use errors, despite it being extremely unlikely that a user would in fact die or be seriously injured even in instances of the occurrence of the use error.

13.6.2 Critical use error - Clinically significant under-dosing

With regard to the hazard associated with under-dosing, only substantial variations in dose delivery to the lung present potential for harm to the user (Molimard et al 2003, Newman et al 2005).

Following this approach, in the case of TOBI Podhaler:

- Sub-optimal techniques that will not significantly negatively impact on therapeutic outcome are not critical use errors. For example, failure to exhale fully prior to inhaling through the Podhaler device is not a critical use error.
- Occasional single instances of no powder being delivered to the lung from a capsule, as a result of a task performance error (e.g. physical slip or memory lapse) are not critical use errors. For example, a single instance of forgetting to pierce a capsule is not a critical use error.
    - This would be true for any capsule-based dry powder inhalation system, except for one that delivers an acute 'rescue' medication where failure to deliver a single dose could have immediate clinically significant consequences.
    - In the case of TOBI Podhaler, the impact of occasional instances of powder delivery errors is further reduced because each dose requires four capsules to be used. An error on a single capsule therefore affects only a quarter of a dose of powder.
- Difficulties or task failures that the user is aware of are not critical use errors. For example, difficulty removing TOBI Podhaler capsules from blister cards is not a critical use error. The user will be aware that they have not administered a dose and can seek assistance from their physician or nurse. They will address, rather than repeat, the task failure.

Critical use errors with the potential to result in clinically significant under-dosing all require routine repetition.

Table 13-2 lists the critical use errors that could lead to the potential for clinically significant under-dosing that the user remains unaware of. For a comprehensive list with discussion of the criticality of all use steps refer to Appendix 5.

Table 13-2 Critical use errors relating to clinically significant under-dosing

Aspect of Use	Description of critical use error	IFU Content
Capsule Piercing	Routine failure to adequately pierce capsules.	Step 9
	Routine failure to release blue button before inhalation.	Step 9
	Routine multiple piercing of capsules	Step 9
Inhalation	Routine instances of exhalation into the mouthpiece after loading and before inhalation.	Step 10
	Routine instances of inadequate seal of mouth around mouthpiece.	Step 11
	Routine failure to inhale deeply (inadequate inhalation technique).	Step 12
Dosage Regime	Routine failure to administer four capsules per dose.	Step 18
	Routine failure to administer two doses per day.	General Notes/ Warnings

Aspect of Use	Description of critical use error	IFU Content
General	Routine instances of swallowing capsules, as opposed to inhalation of capsule contents.	General Notes/ Warnings
	Sustained failure to dispose of a Podhaler device after it has been used for one week.	General Notes/ Warnings
	Failure to identify malfunctioning Podhaler device and use reserve inhaler	General Notes/ Warnings and Step 17
	Repeated washing of Podhaler leaving device damp	Step 21

Note that for the purposes of this single assessment study, it will not be possible to establish through observation whether errors would be repeated in general use. All errors with associated criticality will therefore be recorded, their root cause established in post-dose discussion where possible, and fully reported.

13.7 Study Purpose

The purpose of this HF study is to validate the user interface of TOBI Podhaler by establishing that the product can support safe and effective use for the intended users.

13.8 Study Materials

A monthly pack will be provided that is matching the commercial configuration and presentation as approved by FDA, containing four weekly packs, full PI and a reserve Podhaler device in a case. Each weekly pack contains a Podhaler device, seven daily blister cards and the PIL which contains the IFU. To comply with clinical study medication regulations, a label will be attached to the monthly pack, each weekly pack, blister card and inhaler case indicating clinical trial number and caution statement and the statement “28 mg per capsule” on the monthly pack, weekly pack and blister card will be replaced with “placebo capsule”.

13.9 Study Participants

This study will enroll 50 CF patients in order to obtain evaluable data for 45 subjects in three age groups of approximately 15 subjects each: 6-10 years, 11-17 years and ≥ 18 years.

For subjects under the age of 18 years, consent and assent will be sought respectively from their caregivers and themselves (as applicable). Caregivers will attend sessions with subjects under the age of 18 years. Caregivers should provide assistance to subjects using TOBI Podhaler, particularly those aged 10 years or younger, in line with the PI and PIL. Caregivers of subjects aged 11 and over will be asked to give whatever support they would in reality provide the subject in preparing the administering a new medication.

All subjects and caregivers will be Podhaler device-naïve, having had no prior experience of or exposure to the inhaler or product. Subjects will not receive any training.

In order to assess the reading ability and level of health literacy of study subjects (if aged 14 years or older) and caregivers (if subject is 13 years or younger), the short form REALM-SF test will be administered during screening. Understanding subjects’ reading ability can be helpful in establishing root cause of errors, and in ensuring that the study interview is conducted with due consideration of subjects’ emotional wellbeing.

Detailed clinical study inclusion and exclusion criteria are provided in the main body of the clinical study protocol (Section 4).

13.10 Overview of Study Design

This HF study will involve subjects demonstrating the inhalation of the contents of placebo capsules using the TOBI Podhaler device, without any prior training. This will be a performance-based validation of the user interface with a subjective follow-up.

13.10.1 Performance-based validation

The subject or subject/caregiver pair will be given a TOBI Podhaler monthly pack in a representative commercial configuration. They will be given the opportunity to familiarize themselves with the study materials and will then demonstrate taking a dose from the Podhaler device using placebo powder-filled capsules. No training will be given.

Subjects will then be asked to demonstrate administration of a dose. Subsequently, after all tasks are completed, the HF Interviewer will conduct a discussion to establish root cause of any misunderstanding (i.e. errors or close calls), in order to establish whether they can be attributed to the product interface.

The goal of the routine dose administration task is oral inhalation of the powder contents of four capsules using the Podhaler device. All capsules used by subjects will be inspected by the HF Interviewer after use in order to assess the degree to which the subject has successfully emptied them and achieved the task goal. In all instances of inadequately emptied capsules, or fewer than 4 capsules being used, the interviewer will investigate further through discussion with the subject in order to establish root cause. The post-use inspection of capsules will be conducted after the subject has stated that they believe they have completed the dose administration task, in order to ensure that the capsule-inspection process does not influence their completion of the task.

13.11 Data Collection and Interpretation of Results

The objective of the HF study is to evaluate whether the user interface of TOBI Podhaler can support safe and effective use for patients with CF

Assessment against this objective will be based on:

- recording all use errors and close calls associated with the simulated inhalation of one dose of TOBI Podhaler (i.e., inhaling the contents of four placebo capsules via the Podhaler device) by subjects (CF patients and/or their caregivers. This evidence will include:
  - direct observation of use errors and close calls
  - inadequately emptied capsules identified in post-use inspection by the HF Interviewer.

1. assessing the root cause of use errors and close calls and establishing those which can be attributed to a flaw in the user interface
2. assessing the potential consequences of any errors and, in particular, for those which could result in significant harm to the subject or other user).

In addition, subjective feedback on the user interface will be sought from all subjects and will be recorded, reported and assessed.

The criticality of use errors is noted in Appendix 5. This table will be referred to during analysis and reporting of the study data.

13.12 Study Conclusion

The outcome of the assessment of study data described above is a conclusion relating to whether TOBI Podhaler can be used safely and effectively by intended users.

This conclusion will be a final judgment of whether the study findings validate the user interface or, alternatively, identify any significant and avoidable weaknesses in the interface design.

14 Appendix 2

REALM-Short Form Health Literacy test

The Rapid Estimate of Adult Literacy in Medicine-Short Form (REALM-SF) test is a 7-item word recognition test to provide clinicians with a valid quick assessment of patient health literacy. The REALM-SF has been validated and field tested in diverse research setting, and has excellent agreement with the 66-item REALM instrument in terms of grade-level assignments (Arozullah et al 2007).

Instructions for Administering the REALM-SF

1. Give the patient a laminated copy of the REALM-SF form and score answers on an unlaminated copy that is attached to a clipboard. Hold the clipboard at an angle so that the patient is not distracted by your scoring. Say:

"I want to hear you read as many words as you can from this list. Begin with the first word and read aloud. When you come to a word you cannot read, do the best you can or say, 'blank' and go on to the next word."

2. If the patient takes more than 5 seconds on a word, say "blank" and point to the next word, if necessary, to move the patient along. If the patient begins to miss every word, have him or her pronounce only known words.

Menopause	
Antibiotics	
Exercise	
Jaundice	
Rectal	
Anemia	
Behavior	

Correct:	✓
Incorrect:	**X**
Blank:	

Total Correct _____
(Score)

15 Appendix 3

FDA approved Instructions for Use TOBI Podhaler

Important Information:

- **Your healthcare provider should show you or a caregiver how to use TOBI Podhaler the right way before you use it for the first time.** Ask your healthcare provider if you have any questions or are not sure how to use TOBI Podhaler the right way.
- The recommended dose of TOBI Podhaler is **4 capsules inhaled twice daily**. Each blister card has 8 TOBI Podhaler capsules-**4 capsules for inhalation in the morning** and **4 capsules for inhalation in the evening**.
- **You must inhale all of the powdered medicine from all 4 TOBI Podhaler capsules to get the full dose.** If all of the powdered TOBI Podhaler medicine is not inhaled, you will not get the full dose.
  - After you have inhaled **2** times from a capsule, remove the capsule from the capsule chamber and hold the used capsule up to the light and look through it. It should be empty with only a fine coating of powder left on the inside surface of the capsule **(See Figure S)**.
    - If the capsule **is** empty, **throw it away** and continue following the Instructions for Use.
    - If the capsule **is not** empty, **review below "What to do with a capsule that has not been emptied"** for instructions.
- **You or a caregiver should tell your healthcare provider as soon as possible if you think you or your child has not received the full TOBI Podhaler dose. Your healthcare provider should show you how to use TOBI Podhaler the right way.**

Follow the instructions below for using your TOBI Podhaler. You will breathe in (inhale) the medicine in the TOBI Podhaler capsules using the Podhaler device. If you have any questions, ask your healthcare provider or pharmacist.

TOBI Podhaler is available as a 28-day, 7-day, and 1-day supply package**.**

Each TOBI Podhaler package contains (See Figure A):

- 4 weekly packs (28-day supply), each containing:
  - 56 capsules (7 blister cards of 8 capsules). Each blister card contains 8 TOBI Podhaler capsules (4 capsules for inhalation in the morning and 4 capsules for inhalation in the evening).
  - 1 Podhaler device and its storage case
  - 1 reserve Podhaler device (to be used if needed) and its storage case

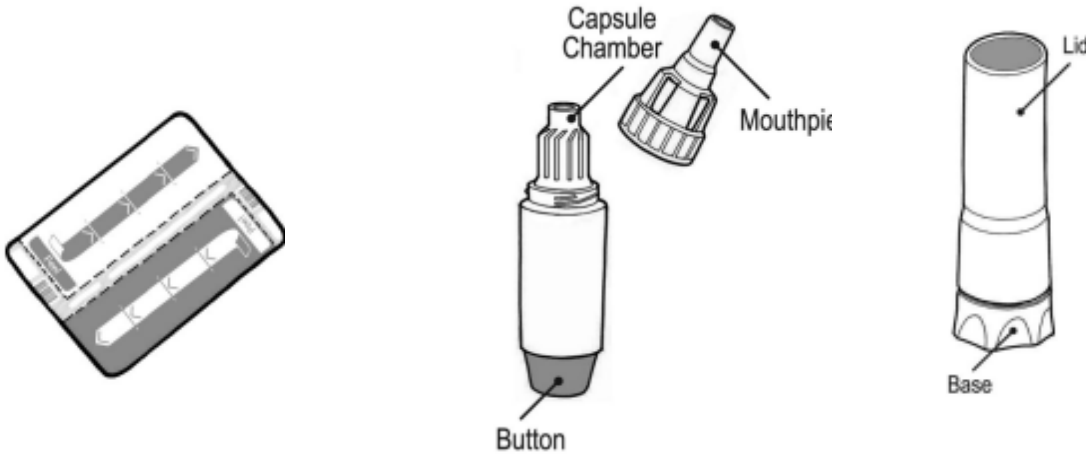
Or:

- A 7-day pack (7-day supply) containing:

- 56 capsules (7 blister cards of 8 capsules). Each blister card contains 8 TOBI Podhaler capsules (4 capsules for inhalation in the morning and 4 capsules for inhalation in the evening).
- 1 Podhaler device and its storage case

Or:

- A 1-day pack (1-day supply) containing:
  - 8 capsules (1 blister card of 8 capsules). Each blister card contains 8 TOBI Podhaler capsules (4 capsules for inhalation in the morning and 4 capsules for inhalation in the evening).
  - 1 Podhaler device and its storage case



Blister card **Podhaler device** **Storage case**

Figure A

Note:

- **Do not** swallow TOBI Podhaler capsules. The powder in the capsule is for you to inhale using the Podhaler device.
- Only use the Podhaler device contained in this pack. **Do not** use TOBI Podhaler capsules with any other device, and **do not** use the Podhaler device to take any other medicine.
- When you start a new weekly (7-day) pack of capsules, use the new Podhaler device that is supplied in the pack and discard the used device and its case. Each Podhaler device is only used for one week (7 days).
- Always keep the TOBI Podhaler capsules in the blister card. Only remove 1 capsule at a time just before you are going to use it.
- Doses should be inhaled as close to 12 hours apart as possible and not less than 6 hours apart.

- Once in a while, very small pieces of the capsules can get into your mouth and you may be able to feel these pieces on your tongue. These small pieces will not hurt you if you swallow or inhale them.
- The reserve Podhaler device provided in the 28-day supply package may be used if the Podhaler device:
  - is wet, dirty, or broken
  - has been dropped
  - does not seem to be piercing the capsule properly (see Step 17)

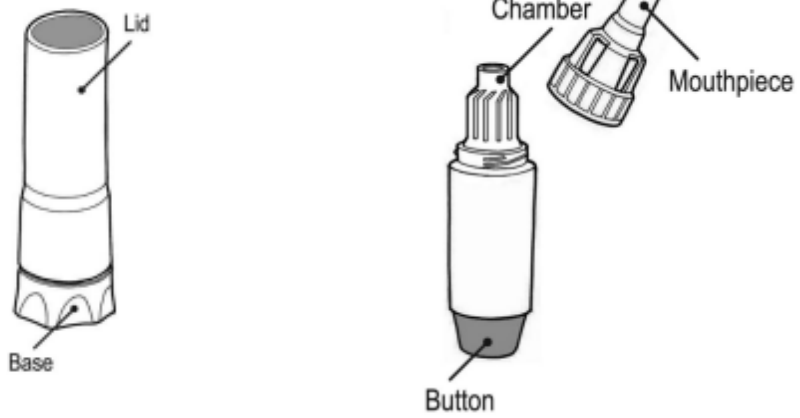
Getting ready:

- **Wash and dry your hands** (See Figure B).

Figure B

Preparing your TOBI Podhaler dose

Your Podhaler device comes in a storage case with a lid. The device itself has a removable mouthpiece, a capsule chamber and a button at its base (See Figure C).



Storage case **Podhaler device**

Figure C

Step 1: Just before use, hold the base of the storage case and unscrew the lid in a counter-clockwise direction (See Figure D). Set the lid aside.

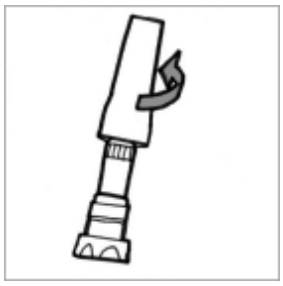


Figure D

Step 2: Leave the Podhaler device in the base of the case while you prepare your dose (See Figure E).

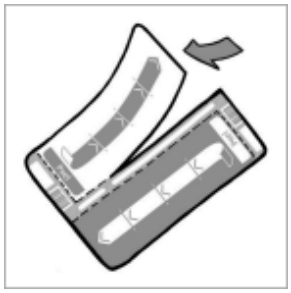
Figure E

Step 3: Hold the body of the Podhaler device and unscrew the mouthpiece in a counter-clockwise direction (See Figure F). Set the mouthpiece aside on a clean, dry surface.

Figure F

Note: Each blister card contains 8 TOBI Podhaler capsules - 4 capsules for inhalation in the morning and 4 capsules for inhalation in the evening.

Step 4: Take 1 blister card and tear the pre-cut lines along the length (See Figure G) then tear at the pre-cut lines along the width (See Figure H).



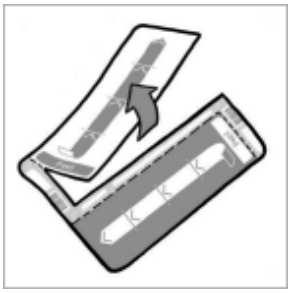


Figure G **Figure H**

Step 5: Peel (by rolling back) the foil that covers 1 TOBI Podhaler capsule on the blister card (See Figure I). Always hold the foil close to where you are peeling.

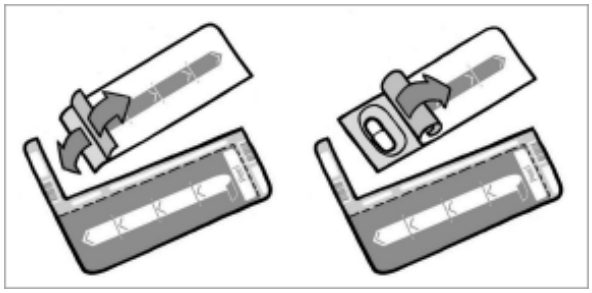


Figure I

Step 6: Take out 1 TOBI Podhaler capsule from the blister card (See Figure J). **Note:** Only peel back the foil from one capsule at a time and remove the capsule just before you are going to use it in the device because the blister protects the capsule from moisture.

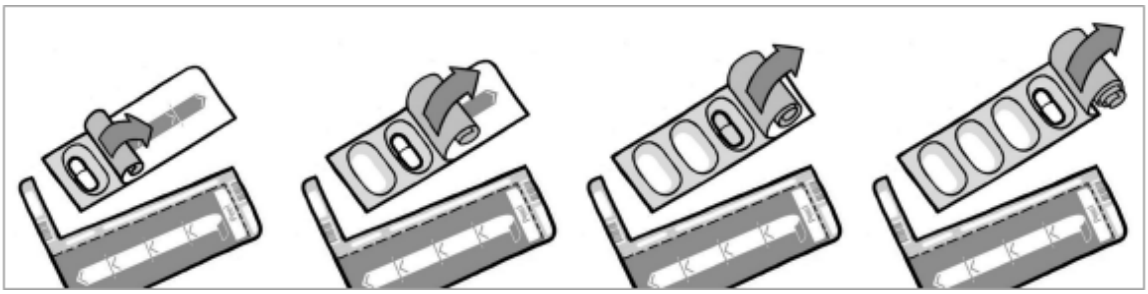


Figure J

Step 7: Place the TOBI Podhaler capsule in the capsule chamber at the top of the Podhaler device right away (See Figure K). **Do not** put the capsule directly into the top of the mouthpiece.

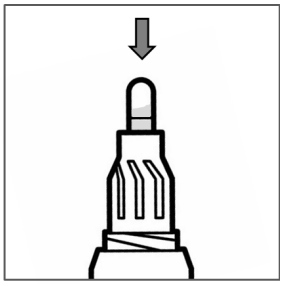


Figure K

Step 8: Put the mouthpiece back on your Podhaler device and screw the mouthpiece in a clockwise direction until it is tight (See Figure L). **Do not** overtighten.

Figure L

Step 9: Remove the Podhaler device from the base of the case. Hold the Podhaler device with the mouthpiece pointing down. Put your thumb on the blue button and press the blue button all the way down (See Figure M). Let go of the blue button. **Do not** press the blue button more than 1 time. The chances of the capsule breaking into pieces will be increased if the capsule is accidentally pierced more than once.

Figure M

Taking your TOBI Podhaler dose (you will need to repeat steps 10 to 14 for each capsule so you inhale each capsule 2 times in order to empty it):

Step 10: Breathe out (exhale) all the way (See Figure N). Do not blow or exhale into the mouthpiece.

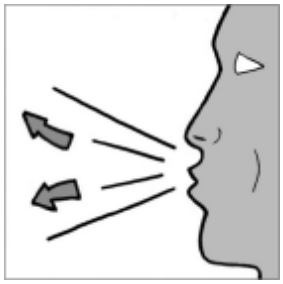


Figure N

Step 11: Place your mouth over the mouthpiece and close your lips tightly around it (See Figure O).

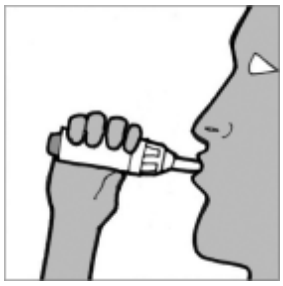


Figure O

Step 12: Inhale deeply with a single breath (See Figure P).

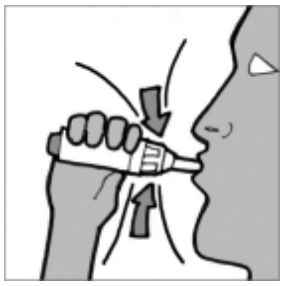


Figure P

Step 13: Remove the Podhaler device from your mouth and **hold your breath** for about 5 seconds.

Step 14: Exhale and take a few normal breaths away from the Podhaler device. **Do not** blow or exhale into the mouthpiece.

Step 15: Repeat steps 10 through 14 **using the same capsule**.

You must **inhale 2 times from each capsule** in order to empty it.

Step 16: Unscrew the mouthpiece and remove the TOBI Podhaler capsule from the capsule chamber (See Figures Q and R below).

Figure Q

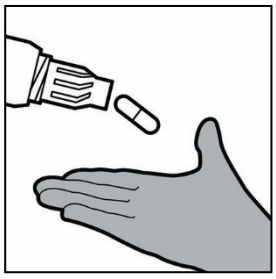


Figure R

Step 17: Hold the used capsule up to the light and look through it. It should be empty with only a fine coating of powder remaining on the inside surface of the capsule (See Figure S). If the capsule **is** empty, throw it away and go to Step 18.

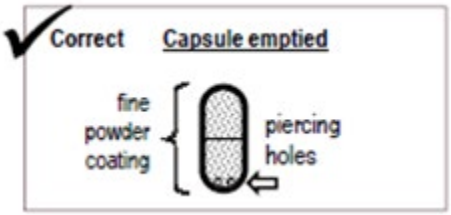


Figure S

If the capsule **is not** empty, see "What to do with a capsule that has not been emptied" below for instructions.

What to do with a capsule that has not been emptied:

- If the capsule is pierced but still contains more than just a fine coating of powder **(See Figure T)** you must inhale from it again twice:
  - Put the capsule back into the Podhaler device capsule chamber with the pierced side of the capsule pointing down.
  - Screw the mouthpiece back on until it is tight.
  - Repeat Steps 10 to 17.

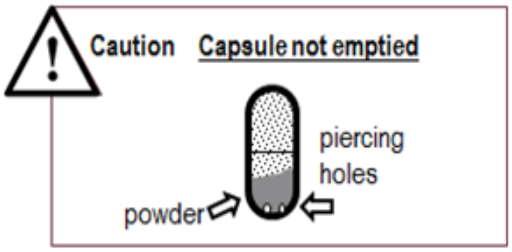


Figure T

- If the capsule is not pierced **(See Figure U)** you must pierce it again and inhale from it twice:

1. Put the capsule back into the Podhaler device capsule chamber.
2. Screw the mouthpiece back on until it is tight.
3. Repeat Steps 9 to 17 making sure to press the blue button all the way down.

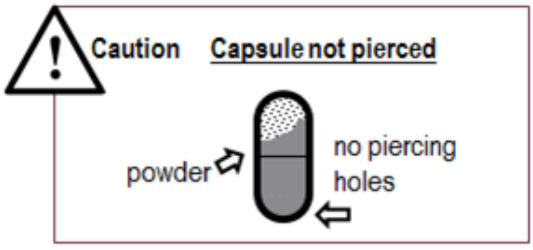


Figure U

Note: If you have tried to pierce the capsule 2 times and it is still not pierced, use the reserve Podhaler device provided in the TOBI Podhaler package instead (only available in the 28-day supply package). If you need a new device, ask your physician.

- Prepare the reserve Podhaler device by following Steps 1 to 3.
- Then, using the same capsule, repeat Steps 7 to 17.

Step 18: Repeat Steps 5 to 17 for 3 more times until your whole dose (4 capsules) has been taken (See Figure V).

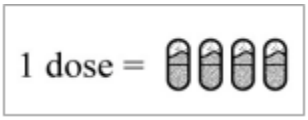


Figure V

After your TOBI Podhaler dose:

Step 19: Throw away all the empty TOBI Podhaler capsules. Do not store the TOBI Podhaler capsules in the Podhaler device.

Step 20: Put the mouthpiece back on to your Podhaler device and twist the mouthpiece in a clockwise direction until it is tight (See Figure L). Do not overtighten.

Step 21: Wipe the mouthpiece with a clean, dry cloth (See Figure W).

Figure W

- **Do not** wash the Podhaler device with water. Your Podhaler device needs to stay dry at all times to work the right way.

Step 22: Place your Podhaler device back in the storage case base.

Step 23: Place the lid back on the storage case base and screw the cover in a clockwise direction until it is tight (See Figure X).

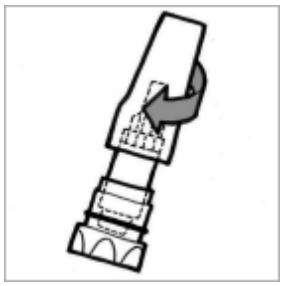


Figure X

How should I store TOBI Podhaler?

- Store your Podhaler device and blister-packaged capsules at room temperature between 68°F to 77°F (20°C to 25°C).

- **Keep the TOBI Podhaler capsules and Podhaler device in a dry place.**
- Store the Podhaler device tightly closed in its case when you are not using it.
- Keep TOBI Podhaler capsules, Podhaler device, and all medicines out of the reach of children.

This Patient Information and Instructions for Use have been approved by the U.S. Food and Drug Administration.

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East Hanover, NJ 07936

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To be replaced by Mylan as the current Sponsor.

16 Appendix 4

Assessment session and interview guide

[Note: the introduction needs to be delivered as appropriately as possible for all ages. The interviewer will adhere to the Introduction script as far as possible; however, modifications in language will be required according to subject's age and whether a caregiver is in attendance, etc. This script has been written simply, with younger children in mind.]

The HF Interviewer will manage all subsequent discussion in line with HF best practice to meet study objectives, seeking to understand root cause of errors and difficulties without prompting or leading the subjects.

Check subjects' first names upon greeting them. Introduce HF Interviewer (and Observer, if applicable) by first name.

Introduction

1. Thank you very much for agreeing to take part in this study – we're very grateful for your time. I know that you've already been given some information about the study, so I'd just like to cover a few points again and give you a chance to ask me any questions.
2. I work for an independent research company. My client is a pharmaceutical company that developed TOBI Podhaler. We will take notes today and record the interview on video, but the notes and video will be stored securely, kept confidential and only seen by members of the project team.
3. As you know, today we're going to be looking at the TOBI Podhaler which is a type of inhaler that is used to inhale medicine. Usually your nurse or doctor would train you to use a new inhaler, but in this study we want to know whether TOBI Podhaler can be used if you haven't been trained but have been given a pack like this from your pharmacist, which contains all the materials and information you would need to take your dose. As indicated on the pack, read the patient information leaflet before use. So in a few minutes I'm going to give you this Podhaler package and you will be free to take whatever time you would like to familiarize yourself with the package contents, just as you would if you were at home using a new inhaler for the first time. When you're ready, I will ask you to show me how you would take a dose of medication.
4. The Podhaler device you're going to try is new, clean and hasn't been used before. The pack does not contain any medication – it contains a placebo inhalation powder that looks and feels just like the real medication but won't help against bacteria.
5. What we're doing today is part of a clinical study and it would be a great help for us if you could treat it as seriously as if you were really taking medication.
6. I also want to assure you that you can stop the interview at any point for any reason. Is everything I've said clear? Do you have any questions for me?
   [Caregivers, and preferably children, must indicate they understand.]

Background questions

[HF Interviewer and HF Observer record all responses on the assessment checklist. Where caregivers are present, questions are asked of both subjects and caregivers]

- Now we can begin. [patients only:] According to my notes you are [x] years of age, is that correct?
- Have you used a nebulizer?
- Are you currently using an inhaler? Which inhaler do you use? Have you used any others regularly? (Which?)
- [Caregivers only] Do you usually help <subject's name> to take their medication when they're using their inhaler/nebulizer?
- Are you left or right handed, or do you use both?
- Do you need glasses or contact lenses to read, and if so, do you have them with you?
- Do you have any problems with strength in your hands, or in handling day to day objects?
- Are you fluent in any language other than English? [If so:] which is your first language? [check also with caregiver – to be recorded if different]
- [Adult patients and caregivers]: can you tell me when you left the education system? (for example, before high school, after high school) or are you still in education?

HF assessment

[Interviewer switches video camera on]

- Here's the monthly pack which you would receive from your pharmacist. I'd like you to imagine that you are at home, preparing to use TOBI Podhaler for the first time. You are free to take as long as you like to look at the package contents and familiarize yourself with them before you take a dose just as you would if you were at home – please try to pretend we're not here. This isn't a test of whether you can guess how to use TOBI Podhaler or how quickly you do it. So please take whatever time you want to familiarize yourself with this monthly package and let me know when you're ready to prepare and take a dose. [Interviewer waits for subject (/caregiver) to indicate that they are ready.]
- Now I'd like you to prepare the inhaler and take a full dose from it just as if you had been prescribed with this medication. [To subjects and caregivers: "Please work together however you would in reality at home to prepare and administer a new medication." As appropriate, if the subject is 10 years or younger , the Interviewer will cite the labelling: "The instructions state that caregivers should help children who are 10 years of age and younger to use TOBI Podhaler, and should keep watching them use their TOBI Podhaler until they are able to use it the right way without help."] There's no hurry — you are free to take your time, pause and look at any of the package contents at any point, just as you would be at home.

Notes for Interviewer and Observer:

Interviewer and Observer will watch closely and intervene should the Subject or Caregiver be acting in a way which may endanger either of their health or well-being.

If the Subject or Caregiver put the capsule in the inhaler **without removing or replacing the mouthpiece** they may inhale the whole capsule and the Interviewer or Observer must intervene.

Other notes:

- If asked a use-related question the Interviewer will respond in a responsive but not leading manner, such as "what would you do if I weren't here?"
- Interviewer and Observer will independently complete the assessment checklist.
- Interviewer will watch closely and note any areas of observed or reported difficulty so that they can be explored later.
- Each used capsule will be visually inspected by the HF Interviewer for the amount of remaining powder. This visual assessment will be done before post-use discussion in order that any failure to empty the capsules can be addressed and root cause established.
- In addition, each capsule will be placed in a numbered container after use so that it can be kept for further analysis if required.
- It is possible that certain steps may not be carried out correctly because there is no drug being really taken – such as holding breath after inhalation (subjects may not 'role play' every step when they are not actually taking a dose of drug although requested to do so by the interviewer.) The interviewer should use his/her discretion to probe the reasons for subjects not following the steps correctly. If a user notes that they would have done a particular step differently if real medication were involved, this will be noted and analyzed and reported.

Post-use discussion

- How was your experience using TOBI Podhaler?
- Can you tell me more about that?
- Can you tell me about anything you found difficult? [If subject mentions confusion:] Why was it confusing?
- Can you tell me about anything you found easy?
  [Interviewer will probe to discover root cause of all errors and, where possible, close calls. For example:
  - Do you think that you/your child received a full dose? Why/why not?
  - Can you tell me about checking the capsules?

  If the Subject or Caregiver mentions making a mistake, the Interviewer will probe:
  - Can you tell me why you did that?
  - Is there anything about the Podhaler device or instructions that encouraged you to do it?
- I'd like to ask you to look (again) at the instructions and tell me if there are any sections that are confusing or incomplete.
  - According to the instructions, how many capsules should you inhale each day?
  - What should you do if you think you or your child has not received the full TOBI Podhaler dose?

Before we finish, do you have any further questions or comments on the inhaler or the instructions? Then thank you again for your time.

17 Appendix 5

Task assessment and criticality table

Item	IFU step	Task	Assessment Method			Discussion of Task Step Criticality
			Inspection of Used Capsules	Observation of Task Performance	Questioning in post-dose discussion	
1	1	Open the inhaler case	-	Yes	Yes if correct performance is not observed	**This task step is essential, but not critical.** Use Error: failure to complete task step. This makes dosing impossible, but it is evident to the user that they have not completed the step. There are therefore no hazardous consequences following inevitably from this use error. It is potentially associated with the use error of swallowing of capsules, but this error is recorded separately.
2	2	Stand Podhaler device upright in base of the case	-	Yes	-	**This task step is desirable, but not essential.** The instruction is provided as a helpful suggestion to make the task easier.
3	3	Unscrew the mouthpiece	-	Yes	Yes if correct performance is not observed	**This task step is essential, but not critical.** Use Error: failure to complete task step. This makes dosing impossible. There are no hazardous consequences following inevitably from this use error, but it does potentially increase the likelihood of the subsequent use error of placing the capsule into the top of the mouthpiece (see item 7 below). This subsequent use error is reported separately.
4	4	Take 1 blister card and tear along the pre-cut lines	-	Yes	-	**This task step is desirable, but not essential.** The instruction is provided as a helpful suggestion to make the task easier.
5	5	Peel back the foil that covers 1 TOBI Podhaler capsule on the blister card	-	Yes	Yes if correct performance is not observed	**This task step is essential, but not critical.** Use Error 1: failure to complete task step. This makes dosing impossible, but it is evident to the user that they have not completed the step. There are therefore no hazardous consequences following inevitably from this use error, which is therefore non-critical in nature.

Item	IFU step	Task	Assessment Method			Discussion of Task Step Criticality
			Inspection of Used Capsules	Observation of Task Performance	Questioning in post-dose discussion	
						Use Error 2: exposing all capsules at once. Avoidance of this use-error is desirable, but not essential. The instruction is a description of optimal technique. There are no hazardous consequences following inevitably from this use error, which is therefore non-critical in nature.
6	**6**	Take out 1 TOBI Podhaler capsule from the blister card.	**-**	**Yes**	**Yes** if correct performance is not observed	**This task step is essential, but not critical.** Use Error: failure to complete task step. This makes dosing impossible, but it is evident to the user that they have not completed the step. There are therefore no hazardous consequences following inevitably from this use error, which is therefore non-critical in nature.
7	**7**	Place the TOBI Podhaler capsule in the capsule-chamber	**-**	**Yes**	**Yes** if correct performance is not observed	**Potential for critical use error** Use Error: placing of capsules into the top of the mouthpiece. This use error creates the potential for choking. Although the risk of significant harm from choking is very low, the potential does exist and therefore this use error is considered critical.
8	**8**	Put the mouthpiece back on the Podhaler device and screw the mouthpiece in a clock-wise direction until it is tight.	**-**	**Yes**	**Yes** if correct performance is not observed	**Potential for critical use error** Use Error: failure to replace mouthpiece. This use error creates the potential for inhalation of the capsule leading to choking. Although the risk of significant harm from choking is very low, the potential does exist and therefore this use error is considered critical.
		Do not overtighten.	**-**	**Yes** Evidence of overtightening can be seen if the thread is damaged	**-**	**This task step is desirable, but not essential** Use Error: overtightening mouthpiece. Avoidance of this use-error is desirable, but not essential. The instruction is a description of optimal technique which reduces the risk of damaging the inhaler. There are no hazardous consequences following inevitably from this use error, which is therefore non-critical in nature.
9	**9**	Hold the Podhaler device with the mouthpiece pointing down.	**-**	**Yes**	**-**	**This task step is desirable, but not essential.** Use Error: failure to invert the Podhaler device during piercing. Avoidance of this use-error is desirable, but not essential. Podhaler device orientation on piercing does not significantly impact dosing.

Item	IFU step	Task	Assessment Method			Discussion of Task Step Criticality
			Inspection of Used Capsules	Observation of Task Performance	Questioning in post-dose discussion	
		Press blue button all the way down	**Yes**	**Yes**	**Yes** if correct performance is not observed	**Potential for critical use error** Use Error: failure to adequately pierce capsules. If this use error is repeated it has the potential to cause clinically significant under-dosing. Repeated uncorrected error is therefore critical. Occasional error is non-critical. (In this single-use assessment, all errors will be investigated, analyzed and reported.) (This use error can be rectified by users following step 17. Understanding of step 17 is recorded separately.)
		Release before inhaling	**Yes**	**Yes**	**Yes** if correct performance is not observed	**Potential for critical use error** Use Error: failure to release before inhaling. This use error results in no dose delivery from the affected capsule. Repeated uncorrected error is therefore critical. Occasional error is non-critical. (In this single-use assessment, all errors will be investigated, analyzed and reported.) (This use error can be rectified by users following step 17. Understanding of step 17 is recorded separately)
		Press only once	**Yes**	**Yes**	**Yes** if correct performance is not observed	**Potential for critical use error** Use Error: multiple piercing of capsule. If this use error is routinely repeated it has the potential to cause clinically significant under-dosing. The likelihood of significant under-dosing is very low, even if the use error is routinely repeated, but the potential does exist and therefore this use error is considered critical if repeated. (In this single-use assessment, all errors will be investigated, analyzed and reported.)
10	**10**	Breathe out completely	**-**	**Yes** (although note that it is not possible to ascertain through observation if a subject has	**-**	**This task step is desirable, but not essential.** Use Error: failure to exhale fully before inhalation. Avoidance of this use-error is desirable, but not essential. The instruction is a description of optimal technique. Sub-optimal technique in practice will not significantly negatively impact on therapeutic outcome.

Item	IFU step	Task	Assessment Method			Discussion of Task Step Criticality
			Inspection of Used Capsules	Observation of Task Performance	Questioning in post-dose discussion	
				exhaled completely)		
		Do not blow or exhale into the mouthpiece.	-	**Yes**	**Yes** if correct performance is not observed	**Potential for critical use error.** Use Error: exhalation into mouthpiece. If this use error occurs, the water vapor in the exhalation breath will be absorbed by the residual powder in the inhaler, thereby increasing its stickiness. Sticky powder in the inhaler can affect the ability of the capsule to rotate and the dose to be delivered. Repeated uncorrected error is therefore critical. Occasional error is non-critical. (In this single-use assessment, all errors will be investigated, analyzed and reported.) (The use error can be rectified by users following step 17, as it will result in inadequate clearance of powder from capsules. Understanding of step 17 is recorded separately)
11	**11**	Make a lip seal around mouthpiece.	-	**Yes**	**Yes** if correct performance is not observed	**Potential for critical use error** Use Error: inadequate seal around mouthpiece. If this use error is routinely repeated it has the potential to cause clinically significant under-dosing. Repeated uncorrected error is critical. Occasional error is non-critical. (The use error can be rectified by users following step 17, as it will result in inadequate clearance of powder from capsules. Understanding of step 17 is recorded separately.)
12	**12**	Inhale deeply with a single breath	-	**Yes**	**Yes** if correct performance is not observed	**Potential for critical use error** Use Error: inadequate inhalation technique. If this use error is routinely repeated it has the potential to cause clinically significant under-dosing. Repeated uncorrected error is critical. Occasional error is non-critical. (The use error can be rectified by users following step 17, as it will result in inadequate clearance of powder from capsules. Understanding of step 17 is recorded separately.)

Item	IFU step	Task	Assessment Method			Discussion of Task Step Criticality
			Inspection of Used Capsules	Observation of Task Performance	Questioning in post-dose discussion	
13	**13**	Remove the Podhaler device from your mouth and hold your breath for about 5 seconds.	**-**	**Yes**	**-**	**This task step is desirable, but not essential.** Use Error: failure to hold breath. Avoidance of this use-error is desirable, but not essential. The instruction is a description of optimal technique. Sub-optimal technique in practice should not significantly negatively impact on therapeutic outcome.
14	**14**	Take a few normal breaths away from the Podhaler device.	**-**	**Yes**	**-**	**This task step is desirable, but not essential.** Use Error: failure to take normal breaths before repeating inhalation. Avoidance of this use-error is desirable, but not essential. The instruction is a description of optimal technique. Sub-optimal technique in practice will not significantly negatively impact on therapeutic outcome.
15	**15**	Repeat steps 10-14 using the same capsule.	**Yes**	**Yes**	**Yes** if correct performance is not observed	**This task step is desirable, but not essential.** Use Error: failure to inhale two times per capsule. Avoidance of this use-error is desirable, but not essential – it is possible to clear the capsule after one inhalation. The instruction is a description of optimal technique. If the use error does result in inadequate clearance of powder from capsules, this can be rectified by users following step 17. Understanding of step 17 is recorded separately.
16	**16**	Remove the TOBI Podhaler capsule from the capsule-chamber	**-**	**Yes**	**Yes** if correct performance is not observed	**This task step is essential, but not critical** Use Error: failure to remove capsule. This makes subsequent dosing impossible, but it is evident to the user that they have not completed the step. There are therefore no hazardous consequences following inevitably from this use error.
17	**17**	Check capsule	**-**	**Yes**	**Yes** if correct performance is not observed	**This task step is desirable, but not essential.** Use Error: failure to check capsule after inhalation. Avoidance of this use-error is desirable, but not essential. The instruction is a description of optimal technique which reduces the risk of any capsules remaining inadequately emptied following earlier errors or failures in steps 5 to 15 above. Note however that any failure to empty a capsule will be investigated in post-dose discussion, so that the root cause of failure can be determined, and fully reported.

Item	IFU step	Task	Assessment Method			Discussion of Task Step Criticality
			Inspection of Used Capsules	Observation of Task Performance	Questioning in post-dose discussion	
		Appropriate response to any powder remaining in capsule:				
		- re-inhale if more than coating remains, replacing capsule correct way	**Yes**	**Yes**	**Yes** if correct performance is not observed	**This task step is desirable, but not essential.** Use Error: failure to correctly re-insert capsule and repeat inhalation. Avoidance of this use-error is desirable, but not essential. The instruction is a description of optimal technique which reduces the risk of any capsules remaining inadequately emptied following earlier errors or failures in steps 5 to 15 above. Note however that any failure to empty a capsule will be investigated in post-dose discussion, so that the root cause of failure can be determined, and fully reported.
		-re-insert and re-pierce if it does not appear to be pierced			**Yes** if correct performance is not observed	**This task step is desirable, but not essential.** Use Error: failure to correctly re-insert, re-pierce and re-inhale. Avoidance of this use-error is desirable, but not essential. The instruction is a description of optimal technique which reduces the risk of any capsules remaining inadequately emptied following earlier errors or failures in steps 5 to 15 above. Note however that any failure to empty a capsule will be investigated in post-dose discussion, so that the root cause of failure can be determined, and fully reported.
		- use reserve Podhaler device if still does not appear to be pierced	-		**Yes** if correct performance is not observed	**Potential for critical use error.** Use Error: failure to use reserve Podhaler device in cases of capsules remaining inadequately pierced after correct re-insertion and re-piercing. This use error has the potential to cause clinically significant under-dosing and is therefore critical.
18	**18**	Repeat Steps 5 to 17 for 3 more times until your whole dose (4 capsules) has been taken	**Yes**	**Yes**	**Yes** if correct performance is not observed	**Potential for critical use error** Use Error: failure to administer four capsules per dose. If this use error is routinely repeated it will result in clinically significant under-dosing. Repeated error is critical. Occasional error is non-critical. In this single-use assessment, a failure to administer four capsules per dose will be viewed as

Item	IFU step	Task	Assessment Method			Discussion of Task Step Criticality
			Inspection of Used Capsules	Observation of Task Performance	Questioning in post-dose discussion	
						potentially critical and investigated in post-dose discussion to establish root cause.
19	**19**	Discard all the empty TOBI Podhaler capsules.	**-**	**-**	**-**	**This task step is desirable, but not essential.** The instruction is provided as a helpful suggestion.
20	**20**	Replace the mouthpiece	**-**	**-**	**Yes** if correct performance is not observed	**This task step is desirable, but not essential** The instruction is provided as a helpful suggestion.
		Do not overtighten.	**-**	**Yes**	**Yes** if correct performance is not observed	**This task step is desirable, but not essential.** Use Error: overtightening mouthpiece. Avoidance of this use-error is desirable, but not essential. The instruction is a description of optimal technique which reduces the risk of damaging the inhaler. There are no hazardous consequences following inevitably from this use error, which is therefore non-critical in nature.
21	**21**	Wipe the mouthpiece with a clean, dry cloth.	**-**	**-**	**Yes** if correct performance is not observed	**This task step is desirable, but not essential** Use Error: failure to wipe mouthpiece after use. Avoidance of this use-error is desirable, but not essential. The instruction is a description of best practice relating to keeping the inhaler exterior clean. There are no hazardous consequences following inevitably from this use error, which is therefore non-critical in nature.

Item	IFU step	Task	Assessment Method			Discussion of Task Step Criticality
			Inspection of Used Capsules	Observation of Task Performance	Questioning in post-dose discussion	
		Do not wash the Podhaler device with water	-	-	N/A	**Potential for critical use error.** Use Error: device washed with water. This use error has the potential to cause clinically significant under-dosing and is therefore critical. Note that this cannot be assessed via observation in a single study session. However, comprehension of the IFU section related to cleaning the Podhaler device was assessed in the 2412 IFU validation study and all study subjects could find and understand the information. It is therefore not intended to re-assess comprehension in this study
22	22	Place your Podhaler device back in the storage case base.	-	Yes	-	**This task step is desirable, but not essential.** Use Error: failure to replace device in case. Avoidance of this use-error is desirable, but not essential. The instruction is a description of best practice relating to protecting the inhaler when not in use. There are no hazardous consequences following inevitably from this use error, which is therefore non-critical in nature.
23	23	Place the lid back on the storage case base and screw the cover in a clockwise direction until it is tight	-	Yes	-	**This task step is desirable, but not essential.** Use Error: failure to adequate close case. Avoidance of this use-error is desirable, but not essential. The instruction is a description of best practice relating to protecting the inhaler when not in use. There are no hazardous consequences following inevitably from this use error, which is therefore non-critical in nature.
24	-	You will breathe-in (inhale) the medicine in the TOBI Podhaler capsules using the Podhaler device. Do not swallow TOBI Podhaler capsules. The powder in the capsule is for you to inhale using the Podhaler device.	-	Yes	Yes	**Potential for critical use error.** Use Error: swallowing capsules. If this use error is repeated it will result in clinically significant under-dosing. Repeated error is critical. Occasional error is non-critical. (There is no hazard associated with capsule ingestion.) In this single-use assessment, any attempt to swallow a capsule will be viewed as potentially critical and investigated in post-dose discussion to establish root cause. However, comprehension of the IFU instruction not to swallow capsules was assessed in the 2412 IFU validation study and all study subjects answered the

Item	IFU step	Task	Assessment Method			Discussion of Task Step Criticality
			Inspection of Used Capsules	Observation of Task Performance	Questioning in post-dose discussion	
						question correctly. It is therefore not intended to re-assess comprehension in this study.
25	-	Each blister card contains … 4 capsules for inhalation in the morning and 4 capsules for inhalation in the evening	-	-	**Yes** If comprehension not reflected during dosing task, a question will be asked post use.	**Potential for critical use error** Use Error: failure to administer two doses a day. If this use error is routinely repeated it has potential to cause clinically significant under-dosing. Repeated error is critical. Occasional error is non-critical. Note that this cannot be assessed via observation in a single study session. However, comprehension of the IFU section related to dose frequency was assessed in the 2412 IFU validation study and all study subjects could find and understand the information in the IFU and/or on the blister cards. However, as the wording in the IFU has changed, comprehension will be re-assessed.
26	-	Doses should be inhaled as close to 12 hours apart as possible and not less than 6 hours apart.	-	-	**N/A** – cannot be observed, comprehension of IFU already validated	**This task step is desirable, but not essential** Use Error: administration of a dose less than six hours after the previous dose. Avoidance of this use-error is desirable, but not essential. The instruction is a description of best practice relating to dosing. The impact of overdosing, even in the case of repeated close exposures, is not critical. Use Error: administration more than 12 hours after the previous dose. Avoidance of this use-error is desirable, but not essential. The impact of underdosing is not critical. There are no hazardous consequences following inevitably from this use error, which is therefore non-critical in nature. Note that this cannot be assessed via observation in a single study session. However, comprehension of the IFU section related to dose frequency was assessed in the 2412 IFU validation study and all study subjects could find and understand the information in the IFU and/or on the blister cards. It is therefore not intended to re-assess comprehension in this study.

Item	IFU step	Task	Assessment Method			Discussion of Task Step Criticality
			Inspection of Used Capsules	Observation of Task Performance	Questioning in post-dose discussion	
27	-	Store your Podhaler device and blister-packaged capsules at room temperature between 68F to 77F Keep the TOBI Podhaler capsules and Podhaler device in a dry place Keep TOBI Podhaler capsules, Podhaler device, and all medicines out of the reach of children.	-	-	**N/A –** cannot be observed, comprehension of IFU already validated	**This task step is desirable, but not essential** Use Error: storage of TOBI Podhaler in a damp place. Avoidance of this use-error is desirable, but not essential. The instruction is a description of best practice relating to the care of the system. There are no hazardous consequences following inevitably from this use error, which is therefore non-critical in nature. Note that this cannot be assessed via observation in a single study session. However, comprehension of the IFU section related to storage was assessed in the 2412 IFU validation study and all study subjects could find and understand the information in the IFU. It is therefore not intended to re-assess comprehension in this study
28	-	Store the Podhaler device tightly closed in its case when you are not using it	-	-	**N/A –** cannot be observed, comprehension of IFU already validated	**This task step is desirable, but not essential** Use Error: failure to store device in case. Avoidance of this use-error is desirable, but not essential. The instruction is a description of best practice relating to protecting the inhaler when not in use. There are no hazardous consequences following inevitably from this use error, which is therefore non-critical in nature.
29	-	When you start a new weekly pack … use the new Podhaler device that is supplied … and discard the used device and its case. Each Podhaler device is only used for one week (7 days)	-	-	**N/A –** cannot be observed, comprehension of IFU already validated	**Potential for critical use error.** Use Error: failure to dispose of a Podhaler device after one week's use. The performance of the inhaler will decline over time. Sustained use and failure to dispose of a single Podhaler device could be critical. Note that this cannot be assessed via observation in a single study session. However, comprehension of the IFU section related to disposing of the Podhaler after one week was assessed in the 2412 IFU validation study and all study subjects could find and understand the information in the IFU. It is therefore not intended to re-assess comprehension in this study.

Item	IFU step	Task	Assessment Method			Discussion of Task Step Criticality
			Inspection of Used Capsules	Observation of Task Performance	Questioning in post-dose discussion	
30	-	The reserve Podhaler device provided in the package may be used if the Podhaler device: - is wet, dirty, or broken - has been dropped - does not seem to be piercing the capsule properly	-	**Yes** (where a reserve Podhaler is required)	**Yes** if correct performance is not observed	**Potential for critical use error.** Use Error: use of a wet, dirty, broken or faulty Podhaler device. This use error has the potential to cause clinically significant under-dosing. Routinely repeated error is critical. Occasional error is non-critical. Note that this cannot be assessed via observation in a single study session. However, comprehension of the IFU section related to use of the reserve Podhaler device was assessed in the 2412 IFU validation study and all study subjects could find and understand the information in the IFU. It is therefore not intended to re-assess comprehension in this study.
31	-	Only use the Podhaler device contained in this pack. **Do not** use TOBI Podhaler capsules with any other device	-	-	**N/A –** cannot be observed, comprehension of IFU already validated	**Following this instruction is essential, but not critical.** Use Error: use of capsules with a different inhaler. This initially is likely to result in impaired (partial) dose delivery to the lung, with delivery declining over time until dosing is impossible. This will be evident to the user. There are therefore no hazardous consequences following inevitably from this use error. Note that this cannot be assessed via observation in a single study session. However, comprehension of the IFU section related to capsule use was assessed in the 2412 IFU validation study and all study subjects could find and understand the information in the IFU. It is therefore not intended to re-assess comprehension in this study.
32	-	**Do not** use the Podhaler device to take any other medicine	-	-	**N/A –** cannot be observed, comprehension of IFU already validated	**Following this instruction is desirable, but not essential** Use Error: use of Podhaler device to deliver another medicine. Avoidance of this use-error is desirable, but not essential. The instruction is a description of best practice relating to the delivery of other medicine. There are no hazardous consequences following from this use error, which is therefore non-critical in nature. Note that this cannot be assessed via observation in a single study session. However, comprehension of the IFU section related to Podhaler device/capsule use was assessed in the 2412 IFU validation study and all study subjects could find and understand the information in the IFU. It is therefore not intended to re-assess comprehension in this study.

SIGNATURE PAGE

Protocol Description	Study number: CTBM100C2419 A multicenter, human factors validation study in cystic fibrosis patients aged 6 years and older to evaluate the user interface of TOBI® Podhaler™ (tobramycin inhalation powder) using placebo capsules
Product Code	Tobramycin
Protocol Version	02
Protocol Version Date	12 NOV 2018

I have read this protocol and affirm that the information contained herein is complete and accurate.

Date: 20 NOV 2018

Therapeutic Area Head Vaccines
Hanka de Voogd MD