TBM100/Tobramycin

CTBM100CDE02 / NCT02248922

An 8 week open-label interventional multicenter study to evaluate the lung clearance index as endpoint for clinical trials in cystic fibrosis patients ≥ 6 years of age, chronically infected with *Pseudomonas aeruginos*a

Author(s): [redacted]

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Signature Pages

TBM100/Tobramycin/TOBI Podhaler®

CTBM100CDE02

Approved by the following

Signatures of Novartis Personnel:

[redacted] _____ _____
(Clinical Trial Leader) signature date

[redacted] _____ _____
(Trial Statistician) signature date

[redacted] _____ _____
(Head Therapeutic Area) signature date

Signature of Coordinating Investigator (LKP according to German Drug Law):

[redacted] _____ _____

(Coordinating Investigator [LKP]) signature date

Signature Page for Investigator

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I have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with the principles outlined in the Declaration of Helsinki. Note: Any deviations from this protocol require a formal amendment to be approved by the responsible ethics committee.

(Investigator)	signature	date

Center name / location:

institution (where applicable)	city

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List of post-text supplements

None.

List of tables

List of abbreviations

AE	adverse event
ALT	alanine aminotransferase/glutamic pyruvic transaminase/GPT
AST	aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
b.i.d.	bis in die/twice a day
CF	cystic fibrosis
CFU	colony-forming units
CRF	Case Report/Record Form
CPO	Country Pharma Organization
CRO	Contract Research Organization
CSR	Clinical Study Report
DS&E	Drug Safety and Epidemiology
ECG	Electrocardiogram
ECFS	European Cystic Fibrosis Society
FEV_1	forced expiratory volume at 1 second
FRC	Functional residual capacity
HRCT	High-Resolution Computer tomography
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
i.v.	intravenous(ly)
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
LCI	lung clearance index

MBW	multiple breath inert gas washout
MIC	minimal inhibitory concentration
o.d.	omnia die/once a day
PAES	post-authorisation Efficacy Studies
PASS	post-authorization safety study
p.o.	per os/by mouth/orally
SAE	serious adverse event
S_{acin}	N_2 slope acinar airways
S_{cond}	N_2 slope conductive airways
SOP	standard operation procedure
SPCS	Study Protocol Concept Sheet
TAQ	treatment adherence questionnaire
WOCBP	Women of child-bearing potential

Glossary of terms

Assessment	A procedure used to generate data required by the study
Control drug	A study drug used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e., prior to starting any of the procedures described in the protocol)
Investigational drug	The study drug whose properties are being tested in the study
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Patient number	A number assigned to each patient who enrolls in the study; when combined with the center number, a unique identifier for each patient in the study is created.
Phase	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival

Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Study drug	Any drug administered to the patient as part of the required study procedures; includes investigational drug, combination of drugs and any control drugs including placebo
Study drug discontinuation	Point/time when patient permanently stops taking study drug for any reason; may or may not also be the point/time of premature patient withdrawal
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints

Amendment 2

Amendment rationale

The protocol is being amended to allow for a more clear and detailed documentation of screening failures with a following re-screening of the patient. In order to limit eCRF page numbers per patient and to optimize the database structure and thus the usability of the data capturing system, a change of the individual number for patients who will be rescreend will be permitted. Furthermore, the change of patient no. in re-screened patients will allow for a unique and well matched visit numbering in the data capturing and the study management system.

Changes to the protocol

Section 6.1, Patient numbering: The term "*and the patient no. for that individual must not be changed, even if the patient is re-screened*" has been removed.

The changes in this amended protocol are non-substantial.

Amendment 1

Amendment rationale

The protocol is being amended:

1. To clarify the LCI assessment, and to align the protocol with the standard assessment approach for LCI of the device manufacturer. The revised section 7.4.1 reflects now the workflow implemented in the Exhalyzer D device by the actual "Spiroware" software version. Following Investigator-feedback, the upper limit for the FRC coefficient of variation has been increased from 10% to 25% to help reducing the number of MBW measurements needed in pediatric CF patients with moderate lung disease. In addition, this change allows for the documentation of values for LCI and FRC which have been automatically calculated by the device-software. A more detailed and step-by-step description for the LCI assessment makes it easier for the study team to follow the protocol.
2. To add the change of pulmonary air trapping after 1 week, 4 weeks, and 8 weeks versus baseline to the protocol as an explorative objective. Air trapping will be assessed by the difference in FRC measured by bodyplethysmography (FRC_{ples}) and FRC measured by MBW (FRC_{MBW}). In this study, spirometry is done by bodyplethysmography. Thus, FRC_{ples} is already documented in the source documents. Beneficial effects of treatment with inhaled tobramycin may include a reduction of air trapping by recruitment of lung units previously not contributing to ventilation. If the time constant in newly recruited units is slower, ventilation inhomogeneity, and therefore LCI, may increase despite the positive treatment effect (Robinson 2009).
3. Following feedback of investigators, the guidance for the spirometric timeframe has been updated according to Borsboom 1999, to allow for a more flexible assessment planning.
4. Finally, a couple of minor changes have been made to help investigators follow the protocol, eg. clarification regarding use of rescue medication and a table has been added about washout of prohibited medication.

Changes to the protocol

Section 3.2: *To explore the change in air trapping (FRC_{ples} - FRC_{MBW}) after 1 week, 4 weeks, and 8 weeks versus Baseline, respectively*, has been added as exploratory objective. The third bullet point has been clarified.Section 4.: The term *and reconfirm* has been deleted

Section 5.: *Germany* has been replaced by *DACH region*

Section 6.4: The term *and in accordance with the SmPC* has been added.

Section 6.6.4.1: An error regarding the compliance assessment has been corrected

Section 6.6.7: Definition and the use of rescue medication has been clarified

Section 6.6.8: A table about washout of prohibited and concomitant medication has been added, *inhaled steroids* was changed in *oral or inhaled steroids*

Section 7: Added FRC_{ples} assessment to the assessment schedule; Sputum can be collected by the patient at evening on the day before visit 2 if an early morning Baseline visit is not possible. Timeframe between MBW and spirometry assessment has been clarified.

Section 7.4.1: Upper limits for the FRC and LCI coefficient of variation have been increased to 25% and 10% respectively, the LCI assessment part has been changed to a more detailed step-by-step description. Washout timeframes for concomitant medication have been replaced by a reference to section 6.6.8. and guidance for reassessment of LCI has been clarified

Section 7.4.2: The guidance for the spirometric timeframe has been updated: Approximately same timepoints at visits 2-5 for measurements in the morning and a more flexible timeframe for measurements after 11:00

Section 9.3: *Local laboratory data* has been changed to *central laboratory data*

Section 10.5.1: The term *All other secondary and exploratory endpoints will be analyzed descriptively* has been added

Section 11: The rationale for the new explorative objective has been added.

Section 12: The references *Robinson 2009* and *Borsboom 1999* have been added

The changes in this amended protocol are substantial. An approval of this amended protocol by the Institutional Review Board (IRBs)/ Independent Ethics Committee (IECs) and Health Authorities prior to implementation is required.

1 Background

Cystic fibrosis (CF) patients are susceptible to respiratory infection with Pseudomonas aeruginosa, which is associated with decline in lung function and increased morbidity and mortality. Inhalation of Tobramycin, administered in repeated cycles of 28 days twice daily followed by 28 days off-drug, has been established as an effective and safe treatment of chronic *P. aeruginosa* infections in CF patients aged 6 years and older (Ramsey 1999, TOBI® 2013, Bramitob® 2013, Konstan et al 2011a) and is currently antibiotic standard maintenance therapy in CF.
Three different drug formulations are available in Germany: Tobramycin 300mg/5mL solution for nebulizers (TOBI, Novartis; Steri-neb, TEVA), Tobramycin 300mg/4mL solution for nebulizers (Bramitob, Chiesi) and Tobramycin powder inhaler (TOBI Podhaler, Novartis).

The only parameter of lung function that is currently recognized as a surrogate endpoint in CF trials is the forced expiratory volume in one second (FEV_1). However, FEV_1 mainly reflects large conducting airways (Macklem 1998) and is relatively insensitive to changes in the small airways, where CF lung disease starts. Bronchoscopic and HRCT data demonstrated, that significant structural lung damage can be present despite normal spirometry (Ellemunter et al 2010; Gustafsson et al 2008; de Jong et al 2006). Moreover, as a consequence of improved patient management, many children have FEV_1 within the normal range and the rate of decline of FEV_1 has steadily decreased over the last decade (Konstan et al 2011b; Que et al 2006). Thus, power calculations show that many hundreds of children would need to be treated for a long time to see any beneficial effect of a novel therapeutic approach in early lung disease when FEV_1 is used as the primary surrogate outcome parameter (Rosenfeld 2007; Davis et al 2007). Accordingly, there is a need for parameters that are more sensitive and allow detection of changes in disease severity, either naturally occurring or in response to interventions both long-term and short-term.

The potential of the method of multiple-breath wash-out (MBW) has been hampered by the lack of a convenient method, but Horsley, and more recently, a study by Fuchs et al. demonstrated the sensitivity and practicability of the read out parameter Lung clearance index (LCI) in healthy volunteers and CF patients when measured with the newly developed MBW devices Exhalyzer D, EasyOne Pro MBW module, and Innocor respectively, now suitable for clinical practice (Fuchs et al 2008; Fuchs et al 2012; Horsley et al 2008; Kent et al 2014).

The MBW system is based on the wash out of an inhaled inert tracer gas from the lungs during relaxed breathing. LCI is defined as the number of lung volume turnovers needed until the lungs are cleared from the tracer gas. An increased LCI (> 7.5) indicates ventilation inhomogeneity and thus, changes in peripheral airways.
The technique is non-invasive, without radiation exposure, easy to perform (requires only tidal breathing, and no additional coordination, cooperation, or forced maneuvers) and can be performed at all ages, including infancy and pre-school ages.

A previous study conducted in 142 children with CF, prospectively evaluated over an age range of 6 to 20 years, showed that the LCI predicts progression of pulmonary disease earlier

in life and with higher accuracy than FEV_1 did (Kraemer et al 2005). By now, superior sensitivity of LCI has also been shown in adults with CF, where patients with normal spirometry showed increased values of LCI (Horsley et al 2008). In contrast to FEV_1, LCI has also been shown to correlate with CT parameters and possess the greatest sensitivity for detecting structural CT abnormalities (a normal LCI almost ruled out the presence of CT abnormalities in a recent study (Gustafsson et al 2008). But so far, data about LCI used as parameter for measuring response to treatment is very limited and for the use as clinical endpoint in studies with inhaled antibiotics, LCI still needs to be evaluated.
One disadvantage of the LCI is that obstructed and poorly ventilated lung regions do not contribute to the overall measurement, thus limiting the value of LCI assessment in patients with severe lung disease.

In conclusion, previous studies suggest that LCI may be a more sensitive surrogate parameter to assess early lung disease, treatment effects in patients with milder lung disease and/or disease progression in CF patients. CF Patients on regular antipseudomonal standard inhalation therapy in an on / off regimen (e. g. Tobramycin 300mg/5mL b.i.d) are showing well characterized differences in FEV_1 between on and off-cycles (Ramsey et al 1999; Konstan et al 2011a), thus allowing an evaluation of LCI on basis of these intraindividually observed FEV_1 alterations in a comparatively simple study design.

2 Study purpose

The purpose of the study is to evaluate LCI by a standardized procedure in a well characterized study setting and to assess feasibility of LCI as a more sensitive method than FEV_1 to measure effectiveness of antibiotic therapy in patients with CF aged 6 years and older with mild to moderate lung disease.

3 Objectives (and related endpoints)

The primary objective is to assess the change of LCI after 4 weeks following onset of study drug inhalation versus Baseline.

3.1 Secondary objective(s)

- Change of FEV1 after 4 weeks following onset of study drug inhalation versus Baseline.
- Change in CFU after 4 weeks following onset of study drug inhalation versus Baseline
- Change of LCI after 1 week following onset of study drug inhalation versus Baseline.
- Change of LCI, FEV1 and CFU between week 4 (end of Study drug inhalation in the current treatment cycle) and week 8 (prior to start of Study drug inhalation in the following treatment cycle).
- Correlation between the changes of LCI, FEV_1 and CFU after 1 week, 4 weeks, and 8 weeks versus Baseline, respectively.

3.2 Exploratory objective(s)

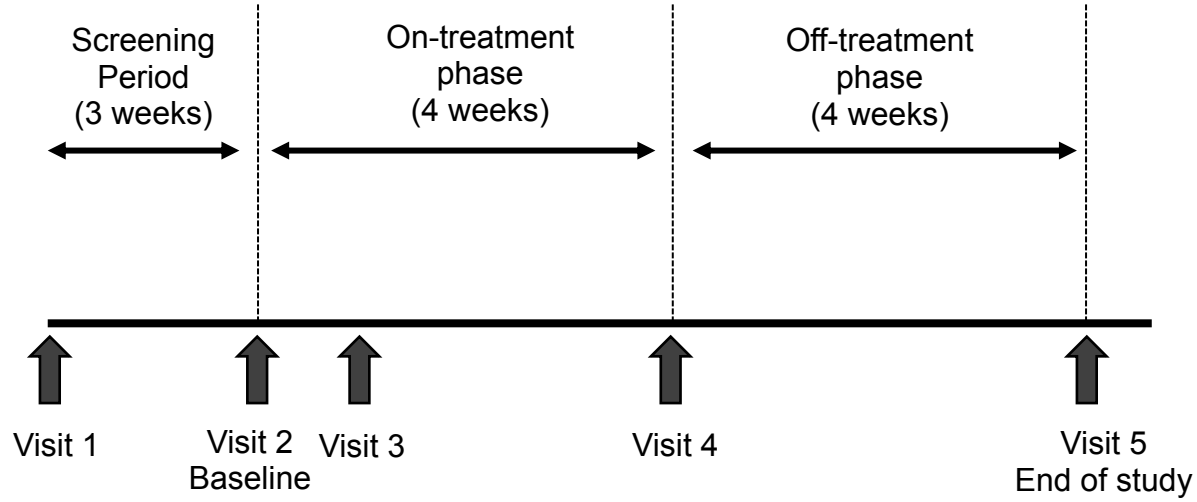
- To explore the change in LCI between Baseline and week 4 (week 0-4), and week 4 and week 8 (week 4-8), respectively, in patients using Tobramycin inhalation powder compared to patients using Tobramycin inhalation solution.
- To assess and compare S_{acin} and S_{cond} at baseline and at Visit 4 in patients using Tobramycin inhalation powder vs. patients using Tobramycin inhalation solution.
- To assess the changes in FEV_1 and CFU from Baseline to Visit 3 (week 1) and to compare the change in FEV_1 with the change in CFU and the change in LCI from baseline to Visit 3 (week 1) with the corresponding changes in FEV1 and CFU.
- To explore the change in air trapping (FRC_{ples} - FRC_{MBW}) after 1 week, 4 weeks, and 8 weeks versus Baseline, respectively.
- To explore the association of additional markers of disease progression (need for i.v. antipseudomonal therapy, hospitalization due to exacerbations of lung disease) on LCI at Baseline.
- To assess and compare the ratio of patients with pathological LCI and pathological FEV_1 and their mean deviation from normal LCI and FEV_1 at Baseline.
- To assess and compare the ratio of patients with pathological LCI and pathological FEV_1 and their mean deviation from normal LCI and FEV_1 at week 4.

4 Study design

This study uses an open-label, single arm design in patients suffering from CF, aged 6 years and older, with an elevated LCI of ≥ 7.5 at screening, who have a chronic pulmonary infection with *P. aeruginosa* (confirmed within the last 12 month and at screening), and who are receiving inhaled Tobramycin therapy in a 28 days on / off regime in the past 3 month before screening.

The study will consist of a 5 – 26 days screening period to test the presence of *P. aeruginosa*, a baseline visit, followed by the treatment phase of 28 days on-treatment period and subsequently 28 days off-treatment period. During the study a total of 5 visits is designated. A schematic overview is given in Table 4-1; for detailed visit schedule and assessments please refer to Table 7-1.

Table 4-1 Study design



5 Population

The study population will consist of a representative group of males and females aged ≥ 6 years at the time of screening with a diagnosis of CF, with an LCI of ≥ 7.5 at screening who have a pulmonary infection with *P. aeruginosa*. It is intended that 35 patients (children, adolescents and young adults) will be recruited in the DACH region at approximately 8 study sites.

5.1 Inclusion/exclusion criteria

The investigator must ensure that all patients who meet the following inclusion and do not fulfill any of the exclusion criteria are offered enrollment in the study. No additional exclusion parameters can be applied by the investigator, in order that the study population will be representative of all eligible patients of the respective CF center. Patients who are not fulfilling all criteria, may be rescreened in the following off-treatment phase.

Inclusion criteria

Patients eligible for inclusion in this study have to fulfill all of the following criteria:

1. Provide written informed consent and assent (as appropriate for minors) prior to the performance of any study-related procedure.
2. Confirmed diagnosis of CF by one or more of the following tests for CF (current or historic):
    a. quantitative pilocarpine iontophoresis sweat chloride test of greater than 60 mmol/L or 60 mEq/L
    b. genotype with 2 identifiable CF-causing mutations
    c. an abnormal nasal transepithelial potential difference characteristic of CF
3. Male and female patients 6 - 50 years of age at screening (Visit 1).

4. Patients with elevated LCI of ≥ 7.5 at screening, confirmed by a central MBW specialist.
5. Patients with FEV1 of ≥ 50% predicted at screening
6. *P. aeruginosa* must be present in two sputum or deep cough throat swab cultures or bronchoalveolar lavage (BAL) (only for BAL, a threshold level of 10^3 CFU/mL is required) within 12 months prior to screening or in one culture within 12 months prior to screening and in the sputum or deep cough throat swab culture at screening
7. Use of inhaled Tobramycin in a 28 days on / off regimen in the past 3 months before screening, as prescribed by the treating physician.
8. Clinically stable in the opinion of the investigator and likely to be able to participate in the study until the end of the study (Visit 5)

Exclusion criteria

Exclusion criteria:

1. History of sputum culture or deep cough throat swab (or BAL) culture yielding *Burkholderia cenocepacia* complex within 2 years prior to screening and / or sputum culture yielding *B. cenocepacia* complex at screening (Visit 1).
2. Hemoptysis more than 60 mL at any time within 30 days prior to screening (Visit 1).
3. History of hearing loss or chronic tinnitus.
4. Serum creatinine 2mg/dL or greater, BUN 40 mg/dL or greater, known local or systemic hypersensitivity to aminoglycosides.
5. Patients who are regularly receiving more than 1 class of inhaled anti-pseudomonal antibiotic during the study or in the past 56 days (8 weeks) prior to baseline visit (Visit 2).
6. Patients who have used oral or intravenous anti-pseudomonal antibiotics within 28 days prior to on-phase of study drug (Visit 2). These patients may be rescreened after 1 month following stop of i.v. treatment.
7. Change in dose, formulation or strength of the study drug in the past treatment cycle before screening.
8. Patients following onset or discontinuation of therapy with macrolides, chest physiotherapy, nebulized hypertonic saline, dornase alpha, long acting bronchodilators, inhaled steroids or inhaled mannitol during the study and within 56 days (8 weeks) prior to baseline visit.(V2)
9. Use of loop diuretics within 7 days prior to first study medication administration (Visit 2).
10. Administration of any investigational drug within 30 days or 5 half-lives, whichever is longer, prior to screening (Visit 1).
11. Signs and symptoms of acute pulmonary disease, e.g. pneumonia, pneumothorax.
12. Body mass index less than 12 kg/m^2.
13. Body weight of less than 15 kg.

14. History of malignancy of any organ system, treated or untreated, regardless of whether there is evidence of local recurrence or metastases.
15. Patients with known or suspected neuromuscular disorders, e. g. Parkinson´s disease, Myasthenia gravis.
16. Patients or caregivers who are considered potentially unreliable or considered unlikely to be compliant within the trial.
17. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test (> 5 mIU/mL).
18. Women who are menstruating and capable of becoming pregnant* and either not practicing a medically approved method of contraception (Pearl Index <1**) or not practicing total abstinence (when this is in line with the preferred and usual lifestyle of the patient) during and up to at least 4 weeks after the end of treatment. A negative pregnancy test (serum) for all women and for girls entering menarche is required with sufficient lead time before inclusion
    *definition of post-menopausal: 12 months of natural (spontaneous) amenorrhea or 6 months of spontaneous amenorrhea with serum FSH levels >40 mIU/mL or 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy
    **examples of particularly reliable methods with Pearl Index (PI) <1, according to guidelines of Deutsche Gesellschaft für Gynäkologie und Geburtshilfe:
    - hormonal oral contraception (Combination of estrogen and gestagen, PI=0.1-0.9)
    - hormonal vaginal ring (combination of estrogen and gestagen, PI=0.65 uncorr.; 0.4 corr.)
    - hormonal transdermal patch (combination of estrogen and gestagen PI= 0.72 uncorr.; 0.9 corr.)
    - Estrogen-free ovulation inhibitors (containing desogestrel (PI=0.14)
    - Implanted hormones containing etonogestrel (PI=0-0.08)
    - Injectable 3-month depot progestins (PI=0.3-1.4; 0.88 corr.)
    - Intra-uterine progestine device (synthetic progestin containing IUDs,PI=0.16)

    Oral contraceptive without estrogen (e.g. "mini-pills"), nonsynthetic progesterone only IUDs, female condoms, cervical shield, periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception..
19. Study personnel or first degree relatives of investigator(s) must not be included in the study.

5.2 Premature patient withdrawal

Patients must be withdrawn from the study for any of the following reasons:

- Withdrawal of informed consent
- Pregnancy

- Discontinuation of study drug treatment for more than 3 days during the on treatment phase
- Use of prohibited medication (see Table 6-1)

Patients also should be withdrawn at any time if the investigator concludes that it would be in the patient's best interest for any reason. Protocol violations should not lead to patient withdrawal unless they indicate a significant risk to the patient's safety.

Patients may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, or fail to return for visits, or become lost to follow up for any other reason.

If premature withdrawal occurs for any reason, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the Study Completion CRF.

For patients who are lost to follow-up (i.e., those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

Patients who are prematurely withdrawn from the study will not be replaced by newly enrolled patients.

6 Treatment

6.1 Patient numbering

Each patient in the study is uniquely identified by a patient number which is a combination of his/her center number and subject number. The center number is assigned by Novartis to the investigative site. Upon signing the informed consent form, the patient is assigned a patient number by the investigator. At each site the first patient is assigned patient number 1, and subsequent patients are assigned consecutive numbers (e.g., the second patient is assigned patient number 2, the third patient is assigned patient number 3). Once assigned to a patient, a patient number will not be reused for any other patient. If the patient fails to enter the trial for any reason, the reason for not being enrolled to the trial will be entered on the Screening Log.

The patient list has to be kept separate from the other study documents and must not be transferred to the sponsor for any reason.

6.2 Investigational and control drugs

Tobramycin, either as Tobramycin inhalation solution (TIS, 300mg/5mL or 300mg/4mL) to be nebulized or as Tobramycin inhalation powder (TIP, 112mg), as prescribed by the treating physician. Neither TIS nor TIP will be provided to the patient.

6.3 Treatment arms

This is a single arm study including solely patients treated routinely with inhaled Tobramycin (study drug) in a 28 days on / off treatment regimen.

6.4 Treatment assignment

All patients will continue their standard maintenance-therapy with Tobramycin inhalation (study drug) in a 28 days on / off cycle, as prescribed by the treating physician and in accordance with the SmPC.

6.5 Treatment blinding

Not applicable. This study has an open-label design.

6.6 Treating the patient

6.6.1 Dispensing the study drug

Patients will be treated by standard of care according to investigators' routine. Commercially available product will be used as prescribed by the treating physician.

6.6.2 Instructions for use of study drug

Study drug will be used according to the prescription of the treating physician, in a 28 on / off treatment regimen and in accordance with the SmPC.

6.6.3 Study drug supply and resupply, storage, and tracking

Medication will be stored by the patient following the guidance in the SmPC. Study drug will not be provided to the patient by Novartis.

6.6.4 Study drug compliance and accountability

6.6.4.1 Study drug compliance

In this study, patients will be treated by standard of care in investigators' routine dosing frequency. Compliance will be assessed by the investigator and/or study personnel at patient visit 3, 4 and, if needed, 5. Information provided by the patient will be captured in the source data and in the CRF. To support the patient in reporting his compliance at visits 3 and 4, a medication diary will be provided.

6.6.4.2 Study drug accountability

Not applicable. Study drug will not be provided to the patient.

6.6.5 Disposal and destruction

Not applicable. Study drug will not be provided to the patient.

6.6.6 Permitted study drug dose adjustments and interruptions

Study drug dose adjustments are not permitted.

Any interruption of the inhalation of antipseudomonal antibiotics must be recorded on the Dosage Administration Record CRF. Discontinuation of study drug treatment for more than 3 days during the on treatment phase leads to premature study withdrawal.

6.6.7 Rescue medication

Rescue medication is any on demand medication at acute clinical deterioration of the patient, independent of the currently used standard therapy. Short acting bronchodilators are allowed at any time, except 6 hours or less prior to each FEV1/Spirometry and LCI measurement. For other rescue medication or concomitant treatments to relieve symptoms of the underlying disease, see Section 6.6.8.

Drug and dose of used rescue medication must be recorded on the Concomitant medications/Significant non-drug therapies after start of study drug CRF.

6.6.8 Other concomitant treatment

If a patient experiences a pulmonary exacerbation and/or worsening the disease condition he/she will be treated as deemed appropriate by the investigator. Following treatment for the Pulmonary exacerbation and/or worsening the condition, the patient will be expected to continue in the study if, in the opinion of the investigator, he/she can be safely returned to their pre-Pulmonary exacerbation concomitant medications. If the patient requires the prohibited treatment listed in Table 6-1, then he/she should be withdrawn from the study.

Table 6-1 Prohibited treatment

Medication	Action to be taken
Any inhaled antipseudomonal antibiotics other than tobramycin	Discontinue the study
Loop Diuretics	Discontinue the study
Any iv or oral antipseudomonal antibiotic 28 days prior baseline (V1) and 23 days prior end of study visit (V5)	Discontinue the study
Any other investigational treatments	Discontinue the study
Short Acting Beta Agonists (SABA)	Held treatment at least 6 hrs prior to each FEV1/Spirometry and LCI measurement.
Long Acting Beta Agonists (LABA) and	Held treatment at least 12 hrs prior to each

Long Acting Muscarinic Antagonists (LAMA)	FEV1/Spirometry and LCI measurement.

Table 6-2 Washout of prohibited treatment and study treatment/concomitant medication prior to study visits

Treatment/medication	Wash-out time	Timepoint	Remarks
SABA	6hours (h)	Prior to FEV1/LCI Assessment	
LABA / LAMA	12h	Prior to FEV1/LCI Assessment	
iv/oral Antibiotics	allowed in on-Phase + 5 Days in following off	Prior to Visit 5	Inhalation of Tobramycin stopped for more than 3 days: Discontinue the study
iv/oral Antibiotics	28 days	Prior to Visit 2	
Inhalation of Tobramycin	1h	Prior to FEV1/LCI Assessment	
Inhalation of Tobramycin	10h	Prior to sputum sampling (Sputum may be collected at home prior to visit)	Example for V3/4: Sputum sampling at home followed by Inhalation. Visit 4 on the next day.
Inhalation of Colistin or Aztreonam	56 days	Prior to visit 2	
Change in physiotherapy or inhalative concomitant medication, eg macrolides or steroids	56 days	Prior to visit 2	Macrolides, physiotherapy, pulmozyme, hypertonic saline, bronchitol, steroids, bronchodilators. Stable treatment is allowed.
Any other study drug	30 days	Prior to visit 1	30 days or 5x T 1/2, whitchever is longer

The following treatments **are permitted** between start of the study drug administration and completion/termination and should be accurately documented in the CRF:

- Anti-pseudomonal antibiotics
    - Intravenous or oral Anti-pseudomonal antibiotics are allowed for the treatment of Pulmonary exacerbation during the on-phase as needed by patient condition if i.v. treatment is completed 5 days latest after the end of the on-phase.
    - If patients are prescribed i.v. aminoglycosides for symptoms of pulmonary exacerbation, continuation of inhalation of Study drug is at the investigator´s discretion.
        - If inhalation of Study drug is continued during i.v. aminoglycoside therapy, patients will continue with the study schedule for the remainder of the study; however, therapeutic drug monitoring is strongly recommended with appropriate modification of the i.v. aminoglycoside dose as necessary;
        - Inhalation of antibiotics can be interrupted during i.v. aminoglycoside therapy (eg. due to elevated serum levels of study drug) for a maximum of 3 days. Patients should restart inhalation of antibiotics in order to complete the 28 days cycle as close as possible to their initial study schedule.
    - Pre-planned anti-pseudomonal antibiotics (i.v.) in the absence of an AE (prophylaxis of Pulmonary exacerbation) are not permitted during the study and 28 days prior Baseline Visit (V2)
- Macrolides (anti-inflammatory regimen)
  Patients should have been initiated or terminated on oral chronic macrolide therapy (i.e., macrolides prescribed for more than 14 days) more than 56 days (8 weeks) prior Baseline Visit (V2) and should remain on treatment or off treatment respectively through the completion/termination visit.
- Bronchodilators
  Patients should have been kept on the same regimen more than 56 days (8 weeks) prior to Baseline Visit (V2) through the completion/termination visit. If patients are taking short acting bronchodilators, they should have been inhaled 6 hours prior to any spirometric assessments or MBW measurement and long-acting bronchodilators should have been inhaled their last dose at least 12 hours prior to any spirometric or LCI assessments.
- Inhaled hypertonic saline
  Patients should have been initiated on therapy more than 56 days (8 weeks) prior Baseline Visit (V2) and should remain on unaltered treatment through the completion/termination visit. In addition, patients should be instructed to take their hypertonic saline at least 1 hour before their spirometric or LCI assessments. Patients should be consistent with the timing of taking their hypertonic saline at home or at the clinic prior to their spirometric or LCI assessments.
- Inhaled Mannitol

Patients should have been initiated on therapy more than 56 days (8 weeks) prior Baseline Visit (V2) and should remain on unaltered treatment through the completion/termination visit. In addition, patients should be instructed to take their mannitol at least 1 hour before their spirometric or LCI assessments. Patients should be consistent with the timing of taking their hypertonic saline at home or at clinic prior to their spirometric or LCI assessments.

- Dornase alfa
  Patients should have been initiated on therapy more than 56 days (8 weeks) prior Baseline Visit (V2) and should remain on unaltered treatment through the completion/termination visit.
- Oral or Inhaled corticosteroids
  Patients should have been initiated on therapy more than 56 days (8 weeks) prior to Baseline and should remain on unaltered treatment through the completion/termination visit.
- Use of oxygen, nutritional supplements, and enzymes is unrestricted at all times.

Use of all anti-pseudomonal antibiotics and macrolides administered within 12 months prior to screening will be recorded in the CRF.

The investigator should instruct the patient to notify the study site about any new medications he/she takes after the start of the study. All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled in the study must be documented in the source data and listed on the Concomitant medications/Significant non-drug therapies in the CRF.

6.6.8.1 Caution for concomitant use

Based on the interaction profile for tobramycin following intravenous and aerosolized administration, concurrent and/or sequential use of Study drug with other drugs with neurotoxic, nephrotoxic, or ototoxic potential should be avoided.
Other medicinal products that have been reported to increase the potential toxicity of parenterally administered aminoglycosides include:

- amphotericin B, cefalotin, ciclosporin, tacrolimus, polymyxins (risk of increased nephrotoxicity);
- platinum compounds (risk of increased nephrotoxicity and ototoxicity);
- anticholinesterases, botulinum toxin (neuromuscular effects).

Continuation of inhalation of Tobramycin or concomitant use of these substances is at the investigator's discretion. A close monitoring is strongly recommended

6.6.9 Study drug discontinuation

Study drug must be discontinued for a given patient if the investigator determines that continuing it would result in a significant safety risk for that patient. The following laboratory abnormalities **require** study drug discontinuation:

- above-normal BUN (40mg/dl or greater) following an earlier result within the normal range
- above-normal creatinine (2mg/dl or greater) following an earlier result within the normal range

In addition, the study drug has to be discontinued on any sign of hypersensitivity against Tobramycin and on signs of oto- or nephrotoxicity. In case of oto-or nephrotoxicity, an assessment of Tobramycin serum level is recommended. If the level is fallen below 2µg/ml, a restart of study drug may be considered by the investigator. A therapeutic drug monitoring should be initiated in patients with a history of any renal dysfunction and study drug has to be discontinued if the Tobramycin serum level exceeds 12µg/ml.

The last date of study drug intake should be entered into the Study Completion CRF and the reason for discontinuing study drug should be given on the comments page. If a patient who discontinued study drug therapy performed all scheduled study procedures and measurements, he will be counted as a study completer.

6.6.10 Emergency unblinding of treatment assignment

Not applicable. This study has an open-label design.

6.6.11 Study completion and post-study treatment

The study will be considered completed for an individual patient when he/she completes Study Visit 5. After this date, any SAEs occurring in this patient for the following 30 days will be reported (see Section 8.2). The investigator will follow-up any AEs ongoing or for which no final outcome can be reported at the termination visit. Pregnancies will be followed-up until birth (see Section 8.3).

The study as a whole will be completed once the clinical data base has been locked. It is intended that 35 patients will be recruited. Recruitment into the study is to be terminated by the sponsor once the targeted number of patients who start the study treatment has been met or is foreseen to be met with the patients already in screening. Any patient already in the screening phase at the time of termination of recruitment can still undergo the start of study processes.

After premature withdrawal Study Visit as designated for end of study should be scheduled as soon as possible.

The study can be terminated for reasons stipulated in the study contract. Should this be necessary, the patients should be contacted and scheduled for their end of study assessments as described in Section 7. Novartis will be responsible for informing IRBs and/or IECs of the early termination of the study.

7 Visit schedule and assessments

Table 7-1 lists all of the assessments and indicates with an "X" the visits when they are performed.

Patients should be seen for all visits on the designated day as shown in Table 7-1.

Patients who discontinue study drug therapy before completing the study, and those who prematurely withdraw from the study for any reason, should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit (visit 5) will be performed.

If they refuse to return for these assessments or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to determine at a minimum the safety evaluations during the 30 days following the last dose of study drug therapy, including final contact at the 30-day point. Documentation of attempts to contact the patient should be recorded in the patient record.

All data obtained from the assessments listed in Table 7.1 and described in detail in the subsections below must be supported in the patient's source documentation.

Table 7-1 Assessment schedule

Visit	1	2	3	4	5*
Procedure \ days	-26 to -5 Screening	1 Baseline	7 Week 1 (+/- 2 days)	28 Week 4 (- 3 days)	56 End of Study (- 3 days)
Inclusion / exclusion criteria	x	x			
Demographic data	x				
Obtain informed consent	x				
Physical examination	x	x			x
Vital signs	x	x	x	x	x
Height and weight / BMI	x	x	x	x	x
Clinical chemistry [a]	x				x
Sputum (microbiology) [b]	x	x	x	x	x
Lung function (spirometry)[c]	x	x	x	x	x
FRC (bodyplethysmography)		x	x	x	x
LCI/ MBW	x	x	x	x	x
Serum pregnancy test	x				x
Urine pregnancy test		x			
Adverse events		x	x	x	x
Serious Adverse events	x	x	x	x	x
Concomitant medication	x	x	x	x	x

* When a patient prematurely discontinues the study before study completion, all procedures at Visit 5 should be performed.

a. Clinical chemistry: urea, creatinine, CRP

b. Pre-treatment sputum to be collected, preferably the first morning specimen; if the patient is unable to produce a sputum specimen, a deep cough throat swab or an induced sputum sample will be collected, at the investigator's discretion.

c. Spirometry should be done using a bodyplethysmograph to allow for FRC_{ples} assessment in parallel

At screening (Visit 1), for patients who have consented to study participation, or on whose behalf informed consent has been obtained and who have assented to study participation, the following will be recorded: patient demographics, concomitant medication, the results from a physical examination including height and weight, Spirometry (FEV1), vital signs and LCI/ MBW. Blood, will be collected for serum pregnancy test (where applicable) and for safety laboratory testing. Sputum (or deep throat cough swabs, where applicable) will be collected to assess *Burkholderia cenocepacia complex* in all patients and *Pseudomonas aeruginosa* in patients for whom only one positive sputum culture in the year before screening is documented.

Following the screening period, the eligible patients who meet all inclusion/exclusion criteria will be enrolled in the study. All screening safety evaluation results must be available prior to enrollment. Sputum sampling at Baseline (V2) will be conducted before first inhalation of Study drug in the current treatment cycle to collect the baseline values. Thus, it is recommended to schedule visit 2 early in the morning. If this is not possible, Sputum can be collected by the patient at home before first inhalation (either in the evening the day before

V2 or on the day of V2 in the morning before first inhalation). Spirometric and LCI/MBW measurements will be conducted before or at least 1h after inhalation of Study drug, measurements should start with LCI/MBW followed by spirometry after a delay of at least 15 minutes.
Urine sampling for pregnancy testing will be conducted where applicable. A physical examination will be performed, vital signs and concomitant medication will be recorded. Height, and weight and Body mass Index (BMI) will be recorded.

Visit 3 will take place one week after baseline visit (+/- 2 days). Sputum sampling will be conducted before inhalation of antibiotics or at least 10h after. LCI/MBW and Spirometric measurements will be conducted before or at least 1h after inhalation of Study drug, measurements should start with LCI/MBW followed by spirometry after a delay of at least 15 minutes. Clinical signs and symptoms, BMI, height and weight, vital signs, concomitant medications, adverse events and assessment of dosing frequency and compliance will be recorded.

Visit 4 will take place 4 weeks after baseline visit at the last day of the on-cycle (- 3 days) but not thereafter. Sputum sampling will be conducted before inhalation of antibiotics or at least 10h after. Spirometric and LCI/MBW measurements will be conducted before or at least 1h after inhalation of Study drug, measurements should start with LCI/MBW followed by spirometry after a delay of at least 15 minutes. Vital signs, BMI, height and weight will be recorded. Following Visit 4, patients will enter the off-treatment period for 28 days (no antibiotics inhalation, but standard care maintained).

Completion/Termination: Patients return for a completion visit on the last day of the 28 days off-treatment period (- 3 days) but not thereafter (Visit 5). The required procedures are a physical examination including recording of height and weight, BMI, vital signs, spirometry and LCI/MBW measurement (starting with LCI/MBW followed by spirometry with a delay of at least 15 minutes), and recording of adverse events and concomitant medications. Blood, sputum (or deep throat cough swabs, where applicable), will be collected for safety laboratory testing and serum pregnancy test (where applicable).

If the patient terminates early from the study, all examinations of Visit 5 should be performed as a discontinuation visit. Reasons for discontinuations should be captured in the source documentation and by fully completing the relevant CRF Form sections with all information available to the investigator.

7.1 Information to be collected on screening failures

Patients may discontinue from the study between Visit 1 and prior to start the first intake of antibiotics in context to the study at Visit 2. These patients are considered screening failures.

Only demography data, occurred SAEs and the primary reason for discontinuation (screening failure log) are collected for those patients who fail to enter the treatment phase. It is not necessary to complete all the required evaluations at the time of discontinuation unless medically indicated.

Potential severe adverse events which may have occurred from time of signing informed consent/written assent until screening failure time should be documented in the patient medical records. Reporting during this time period should be followed as described in Section 8.2.

7.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all patients include: date of birth, age, sex, race and ethnicity. Furthermore, relevant medical history and current medical conditions present up to 6 months prior to signing of the informed consent will be collected. Whenever possible, diagnoses and not symptoms will be recorded.

Conditions and signs/symptoms associated with CF disease but not limited to pancreatic insufficiency, sinusitis, diabetes mellitus, and clubbing will be captured by using specific CF related CRF page. Previous medication to be listed includes information for all anti-pseudomonal antibiotics and macrolides administered within the last 12 months prior to Visit 1.

7.3 Treatment exposure and compliance

Assessment of compliance will be based on:

- The number of dosing sessions per day (e.g. morning and evening)
- The number of actual days on treatment (e.g. out of 28 in each cycle) and in the study

Compliance will be assessed by the investigator and/or study personnel at each visit using information provided by the patient via a patient diary.

7.4 Efficacy

7.4.1 Lung clearance index assessment

In general, LCI uses MBW of an inert gas (nitric oxide/oxygen) to measure ventilation inhomogeneity caused by airway narrowing from inflammation or partial mucus obstruction. Wash-out is completed by definition at the time point when the inhaled gas concentration declined to 1/40th of its concentration at baseline. Washout takes longer in Patients with more

severe disease as gas is trapped in narrowed airways (leading to a higher LCI). Alternatively, LCI can also be determined by the decline in concentration of exhaled nitrogen during inhalation of oxygen.

In this study, LCI will be determined according to the manufacturer's/Exhalyzer D SOP based on the current MBW guidelines of the European Cystic Fibrosis Society (ECFS), using the Exhalyzer D device and inhalation of oxygen to wash out nitrogen from the airways. A user guide with the MBW SOP for this study and a device specific training by the manufacturer will be provided to every study site. LCI will be assessed using the same equipment throughout all sites. This equipment will be provided by the sponsor during the study if it is not already available at the site.

Children aged 6-10 may perform only two consecutive MBW measurements. Two additional measurements can be performed after a break of 15 minutes. From age 10-14, only 3 consecutive measurements are allowed that may be repeated after a break of 15 minutes. There is no limit for older patients.

[redacted]

- [redacted]
- [redacted]
- [redacted]

For MBW measurements, the subjects should breathe seated, in an upright position with head in midline. They should wear a nose clip and maintain tight mouthpiece seal. For washout of concomitant medication, prior to MBW, see section 6.6.8.

Lung function measurements should start with LCI/MBW followed by spirometry after a delay of at least 15 minutes following the conclusion of the MBW assessment.

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

1. [redacted]
2. [redacted]
3. [redacted]

For the measurements used to calculate the mean value, a quality control will be done by a central assessor (MBW specialist). For exploration and control reasons, the S_{cond} and S_{acin} values (slope analysis) will be recorded as well.

If the quality of the measurements is too low according to the judgement of the specialist:

- MBW at Visit 1 may be repeated in the screening timeframe
- If MBW at Visit 2 cannot be repeated at the same day, the patient has to be withdrawn
- MBW's at Visits 3 and 4 have to be repeated within 5 days after initial measurement or the patient has to be withdrawn.
- MBW at Visit 5 cannot be repeated on the following day if the patient has already restarted inhalation of Tobramycin in the new treatment cycle.

7.4.2 Spirometry assessment

FEV_1 will be assessed as a pulmonary function by using spirometry. A bodyplethysmograph should be used for spirometry to allow for an assessment of FRC_{ples} in parallel.

During each visit, pulmonary function test will be measured. For all clinic spirometry assessments, three acceptable maneuvers (a maximum of 8 maneuvers) should be performed for each time-point. The FEV1 value recorded must be the highest value measured irrespective of whether or not they occur on the same curve. All displaceable volumes will be reported in liters (L) at the following conditions: normal body temperature (37° C), ambient pressure, saturated with water vapor (BTPS).

Spirometry performance of spirometric testing should be in accordance with ATS standards (Miller et al, 2005). Staff will be trained at the investigator's meeting to perform spirometry assessments. Whenever possible the same staff member should evaluate and coach a given patient at each visit throughout the study. In addition the spirometer should be calibrated every morning before taking any spirometric measurements for this study. Calibration reports

should be stored as source data. Spirometric measurements shall be conducted at approximately the same time of day Therefore, investigators and patients should make every effort to conduct the spirometry at the same time of day during the study (max. +/- 1h difference). If the Investigator foresees difficulties in conducting the spirometry at the same time, eg. due to cohort separation in the CF-Center, spirometry should be scheduled always in the afternoon (after 11:00 AM) to minimize effects of diurnal variability in pulmonary function (Borsboom 1999).

Activities that should preferably be avoided prior to lung function testing (Miller 2005)

- Smoking within at least 1 h of testing
- Consuming alcohol within 4 h of testing
- Performing vigorous exercise within 30 min of testing
- Wearing clothing that substantially restricts full chest and abdominal expansion
- Eating a large meal within 2 h of testing

7.4.3 Microbiological assessment

For microbiological assessment, sputum will be collected in sterile containers. If a patient is unable to expectorate, a deep-throat cough swab may be collected or sputum may be induced at the investigator's discretion. Sputum will be cultured for the presence of *P. aeruginosa* (quantitative test) and *B. cepacia complex,*. Deep-throat cough swab specimens will be evaluated qualitatively only.

Tobramycin MIC values for *P. aeruginosa* will be determined for specimens obtained at the visits listed previously to assess change in pathogen susceptibility to applied study drug before and after the treatment.

Microbiological assessment will be performed in a central laboratory.

7.5 Safety

7.5.1 Adverse events

For details on adverse event collection and reporting, refer to section 8.

7.5.2 Physical examination

Physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, additional exams may be performed.
Information for all physical examinations must be included in the source documentation at the study site and will not be recorded in the CRF.

Any clinically significant conditions that are present prior to baseline visit, must be recorded on the Relevant Medical History/Current Medical Conditions pages of the CRF.

Significant findings identified after enrollment to the study which meet the definition of an Adverse Event must be recorded on the Adverse Event part in the CRF.

7.5.3 Vital signs

Systolic/diastolic blood pressure, radial pulse rate (over a 30 s interval), respiratory rate and body temperature will be recorded. Single measurements will be performed before inhalation of study medication on the treatment period.

All blood pressure measurements should be taken after the patient has rested in the sitting position for at least 10 min.

7.5.4 Laboratory evaluations

Non-fasting standard laboratory tests will be conducted as indicated in Table 7-1. Subjects should avoid smoking within the hour preceding the blood draws.
A central laboratory will be used for analysis of all specimens listed below, unless noted otherwise. Standard urine pregnancy test will be provided by the central lab and may be performed at site/in a local laboratory. Refer the Laboratory Manual for identification of laboratory reference range values and the schema for notification of site staff and Novartis for out of range values.
Standard laboratory tests:

- Clinical chemistry: Clinical chemistries will include urea, creatinine and CRP.

7.5.5 Pregnancy test and assessments of fertility

All female patients after the onset of menarche, who are not surgically sterile, will have a serum pregnancy test carried out by the central laboratory from the blood sampled for safety laboratory examination at Visits 1 and 5 (or discontinuation visit). Additionally, a urine pregnancy test will be done at Visit 2. A positive serum pregnancy test at Visit 1 leads to the exclusion of the patient from the study prior to the start of study drug administration in context of the study. In case of a positive urine pregnancy test at Visit 2, the result should be verified by a serum pregnancy test. If positive, the patient must be discontinued from the trial - alike for all positive test results throughout the study. In case of positive test results the pregnancy must be followed up until after birth.

7.6 Tolerability/acceptability

Not applicable

7.7 Resource utilization

Not applicable

7.8 Treatment Assessment

Not applicable

7.9 Pharmacokinetics

Not applicable

7.10 Pharmacogenetics/pharmacogenomics

Not applicable

7.11 Other biomarkers

Not applicable

8 Safety monitoring

8.1 Adverse events

8.1.1 Adverse event definition and reporting

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after signing of informed consent, even if the event is not considered to be related to the diagnostic method of the study.

Medical conditions/diseases present before first intake of study drug are only considered adverse events if they worsen after study start. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, require dose reduction or temporary or permanent study drug discontinuation or require therapy. All adverse events with a date of onset up to 30 days following the last dose of study drug/the last study examination must be reported.

The occurrence of adverse events should be sought by non-directive questioning of the patient and his/her parents (for minors) 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, laboratory test, or other assessments. All adverse events must be recorded on the Adverse Events CRF with the following information:

1. the severity grade (mild, moderate, severe)
2. its relationship to the study drug(s) (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)
4. whether it constitutes a serious adverse event (SAE)

All adverse events should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); study drug or study diagnostic method dosage adjusted/temporarily interrupted; study drug or study diagnostic method permanently discontinued due to this adverse event; concomitant medication given; non-drug therapy given; patient hospitalized/patient's hospitalization prolonged. The action taken to treat the adverse event should be recorded on the Adverse Event CRF.

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

8.1.2 Laboratory test abnormalities

Laboratory abnormalities that constitute an Adverse Event in their own right (are considered clinically significant, induce clinical signs or symptoms, require dose reduction or temporary or permanent study drug discontinuation or require concomitant therapy), should be recorded on the Adverse Event CRF page. Whenever possible, a diagnosis, rather than a symptom should be provided. Laboratory abnormalities that meet the criteria for an Adverse Event should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events.

A grade 3 or 4 event or laboratory abnormality (severe) as per CTCAE (if applicable) does not automatically indicate an SAE unless it meets the definition of serious as defined below and/or as per investigator´s discretion. If a lab event satisfies the regulatory definition of "Serious", such an event must be reported to Novartis within 24 hours of learning of its occurrence. Any laboratory SAEs experienced 30 days after completion of the study period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

8.2 Serious adverse events

8.2.1 Serious adverse event definition, treatment and follow-up

An SAE is defined as an event which:

- 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 the start of study drug
  - 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, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; SAEs in contrast to AEs need to be reported from informed consent on, see Section 8.2.2.

Information about common side effects already known about study drug and diagnostic method can be found in Investigator Brochure (Novartis), or SmPC (other study drugs), respectively, or will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.2.2 Serious adverse event reporting

To ensure patient safety, every SAE, regardless of suspected causality, and until 30 days after the patient has stopped study participation (defined as last visit) must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 day period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug or diagnostic method. For patients who discontinue study medication, SAEs still need to be reported until the end of study, regardless of their suspected relationship to study medication.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess the relationship to study drug, complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the German Novartis Clinical Safety & Epidemiology Department. The telephone and telefax number of the contact persons in the German department of Clinical Safety and Epidemiology, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

All serious AEs occurring during the follow-up will be entered in the Adverse Events CRF pages. In addition, an SAE Report Form should be completed. Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. 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.

If the SAE is not previously documented (new occurrence) and is thought to be related to the Novartis study drug, a Clinical Safety & Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may

need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same drug that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Pregnancy reporting

To ensure patient safety, each pregnancy in a patient on study drug must be reported to Novartis 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.

Instances of pregnancies and positive pregnancy tests should be collected for all patients who have conceived after receiving study drug (following Visit 2 until Visit 4). Pregnancies that are noted prior to administration of study medication but after signing informed consent may require reporting if they are considered to be associated to the conduct of the study by the investigator. Pregnancies that are noted following Visit 4 (off-phase) have to be reported as well (see 8.4).

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the German Novartis Clinical Safety & Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

8.4 Reporting of adverse events and pregnancies after the last dose of study drug taken

All AEs, SAEs, and pregnancies which occurred within 30 days after last intake of last dose of study drug should be reported. After this 30-day period, only SAEs, and pregnancies should be reported until the last visit.

8.5 Data Monitoring Board

Not applicable

9 Data review and database management

9.1 Site monitoring

Before study initiation, at a site initiation visit, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of

entries on the CRFs, the adherence to the protocol and to Good Clinical Practice and the progress of enrollment. Key study personnel must be available to assist the field monitor during these visits.

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.

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety 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 will be disclosed.

9.2 Data collection

Designated investigator staff will enter the data required by the protocol into the CRF using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator staff will enter the data required by the protocol into the Novartis CRFs Automatic validation programs check for data discrepancies in the CRFs and, by generating appropriate error messages, allow modification or verification of the entered data by the investigator staff. The investigator must certify that the data are complete and accurate by signing the CRF pages or a memo that will be sent to him by Novartis personnel after the last transfer of the data prior to analysis. After database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

9.3 Database management and quality control

A clinical research organization (CRO) working on behalf of Novartis reviews the CRFs entered by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an

electronic data query. Designated investigator site staff is required to respond to the query and

confirm or correct 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. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Spirometry data and LCI will be entered on the CRF by the site and transferred to Novartis. MBW plots will be transferred by Fax or secure email to the central MBW specialist. Central laboratory data will be transferred electronically to Novartis using an agreed Data Transfer Specification.

At the conclusion of the study, the occurrence of any protocol violations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and made available for data analysis. Any changes to the database after that time can only be made by joint written agreement between the Trial Statistician and Statistical Reporting and the Clinical Trial Leader.

10 Data analysis

The data will be analyzed by Novartis and/or by the designated CRO. Any data analysis carried out independently by the investigator(s) should be submitted to Novartis before publication or presentation.

It is planned that the data from all centers that participate in this protocol will be used, so that an adequate number of patients will be available for analysis.

Data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, pharmacokinetic measurements, and biomarker measurements.

10.1 Populations for analysis

The safety set will consist of all patients that enter the study (provide Informed Consent). All analyses will be based on the safety set.

10.2 Patient demographics/other baseline characteristics

Appropriate descriptive statistics for demographic, disease history and baseline characteristics will be presented to describe the study population.

Categorical variables will be presented as the number and percentage of patients in each category. Continuous variables will be summarized using descriptive statistics (i.e., n, mean, standard deviation, median, minimum and maximum).

10.3 Treatments (study drug, rescue medication, other concomitant therapies, compliance)

Duration of exposure to Study drug during the treatment cycles and compliance will be summarized.

Summary data listings will be provided for concomitant therapy both prior to and after start of study drug administration. The WHO Drug Reference dictionary will be used for coding of medications.

10.4 Analysis of the primary objective(s)

10.4.1 Variable

The primary variable of this study is the time course and changes in LCI from baseline to week 4.

10.4.2 Statistical hypothesis, model, and method of analysis

Time course and changes in LCI from baseline to week 4 will be estimated using an ANOVA model with factors patient and visit. Estimates will be presented as LS-Means with 95% confidence intervals for each visit as well as for the pairwise differences between visits, additionally, these results will be displayed graphically.

10.4.3 Handling of missing values/censoring/discontinuations

There will be no imputation of missing data.

10.4.4 Supportive analyses

Not applicable.

10.5 Analysis of secondary objectives

10.5.1 Efficacy (secondary)

FEV_1 and CFU will be analyzed analogously to LCI, the correlation between FEV_1 ,CFU and LCI will be explored using scatterplots (for raw values as well as for changes). The correlation coefficients will be calculated together with their 95% confidence intervals and p-values. All other secondary and exploratory endpoints will be analyzed descriptively.

10.5.2 Safety

Safety assessments will be based mainly on the frequency of adverse events. Adverse events will be coded by primary system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA). All AEs will be assigned to the last treatment the patient received before AE start. In the data listings of adverse events, the severity of an AE, whether or not an AE is related to MBW or study drug, and whether or not it is a serious AE, will be indicated. An adverse event related to study drug is defined as one considered by the investigator to have a suspected relationship with the diagnostic method or the study drug. The adverse events will be summarized by the number and percentage of patients in each primary system organ class and preferred term. For summaries by severity of event, the most severe occurrence for a particular preferred term will be used for a given patient. Summary tables of adverse events by treatment and severity will be provided. Multiple occurrences of the same AE or SAE in the same patient in one treatment period will be counted only once, using the worst severity and drug relationship. Data from other tests (e.g. electrocardiogram or vital signs) will be listed, notable values will be flagged, and any other information collected will be listed as appropriate.

Vital signs data will be listed, including change from baseline.

All laboratory data (blood chemistry) will be listed with abnormal values flagged. The laboratory values will be summarized. Incidence of newly occurring or worsening notably abnormal laboratory values will be produced.

10.5.3 Tolerability

Not applicable

10.5.4 Resource utilization

Not applicable.

10.5.5 Health-related Quality of Life

Not applicable

10.5.6 Pharmacokinetics

Not applicable

10.5.7 Pharmacogenetics/pharmacogenomics

Not applicable

10.5.8 Biomarkers

Not applicable

10.5.9 PK/PD

Not applicable

10.6 Interim analysis

No interim analysis will be performed.

10.7 Sample size calculation

For FEV_1, a change of 5% with an intraindividual SD of 9% is expected between on- and off-treatment cycles. Under these assumptions, 28 patients will be required to detect this change with 80% power on a two-sided, 5% significance level. Since LCI is expected to be a more sensitive measure (compared to FEV_1), this patient number should therefore also be sufficient to detect relevant changes in LCI and to explore the correlation between LCI and FEV_1. To compensate for some protocol violations and drop-outs, a total of 35 patients should be recruited into this trial.

10.8 Power for analysis of critical secondary variables

Not applicable.

11 Discussion and rationale for study design features

This study was designed to evaluate LCI by a standardized procedure in a well characterized study setting to assess feasibility of LCI as a more sensitive method to measure effectiveness

of antibiotic therapy in patients with mild lung disease. In principle, a variety of available Devices may be used to measure LCI by multiple breath washout. However, LCI is not yet a fully standardized method and is not used in clinical practice. To secure reliable and comparable data from every single study center, the participating sites will all use the same device, selected from the listed devices in section 1 of the protocol. Appropriate training for the sites will be provided as well as a detailed user guide and MBW Standard operation procedure.

The study will be conducted in patients with CF aged 6 years and older with an upper limit of 50, representing the typical CF patient population, eligible to get inhaled antibiotics prescribed following onset of chronic infection with *Pseudomonas aeruginosa*. Additionally, the need for more sensitive diagnostic methods is highest in early lung disease and thus in children and youths, so children should not be excluded The inclusion of younger children in this study seems appropriate, as MBW is a non-invasive diagnostic method without any radiation exposure and the washout gas used in this trial (oxygen) is part of the normal breathing air and widely used in clinical practice. Furthermore, MBW has already been evaluated not even in this population, but in very young children below age of 6 as well (e. g. Aurora et al 2010, Hall et al 2011). Last but not least, only already prescribed in-label standard therapy is used for the treatment effect needed and no changes in the therapy regimen or any newly developed investigational drug is evaluated in this study.

However, to limit any diagnostic burden for young children, MBW is limited by the protocol to two consecutive measurements at a time for these patients.

Only patients with an abnormal LCI of more than 7.5 at screening during off-phase will be included in order to have most likely a treatment effect on LCI following onset of antibiotic inhalation after the off-phase of the standard therapy (baseline visit). As described above, LCI seems to be a good parameter to measure lung disease status and progression in patients with a milder lung disease. Patients with more severe disease will not tolerate an off-phase. Such patients do typically need a combination of antibiotics, e. g. Colistin / Study drug or Aztreonam Lysinat / Study drug (on/on respectively) as standard maintenance therapy which is not allowed in this study. However, to clearly define the eligible population, the FEV1 of the study population has been restricted to a lower limit of 50% predicted.

Drugs that support lung clearance e. g. Pulmozyme (DNAse) or hypertonic saline or drugs that treat obstructive airways, e. g. long acting ß-Agonists may impact the LCI as well. In order to minimize the influence of these concomitant medications on the treatment effect of inhaled antibiotics, initiation or discontinuation of these therapies in the last 56 days (8 weeks) prior to screening Baseline visit and during the study is not allowed.

Beneficial effects of treatment with inhaled tobramycin may include a reduction of air trapping by recruitment of lung units previously not contributing to ventilation. If their time constants are slower, relative to the previously assessed lung units, ventilation inhomogeneity, and therefore LCI, will increase despite the positive treatment effect (Robinson 2009). Air trapping will be assessed by the difference in FRC measured by bodyplethysmography (FRC_{ples}) and FRC measured by MBW (FRC_{MBW}). As spirometry is done in central European Cystic Fibrosis centers using bodyplethysmography, FRC_{ples} will be routinely documented in the source documents.Inhalation of Study drug, administered in repeated cycles of 28 days

twice daily followed by 28 days off-drug represents current antibiotic standard maintenance therapy in this patient population of CF patients aged 6 years and older CF (Ramsey 1999, TOBI® 2013, Bramitob® 2013, Konstan et al 2011a).

CF Patients chronically infected with *P. aeruginosa* on regular antipseudomonal standard inhalation therapy in an on / off regimen are showing well characterized differences in FEV_1 between on and off-cycles (Ramsey et al 1999; Konstan et al 2011a). Thus, this population allows an evaluation of LCI based on these intraindividually observed FEV_1 alterations, without any changes to their standard therapy.

The microbiology parameter "colony forming units" of pseudomonas aeruginosa has been selected as a third efficacy marker to be compared with LCI as well, because spirometry (FEV1) strongly depends on daily performance and compliance to spirometry of the patient. LCI and FEV1, respectively, should reflect alterations in bacterial colonization.

The study duration of 8 weeks comprises a complete on / off treatment cycle starting with 28 days inhalation followed by 28 days without Study drug inhalation. This design allows to obtain baseline lung function at start of the inhalation cycle (representing minimal lung function at the end of the inhalation pause), the development/improvement of lung function after 1 and after 4 weeks of inhalation therapy (representing maximal lung function) and the subsequent decline in lung function after 4 weeks of cessation of inhalation therapy. The detected intraindividual differences between best and worst lung function then allow to compare LCI and FEV_1 results and to assess feasibility of LCI as primary surrogate outcome parameter in future clinical studies.

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Appendix 1: Ethical considerations and administrative procedures

Regulatory and ethical compliance

This clinical study was designed and shall be implemented 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 Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

Responsibilities of the investigator and IRB/IEC/

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board / Independent Ethics Committee (IRB/IEC) before study start. Approval letters concerning protocol and informed consent will be filed by Novartis. 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 Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

Informed consent procedures

Eligible patients may only be included in the study after providing written, IRB/IEC-approved informed consent.

Women of child bearing potential should be informed that taking the study drug may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study.

Informed consent must be obtained before conducting any study-specific procedures (i.e., all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

Novartis 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.

Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the trial to request approval of a protocol deviation, as no authorized deviations are permitted. If the 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 Novartis and approved by the IRB/IEC it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC. Only amendments that are required for patient safety may be implemented prior to IRB/IEC approval. 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, Novartis should be notified of this action and the IRB/IEC at the study site should be informed within 10 working days.

Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical trial agreement.

Publication of study design and results

Novartis assures that 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 study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study case report form (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities