PCR	Protein-creatinine-ratio
p.o.	oral(ly)
PRO	patient reported outcome
PK	Pharmacokinetic
QOL-B	Quality of Life Questionnaire for Bronchiectasis
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reactions
TD	Study Treatment Discontinuation
TIP	Tobramycin Inhalation Powder hard capsules 28 mg
TOBI	Tobramycin nebulizer solution 300 mg/mL
WHO	World Health Organization
WoC	Withdrawal of Consent

[redacted]

2.2 Secondary objectives

- To assess the effect of different doses of TIP administered o.d. and one b.i.d. dose and different regimens (TIP and TIP/placebo cyclical) on the frequency, rate (by patient-months), severity and time to onset of pulmonary exacerbations at the end of the treatment epoch and over the entire study, each compared to placebo.
- To assess the efficacy profile of different doses of TIP administered o.d. and one b.i.d. dose and different regimens (TIP and TIP/placebo cyclical), as measured by the time to first use, proportion of patients requiring anti-pseudomonal antibiotics (overall, oral, parenteral) and the duration of treatment of anti-pseudomonal antibiotics, each compared to placebo.
- To assess the time to first hospitalization, proportion of patients requiring hospitalization and the duration of hospitalization due to serious respiratory-related AEs (other than those regularly scheduled hospitalization that were planned prior to study start).
- To assess the pharmacokinetic concentrations of tobramycin in serum and in sputum from different doses of TIP administered o.d. and one b.i.d. dose and different regimens (TIP and TIP/placebo cyclical).
- To assess the antimicrobial efficacy of TIP over the entire study duration, as measured by the absolute change in *P. aeruginosa* colony forming units (CFU) in sputum from baseline to each post-baseline treatment visit and during the follow-up visits.
- To evaluate the safety profile of TIP in terms of clinical laboratory results.
- To evaluate the safety profile of TIP in terms of audiology findings throughout the treatment epoch (subgroup of all patients that are in enrolled at sites that are adequately equipped and trained to perform audiologic assessments).
- To evaluate the safety profile of TIP in terms of acute change in forced expiratory volume at 1 second (FEV_1) % predicted values from pre-dose to 30±15 minutes after completion of study drug administration at the clinical site at visits during the treatment epoch.
- To evaluate the impact of treatment with TIP on the Respiratory Symptom Scale Quality of Life Questionnaire for Bronchiectasis (QOL-B) by measuring change from baseline to all post-baseline visits.

2.3 Exploratory objectives

[redacted]

[redacted]

- To explore the characteristics of the post-inhalational events at all visits during the treatment epoch.

- To explore the impact of healthcare resource utilization of TIP treatment.

2.4 Objectives and related endpoints

Table 2-1 Primary objectives and related endpoints- Objectives

OBJECTIVE	Endpoint Title, Description and Reporting Time Frame for analysis and Unit of Measure	Statistical Analysis Section
Primary		
To evaluate the effect of different doses of TIP administered o.d. and one b.i.d. dose on the change in *P. aeruginosa* bacterial load in sputum as assessed by the change in colony forming units (CFUs) from baseline to Day 29 of treatment, each compared to placebo.	Title: *P. aeruginosa* density in sputum Unit of Measure: CFUs per mL Description: Quantitative measurement for *P. aeruginosa* in pre-dose sputum samples measured by central lab as summarized in Section 6.4.1. Time Frame: baseline, Day 29	Section 9.4
To assess the safety and tolerability with different	Title: Safety and tolerability	Section 9.5.2

OBJECTIVE	Endpoint Title, Description and Reporting Time Frame for analysis and Unit of Measure	Statistical Analysis Section
doses of TIP administered o.d.and one b.i.d. and different regimens (TIP and TIP/placebo cyclical) during the treatment epoch (112 days) and during the follow-up epoch (56 days) for each as compared to placebo.	Unit of Measure: percentage of adverse events Description: Rate and severity of local adverse events Time Frame: baseline and post-baseline visits	

3 Investigational plan

3.1 Study design

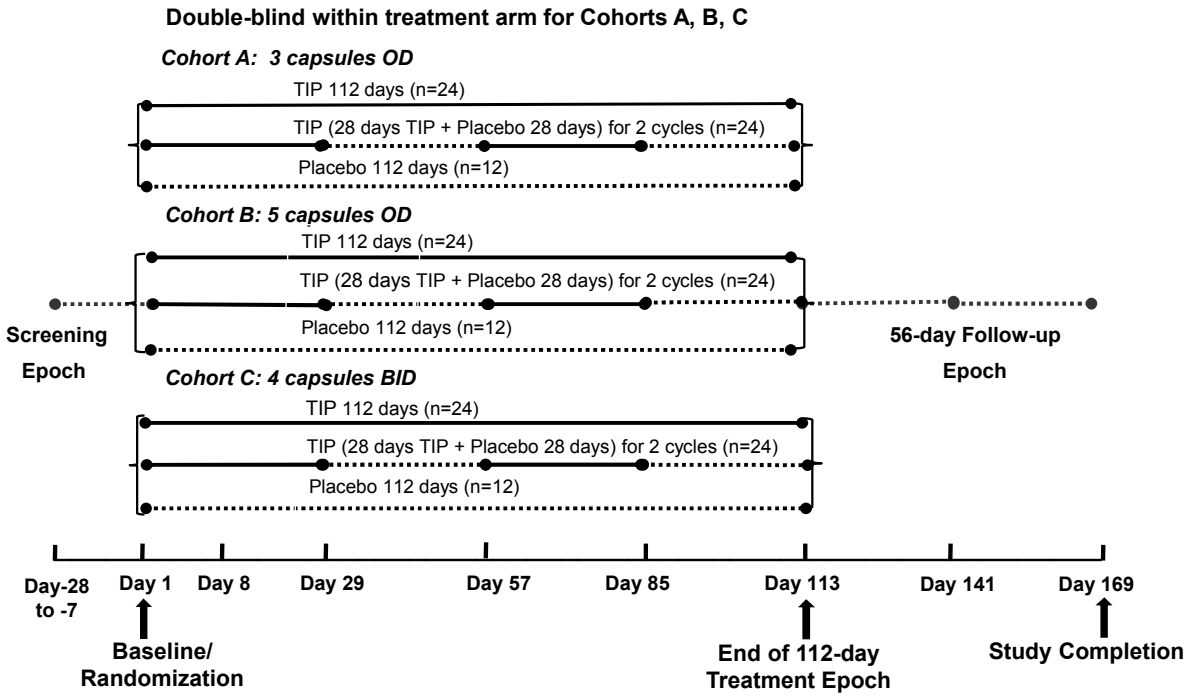
This is a blinded, randomized, dose and regimen finding trial utilizing a 3 treatment cohort design where active TIP doses or placebo in addition to the local standard care within each cohort are delivered once or twice daily. Approximately 180 eligible patients will be randomized to one out of the 3 cohorts in a ratio of 1:1:1. The patients within each cohort will be randomized to blinded TIP or placebo with the following randomization scheme: TIP: TIP/placebo cyclical: placebo, in a 2:2:1 ratio. In total, the study has nine treatment arms distributed among the 3 cohorts (see Section 5.1). Total duration of the study is expected to be up to 196 days with a total of 9 visits, consisting of up to 28 days for the screening epoch; after randomization a 112-day treatment epoch with 6 clinic visits, followed by a 56-day follow-up epoch with 2 clinic visits. Patients will be assessed for safety, tolerability and efficacy (see Assessment Schedule Table 6-1).

At an initial screening visit (Visit 1), informed consent will be obtained before any study related assessment or procedures are performed, inclusion/exclusion criteria will be assessed and current medications reviewed. All patients signing informed consent must be registered in the Interactive Response Technology (IRT). The patients will commence a flexible 7-28 day screening epoch where all screening assessments will be performed and the presence of pulmonary bacterial colonization with *P. aeruginosa* based on sputum culture will be done. Patients who are otherwise eligible may be re-tested for *P. aeruginosa* in the sputum and/or laboratory evaluations during the screening epoch. Any patient can be re-screened once until enrollment has completed. Patients who had an exacerbation during the screening phase can be re-screened twice until recruitment has been completed. The *P. aeruginosa* bacterial load estimation will be done by quantitative identification using standard culture methods (Patel et al 2002). [redacted]. At the completion of the baseline assessments on Day 1 (Visit 2), all patients who meet the eligibility criteria will be randomized to one of the three treatment cohorts and enter the 112-day treatment epoch on the same day. The randomization by cohort and treatment arm will be stratified by use of macrolides. After Visit 101 (Day 1), the patients will attend a visit after 7 days of treatment (Day 8, Visit 102). The next visit is planned on Day 29 (Visit 103), and monthly thereafter (Day 57 Visit 104 to Day 113, end of treatment Visit 106). Following the treatment epoch, patients will enter the 56-day follow-up epoch (no study medication, but

[redacted]

baseline standard care according to the local guidelines) and attend two follow-up epoch visits (Visits 201 and 202).

Figure 3-1 Study design



3.2 Rationale for study design

The patient population will be described in more detail in the Section 4 below.

This study is designed to find a dose and regimen [redacted] in non-CF BE patients with pulmonary *P. aeruginosa* infections. A parallel study design with three treatment cohorts is used to investigate three different TIP doses and regimens versus placebo.

The study will implement a within-cohort blinding approach. If the study were blinded across all arms, all of the subjects in the study would need to inhale the maximal dose of 10 capsules every day to maintain the blind in a double-blind double dummy design (5 morning + 5 evening). In previous double-blind studies in CF patients (EVOLVE and EDIT) it has been noted that tolerability of placebo was overall similar with that of TIP, being most likely driven by the amount of powder inhaled and its oro-pharyngeal deposition (Konstan et al 2011a, Konstan et al 2011b). In order to assess tolerability (defined by the rate of local AEs) related to the dose, within-cohort blinding is planned in this study. For each dose level, the patients will be randomized as follows: TIP:TIP/placebo cyclical: placebo in a 2:2:1 ratio. This randomization scheme will allow the analysis of tolerability across treatment arms within the same cohort for those patients on active study drug without bias from an open design, and will also permit comparison of efficacy outcomes to a pooled placebo group. The randomization scheme has been chosen to ensure that a total of 36 patients are randomized into the three cohorts to receive placebo (12 placebo patients per cohort) and also the number of patients between TIP/placebo cyclical and TIP are evenly distributed 24 patients per treatment arm. It

[redacted]

is not expected that the amount of placebo powder administered will influence efficacy measurements, therefore the placebo patients will be pooled (12 patients per dose, in total 36 patients on placebo for the efficacy endpoint). Patients from both TIP and TIP/placebo cyclical treatment arms will be pooled within the same cohort for the primary endpoint measurement at Day 29, as they both receive the same active treatment during the first 28 days. For further details about the analysis, see Section 9.4.

From the pilot studies in BE patients with the nebulized tobramycin solution it has been suggested that tolerability might be lower in BE patients compared to in CF patients, because of coughing, dyspnea or wheezing. The current design is able to assess the tolerability of different doses and regimens of TIP in this new indication.

The number of arms and regimens were selected on the basis of the dose rationale below.

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

The planned doses to be administered in this study are 84 mg (3 capsules), 140 mg (5 capsules) once daily each and 112 mg (4 capsules) twice daily to identify the TIP dose that exhibits effective bacterial reduction in non-CF BE patients who had one positive sputum cultures in the last 12 months and a positive culture at screening. [redacted] The 112 mg twice daily dose has been established as the safe and effective dose for the treatment of patients with CF (Konstan et al 2011a, Konstan et al 2011b) and is used as reference dose in this study. The dose regimens selected for this study are chosen based on the early pilot studies with TOBI suggesting that BE patients may tolerate inhaled therapy less well than CF patients. Further, in the TPI001 study (Geller et al 2007), the sputum concentrations measured in CF patients after single doses of 3 capsules and 4 capsules provided similar tobramycin sputum concentrations with the ranges of Cmax largely overlapping, the mean slightly above 1000 µg/g sputum. The concentrations achieved for o.d. doses of 3 and 4 capsules of TIP in TPI001 study (Geller et al 2007) have largely exceeded the tobramycin MIC, including the MICs for highly resistant *P. aeruginosa* strains and hence were chosen for this study. The 5 capsule o.d. dose was chosen to evaluate whether it offers superior safety and efficacy compared to the approved 4 capsule b.i.d. dose. One capsule dose was considered, but not retained, because in the TPI001 study the tobramycin Cmax was 258 µg/g sputum, which is close to the upper end of the tobramycin MIC range that is seen in some patients, creating a risk for selection of resistant strains.

Additionally, it is well established that the efficacy of tobramycin, an aminoglycoside, is driven by a concentration-dependent bactericidal effect (Maglio et al 2002, Scaglione and Paraboni 2006); therefore it is suited to once daily dosing, which would substantially enhance patient compliance. The use of tobramycin once daily intravenously in cystic fibrosis patients has been shown to be safe and effective (Smyth et al 2005, Whitehead et al 2002).

The treatment duration of 16 weeks (followed by 8 weeks follow-up) is chosen to test efficacy and safety beyond 4 weeks of treatment. Indeed, there is precedent from the TIP studies in the CF indication, that 4 weeks of treatment are sufficient to achieve bacterial suppression in the lungs (Konstan et al 2011a, Konstan et al 2011b). However based on the TOBI pilot study in

[redacted]

upon investigator's decision, as needed depending on the patient's condition (see Section 5.5.7 Concomitant treatment).

Tobramycin is an aminoglycoside that is active against Gram-negative bacteria including *P. aeruginosa* and has been used parenterally for many years for the treatment of Gram-negative PPMs (including *P. aeruginosa)* in pulmonary infections, including BE. Its efficacy and safety profile is well-established. TOBI® (tobramycin inhalation solution, or TIS) has become the gold standard inhaled antipseudomonal treatment in CF since its launch in 1998. TIP was developed for use in the same CF population as TIS. The approved TIP dose for CF provides comparable sputum and serum pharmacokinetic exposures to the approved TIS dose with respect to tobramycin and has comparable safety and efficacy profiles. TIP is approved for use in CF [redacted] at the dose 112 mg (i.e. 4 capsules of 28 mg each) twice daily. The pharmacokinetics of parenteral tobramycin do not differ significantly in CF patients compared with patients without CF when subject age, fat-free mass, sex and renal function are taken into consideration (Hennig 2013). Therefore the systemic exposure in BE is not expected to differ from the CF patients. Based on the serum pharmacokinetic data from previous studies of TIP in CF patients, a dose of 5 capsules is not expected to exceed the maximum threshold of 12 µg/ml for C_{max} and 2 µg/ml for C_{trough}. Increased variability can be expected in subjects treated with 5 capsules compared to 3 capsules of TIP. To assess the pharmacokinetic properties of tobramycin from TIP in BE patients and to develop a PK model, tobramycin concentrations in serum and sputum will be measured.

The safety and tolerability profile of TIP in BE patients is not yet established. The highest daily dose planned to be tested in this study is the dose that has been demonstrated to be safe and effective in CF patients. The phase II study will define a dose that is effective in suppressing clinically relevant bacterial pathogens which is also safe and well tolerated. Renal and oto-toxicity will be monitored.

4 Population

The study population will consist of approximately 180 male and female BE patients ≥18 years old with clinical diagnosis of non-CF bronchiectasis confirmed radiologically by CT scan, a history of exacerbations requiring systemic antibiotic administration and who had one positive culture for *P. aeruginosa* in sputum in the last 12 months and a *P. aeruginosa* positive culture at screening. Patients also should have an FEV_1 of at least 30% predicted. It is anticipated that approximately 260 patients will need to be screened in order to randomize approximately 180 patients across 3 cohorts of the study with a cohort randomization ratio of 1:1:1 and within each cohort a ratio of 2:2:1 for TIP:TIP/placebo cyclical:placebo randomization. Patients will be stratified by use of macrolides.

4.1 Inclusion criteria

Patients/subjects eligible for inclusion in this study must fulfill **all** of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Male and female patients of ≥ 18 years of age at screening (Visit 1).

[redacted]

[redacted]

[redacted]

Epoch		Screen		Treatment						Follow-up	
Visit		**1**	**2***	**101***	**102**	**103**	**104**	**105**	**106 or TD**	**201**	**202 or PSD**
Day		**-28 to -7**	**1**	**1**	**8**	**29**	**57**	**85**	**113**	**141**	**169**
Pre-dose sputum specimens (2 separate specimens) for central analysis (microbiology, [redacted])				X	X	X	X	X	X	X	X
[redacted]											
Serum specimen for PK tobramycin concentration [f]	0-1 hour post-dose			X	X						
	1-2 hour post-dose			X	X						
Sputum specimen for tobramycin PK concentration [g]	0-1 hour post-dose			X							
	1-2 hour post-dose			X							
	3-4 hour post-dose						X				
	5-6 hour post-dose				X						
Serum specimen for PK sub-study [h]	Pre-dose			X	X						
	0-1 hour post-dose			X	X						
	1-2 hour post-dose			X	X						
	3-4 hour post-dose			X	X						
	5-6 hour post-dose			X	X						
Audiology [i]		X[p]	X[b]			X	X	X	X	X[j]	X[j]
Spirometry [k]	Routine	X								X	X
	Pre-& 30±15 min post dose			X	X	X	X	X	X		
[redacted]											
QOL-B, [redacted]			X		X	X	X	X	X	X	X
[redacted]											
Inhalation Device Training [m]				S							
Dispense study drug via IRT				S		S	S	S			

[redacted]

6.5.3 Height and weight

The patient's height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured. Refer to Table 6-1 for the assessment schedule.

6.5.4 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

Clinically notable laboratory findings are defined in Appendix 1.

6.5.4.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count will be measured.

6.5.4.2 Clinical chemistry

Urea (or BUN), creatinine, glucose, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, gamma glutamyl transpeptidase, sodium, potassium, chloride, calcium, bicarbonate, phosphate, total protein, albumin, and uric acid will be measured. Based on serum creatinine values, estimated glomerular filtration rate (eGFR) will be calculated using the MDRD (Modification of Diet in Renal Disease) criteria.

6.5.4.3 Urinalysis

Measurements for specific gravity, protein (proteinuria at all visits, urine albumin-creatinine ratio and urine protein-creatinine ratio at baseline and when renal alert criteria are met), glucose (glycosuria), and blood (hematuria) in urine will be performed. White blood cell and red blood cell sediments will also be measured.

6.5.5 Post-inhalation events

Events occurring within 5 minutes after inhalation of the study treatment (post-inhalation events) will be observed at the site by site personnel at Visits 101, 102, 103, 104, 105 and 106. The ISC should supervise the study treatment inhalation by the patients whether an event occurred or not.

If the event is determined to be an adverse event, this should be recorded on the Adverse Event CRF. In addition, event details will also be captured in the Post-inhalation Adverse Event CRF. For post-inhalation events that are determined not to be an adverse event, event details will be recorded in the Post-inhalation clinical events CRF.

If a patient prematurely discontinues study drug, airway reactivity should be assessed at the treatment discontinuation (TD) visit provided the patient agrees to inhale study medication during the visit.

[redacted]

6.5.6 Bronchial hyperreactivity

Bronchial hyperreactivity will be measured as the acute relative change from pre-dose to 30±15 minutes post-dose in FEV_1% predicted at Visits 101, 102, 103, 104, 105 and 106. A change of 20% or more is considered a clinically significant indication of bronchospasm/ bronchial hyperreactivity.

It is at the investigators discretion to initiate treatment with a bronchodilator prior to inhalation of study treatment or to consider discontinuation of study treatment in the case that bronchial hyperreactivity is experienced.

If a patient prematurely discontinues study drug, airway reactivity should be assessed at the treatment discontinuation (TD) visit provided the patient agrees to inhale study medication during the visit.

6.5.7 Audiology

The patient should be questioned at each visit about the occurrence of any hearing abnormalities. If any such change is suspected by the patient, the investigator should have the case assessed and followed up by an audiologist, regardless of whether or not the site participates in the audiology sub-study. Audiological assessments will be conducted at selected study sites at Visits 2, 103, 104, 105, 106 (or discontinuation visit) and also at follow-up visits 201 and 202, as relevant. For patients whose audiology is normal up to and including the end of the treatment epoch (Visit 106), there is no need for additional audiology at Visits 201 and 202. If the audiology is abnormal at any visit, it should be repeated at all following visits including the end of study visit.

Patients will have auditory acuity measured using a standard dual-channel audiometer at frequencies from 250 Hz to 8 kHz. Measurements of interoctaves are not necessary. An audiogram (pure-tone air conduction) and tympanogram will be performed by an audiologist. Bone conduction will be performed if the air conduction shows a decrease of 20 dB from the patient's pre-dose measurements in either ear. Novartis and the investigator must be notified within 5 working days if a 20 dB drop versus as compared to the most recent pre-dose value (either screening or baseline) is noted in either ear. In this case, the patient will be withdrawn from treatment and monitored until auditory acuity values return to baseline or until the follow-up visit, whichever occurs first. Only at the baseline visit (Visit 2), the audiology assessment must be performed prior to dosing. At the following visits, audiology can be performed within 3 days before or after the assigned visit.

6.5.8 Pregnancy and assessments of fertility

All female patients after the onset of menarche who are not surgically sterile will have a serum pregnancy test performed by the central laboratory from the blood sample taken for safety laboratory examination at Visits 1 and 106. Additionally, a urine pregnancy test will be done at Visits 2 and 202. A positive serum pregnancy test at Visit 1 leads to the exclusion of the patient from the study prior to the start of study treatment administration. In case of a positive urine pregnancy test at Visit 2, the patient must not commence inhalation of study medication. In these cases, a serum pregnancy test must be performed and the results awaited to verify the pregnancy. If a serum pregnancy test is determined to be positive, the patient

[redacted]

must be discontinued from the trial. In case of positive test results, the pregnancy must be followed up until after birth.

6.5.9 Adverse events of special interest

Certain events have been identified in the TIP AE profile for cystic fibrosis which will have a more detailed assessment. If an adverse event regarding ototoxicity and/or hemoptysis is reported, specific data which may include symptoms, medical history and relevant local assessment will be collected by using a specific CRF.

6.5.10 Hospitalizations for respiratory-related adverse events

Hospitalizations for respiratory-related adverse events will be recorded on a specific CRF. The rate and duration of hospitalization due to serious respiratory-related AEs will be determined, based on the information collected in the CRF.

6.5.11 Appropriateness of safety measurements

The use of systemic aminoglycosides in humans has been related to eighth cranial nerve impairment (Guthrie 2008) manifested as both auditory and vestibular toxicity. The audiological assessment (Section 6.5.7) and questioning the patient at each visit for hearing abnormalities have been included in this study to closely monitor the hearing ability of patients exposed to TIP. Renal function is surveyed by clinical chemistry assessments as nephrotoxic effects have been reported from systemic aminoglycosides (Martinez-Saldago et al 2007). All other safety assessments selected are standard for the indication BE and this patient population.

6.6 Other assessments

6.6.1 Resource utilization

At each scheduled and unscheduled visit, respiratory healthcare resource utilization for hospitalizations will be assessed and recorded on the appropriate CRF. Hospitalization will be defined as any visit to the hospital requiring an overnight stay. The total length of stay including date of admission and discharge will be recorded for respiratory-related in-patient hospitalizations.

Any procedures performed during the hospitalization will be recorded in the appropriate CRF.

If AEs or SAEs are confirmed then the physician must record the events as per instructions given in the protocol.

6.6.2 Pharmacokinetics

Pharmacokinetic properties of tobramycin from different doses of TIP o.d. and b.i.d. will be assessed at Visits 101, 102 and 104.

It is expected that few patients will be able to expectorate spontaneously multiple sputum samples at a given visit. As patients are required to provide pre-dose sputum samples for microbiology assessment (primary endpoint), for the PK sputum specimens all patients will be requested to provide specimens of sputum post-dose per specified interval, at Visits 101 (0-1

[redacted]

h and 1-2 h post-dose measured time interval from the completion of study drug administration), at Visit 102 (5-6 h) and Visit 104 (3-4 h). Sputum samples for tobramycin concentration testing must be at least 200 mg in weight (0.2 ml in volume) and must not be saliva. In patients who are not able to spontaneously produce sputum, one specimen of induced sputum post-dose per specified interval will be collected. No induced sputum sample for PK will be collected at baseline in patients who had induced sputum pre-dose for microbiology assessments.

All patients will also provide serum specimens at Visits 101 and 102 (one specimen per specified interval): 0-1 hours, 1-2 hours, post-dose (measured time interval from the completion of study drug administration).

To evaluate serum PK in approximately 16 patients on active treatment, at least 20-22 patients from each cohort (at least 60 total patients) will participate in a PK sub-study. All patients will be asked to participate in the sub-study until enrollment is fulfilled for each cohort. Patients in this PK subset (20-22 patients/ cohort) will instead provide one serum specimen per specified interval at Visits 101 and 102: pre-dose and post-dose 0-1, 1-2, 3-4 and 5-6 h.

If there is more than one serum or sputum sample to be collected per visit, there has to be a minimum of one hour difference between consecutive sampling points. Samples will be obtained from a peripheral site by phlebotomy or through a temporary i.v. site, but not through an existing central access or catheter.

If a patient discontinues early and is on study drug, the patient will be asked to provide an extra serum and sputum specimen at the treatment discontinuation (TD) visit.

A separate laboratory manual will be provided with instructions on tube labeling, sample collection, processing, storage conditions and shipping of specimens.

The time of sputum and blood collection is to be recorded (e.g. actual time of dosing and actual times of sputum/blood collection have to be recorded on the PK sputum and blood collection CRF pages).

- whether it constitutes a serious adverse event (SAE – See Section 7.2 for definition of SAE)
- action taken regarding study treatment

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

- no action taken (e.g. further observation only)
- study treatment dosage adjusted/temporarily interrupted
- study treatment permanently discontinued due to this adverse event
- concomitant medication given
- non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged (see Section 7.2 for definition of SAE)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

Once an adverse event 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 side effects already known about the investigational drug can be found in the Investigator Brochure (IB). This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the medicinal product that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and has then to be discussed with the patient.

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 Novartis.

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

[redacted]

- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of bronchiectasis, not associated with any deterioration in patient's condition (e.g. preplanned prophylactic i.v. antibiotic therapy)
  - 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 (see 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 (see 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 Novartis 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 Novartis 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 *(either initial or follow-up information)* is collected and recorded on the paper Serious Adverse Event Report Form. The investigator must assess the relationship to *each specific component of study treatment,* complete the SAE Report Form in

[redacted]

Blood sampling for pharmacokinetic sub-study assessments

At study visits 101 and 102, pre- and post-dose serum samples at specified time intervals are collected for pharmacokinetic analyses.

Table 15-3 Time schedule for blood sampling for serum pharmacokinetic assessments in PK sub-study

Visit number	Study day	Scheduled time	Sample number
101	1	Pre-dose	301
101	1	0-1 h post-dose	302
101	1	1-2 h post-dose	303
101	1	3-4 h post-dose	304
101	1	5-6 h post-dose	305
102	8	Pre-dose	312
102	8	0-1 h post-dose	313
102	8	1-2 h post-dose	314
102	8	3-4 h post-dose	315
102	8	5-6 h post-dose	316
~~103~~	~~29~~	~~Pre-dose~~	~~306~~
~~103~~	~~29~~	~~0-1 h post-dose~~	~~307~~
~~103~~	~~29~~	~~1-2 h post-dose~~	~~308~~
~~103~~	~~29~~	~~3-4 h post-dose~~	~~309~~
~~103~~	~~29~~	~~5-6 h post-dose~~	~~310~~
TD*	N/A		311

*For patients in the PK-sub-study who discontinue early, an extra blood sample for PK should be taken at the treatment discontinuation (TD) visit.

As per amendment 2, assessments have been moved from visit 103 to visit 102.

16 Appendix 4: Instructions for use for the T-326 Inhaler

Please read the following instructions carefully to learn how to use and care for your T-326 Inhaler.

Clinical kit:

Each clinical kit contains five weekly packs

Inside your weekly pack:

Each weekly carton contains:

- 1 inhaler and its storage case
- 7 or 14 capsule cards (one card for each dose)
- Each capsule card contains 3, 4, or 5 capsules. One capsule card corresponds to one dose

[redacted]

If your capsule cards contain 3 capsules each:

- You should have a total of 7 capsule cards
- Take one dose (=3 capsules) once a day
- You will use 1 capsule card for each day that you take the medicine

If your capsule cards contain 5 capsules each:

- You should have a total of 7 capsule cards
- Take one dose (=5 capsules) once a day
- You will use 1 capsule card for each day that you take the medicine

If your capsule cards contain 4 capsules each:

- You should have a total of 14 capsule cards
- Take one dose (=4 capsules) twice a day – i.e., once in the morning, once in the evening
- You will use 2 capsule cards for each day that you take the medicine

[redacted]

Glossary of terms

Cohort	A specific group of patients/subjects fulfilling certain criteria
Control drug	Drugs(s) 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
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)
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)
Epoch	A portion of the study which serves a specific purpose. Typical epochs are: screening/recruitment, wash-out, treatment, and follow-up
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.”
Medication pack number	A unique identifier on the label of each investigational drug package
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients/subjects with established disease and in those with newly-diagnosed disease.
Patient/subject ID	A unique number assigned to each patient upon signing the informed consent
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
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
Study Treatment Discontinuation (TD)	When the patient permanently stops taking study treatment prior to the defined study treatment completion date
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
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Withdrawal of consent (WoC)	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data.

[redacted]

BE (Barker et al 2000) it is assumed that a duration of 4 weeks of treatment is too short to translate into improvement in clinical outcomes (reduction of exacerbations, use of i.v. antibiotics). A duration of 112 days allows to test two full cycles (28 days on-/ 28days off-therapy) of cyclical dosing. With regards to the cyclical regimen (TIP/placebo cyclical treatment arms), it is thought that a single cycle is not sufficient to detect a clinical effect. For example, in ORBIT-2, using inhaled dual-release ciprofloxacin for inhalation (Serisier et al 2013), the trends in exacerbation were only observed after the second treatment period. Clinical evidence in bronchiectasis is increasing to suggest that a continuous regimen also might be appropriate. Long-term studies in BE with continuous therapies (Murray et al 2011, Haworth et al 2014), have shown improvements in exacerbations and patient reported outcome (PROs). Murray et al (2011) (12 months daily inhaled gentamicin in BE patients, followed by 3 months off-treatment period) have shown a reduction in exacerbations (gentamicin group: 33.3% vs. saline: 80%). Notably, the treatment effect was lost after 3 months follow-up. Authors have seen no emergence of resistance. Haworth et al (2014) in a double-blind placebo controlled study, 6-months daily therapy with colistin in BE patients, have shown in the overall population trends in favor of the therapy were shown, but which did not reach statistical significance (p=0.11). However, in the adherent patients, the delay in time to exacerbation was statistically significant (p=0.038). Therefore it is proposed to also test a continuous treatment regimen for 16 weeks, a duration that may allow to detection of trends in improving clinical outcomes and PROs, as compared to placebo. Further, 8 weeks of follow-up will inform about the persistence of the clinical effects. Smith et al (1989) suggested that twelve weeks of continuous inhaled tobramycin treatment in CF patients led to increase in MIC. Recent studies of 12-months' and 6-months', respectively, duration (Murray et al 2011 and Haworth et al 2014) in BE patients, did not observe an increase in resistance that translated into a loss in clinical efficacy. Therefore, during the proposed phase II study, tobramycin MIC will be closely monitored at every visit and the microbiology data will be interpreted in the context of change in clinical response. [redacted]

3.4 Rationale for choice of comparator

Placebo is chosen as comparator since no approved active comparator is available for the indication under study. It is considered necessary to include placebo in order to determine which doses and frequency of regimen offer an efficacy benefit in terms of reduction of bacterial load. Both patients and investigators remain blinded to the assignment to active or placebo within the cohort. The subjects would be aware of the number of capsules and the frequency of daily administration of active and placebo that they have been assigned to but have no knowledge of whether they were allocated to active or placebo.

3.5 Purpose and timing of interim analyses/design adaptations

Not applicable.

3.6 Risks and benefits

The risk to patients in this trial will be minimized by compliance with the eligibility criteria. All patients will be closely supervised in this study. Systemic antibiotic treatment is allowed,

[redacted]

3. Proven diagnosis of non-CF BE as documented by computed tomography or high-resolution computed tomography and as assessed by the investigator.
4. At least 2 or more exacerbations treated with oral antibiotics OR 1 or more exacerbation requiring parenteral antibiotic treatment within 12 months prior to screening.
5. $FEV_1 \geq 30\%$ predicted at screening (Visit 1).
6. A stable regimen of local standard treatment for BE (treatments unchanged for 28 days prior to randomization).
7. *P. aeruginosa*, must be documented in a respiratory sample (expectorated sputum, deep-throat cough swab, oro-pharyngeal swab, broncho-alveolar lavage) at least 1 time within 12 months (at least 28 days prior to Visit 1) and also present in the expectorated sputum culture at Visit 1.
8. Must be known sputum producers with a history of daily expectoration.
9. Able to use the T-326 Inhaler as instructed in the protocol in the opinion of the investigator.
10. Clinically stable pulmonary status in the opinion of the investigator.
11. Patients performing daily airway clearance.

4.2 Exclusion criteria

Patients/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 patients/subjects.

1. Patients with a history of cystic fibrosis.
2. Patients with a primary diagnosis of bronchial asthma.
3. Patients with a primary diagnosis of COPD associated with at least a 20 pack year smoking history.
4. Current smokers at Visit 1 or not stopped smoking within 4 weeks prior Visit 1.
5. Signs and symptoms of acute pulmonary or non-pulmonary conditions.
6. Any significant medical condition that is either recently diagnosed or was not stable during the last 3 months, other than pulmonary exacerbations, and that in the opinion of the investigator makes participation in the trial against the patients' best interests.
7. History of local or systemic hypersensitivity to aminoglycosides or inhaled antibiotics (other than bronchial hyperreactivity).
8. Any patient with lung cancer or a history of lung cancer.

9a. Any patient with active cancer or a history of cancer with less than 2 years disease-free survival time (whether or not there is evidence of local recurrence or metastases). Localized basal cell carcinoma (without metastases) of the skin is acceptable. Patients with a history of cancer (excluding lung cancer) and 2 years or more disease-free survival time may be included.

10a. Clinically significant (in the opinion of the investigator) hearing loss that interferes with patients' daily activities (such as normal conversations) or chronic tinnitus. Patients with a past history of clinically significant hearing loss in the opinion of the investigator may be eligible only if their hearing threshold at screening audiometry is 25dB or lower at

[redacted]

Table 6-1 Assessment schedule

Visits should occur on the designated day, or as close to it as possible.

Epoch	Screen		Treatment						Follow-up	
Visit	**1**	**2***	**101***	**102**	**103**	**104**	**105**	**106 or TD**	**201**	**202 or PSD**
Day	**-28 to -7**	**1**	**1**	**8**	**29**	**57**	**85**	**113**	**141**	**169**
Obtain informed consent	X									
Contact IRT	S		S		S	S	S	S	S	S
Randomization via NIRT			S							
Demographics	X									
Relevant Medical history	X									
BE-related Medical History	X									
Smoking history	X									
Pulmonary exacerbations history	X									
Inclusion/exclusion criteria check	X	X								
Physical examination [b]	S	[S][a]			S	S	S	S		S
Vital signs [b]	X		X					X		X
Height	X									
Body weight [b]	X	X						X		X
ECG	S									
Collection of most recent available digital CT-scan			X							
Serum specimen for safety laboratory assessment (standard: hematology, serum chemistry) [redacted]	X		X	X	X	X	X	X	X	X
Urinalysis (standard) [b]	X		X	X	X	X	X	X	X	X
Serum pregnancy test [b, d]	X							X		
Urine pregnancy test [b, d]		X								X
[redacted]										
Sputum specimen analyzed locally for *P. aeruginosa*	S									

[redacted]

Epoch		Screen		Treatment						Follow-up	
Visit		1	2*	101*	102	103	104	105	106 or TD	201	202 or PSD
Day		-28 to -7	1	1	8	29	57	85	113	141	169
Administer study drug at site [n]				X	X	X	X	X	X		
Study drug accountability					S	S	S	S	S		
Review Concomitant medication		X	X		X	X	X	X	X	X	X
Patient electronic diary (e-diary)	Issue patient e-diary			S							
	Download and review patient e-diary				S	S	S	S	S		
	Collect patient e-diary								S		
AE/SAE recordings (including pulmonary exacerbations)		X	X	X	X	X	X	X	X	X	X
Record Respiratory-related Hospitalizations		X	X		X	X	X	X	X	X	X
Review Surgery and Procedures			X	X	X	X	X	X	X	X	X
Record Post inhalation events				X	X	X	X	X	X		
Complete Study Disposition page (Screening)			X								
Complete Study disposition page (End of Treatment)									X		
Complete Study disposition page (Follow-Up)											X
Conduct QOL-B exit interview (subset of patients) [o]											X

TD = Study treatment discontinuation; PSD = Premature subject/patient discontinuation

X = assessment to be recorded on clinical data base

S = these assessments are source documentation only and will not be entered into the CRF

[*] Visit 2 (baseline) and Visit 101 are performed on the same day (Day 1). Patients are required to complete specific 'baseline assessments (Inclusion/Exclusion criteria) prior to being randomized and moving into the treatment epoch (Visit 101).

[a] The physical exam will be repeated at Visit 2 only if findings at previous visit are abnormal and clinically significant.

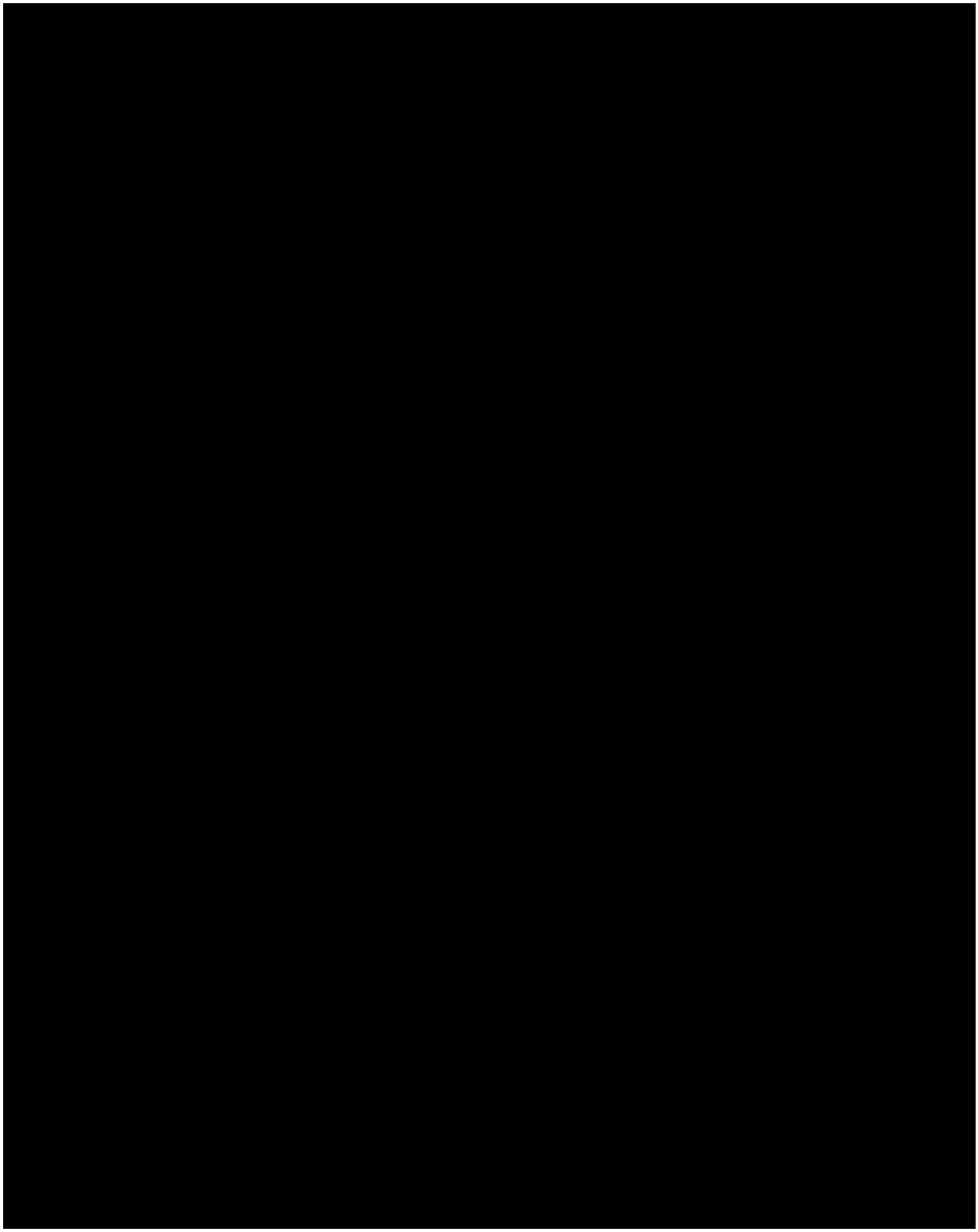
[b] To be performed prior to dosing.

[redacted]

[d] Obtain only for females of child-bearing potential.

[e] Pre-dose sputum specimens (2 separate specimens) will be collected from each patient for central analysis (one each for microbiology [redacted]). If a patient is unable to expectorate, one induced sputum specimen will be taken at baseline. For all post-baseline visits, a deep-throat cough swab can be collected from non-sputum producing patients for microbiology.

[redacted]



English, and send the completed, signed form by fax within 24 hours after awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department. The telephone and fax number of the contact persons in the local department of Drug Safety and Epidemiology, specific to the site, 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. Follow-up information should be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE.

Follow-up information provided must describe whether the event has resolved or continues, if and how it was treated, whether the treatment code was broken or not and whether the patient continued or withdrew from study participation. 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.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment a Drug Safety and 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 study treatment 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 EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

7.3 Liver safety monitoring

Tobramycin is not metabolized in the liver and therefore a hepatotoxicity effect is not expected following exposure to TIP. Standard serum chemistry, including liver enzymes, will be monitored during the study.

7.4 Renal safety monitoring

The following two categories of abnormal renal laboratory values have to be considered during the course of the study:

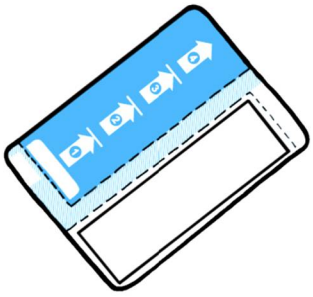
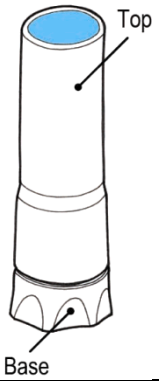
- Serum renal event:
  - confirmed (after ≥24h) increase in serum creatinine of 25 – <50% compared to baseline during normal hydration status
  - acute kidney injury: confirmed serum creatinine increase ≥50% compared to baseline
- Urine renal event
  - confirmed new onset (≥3+) proteinuria
  - confirmed new onset (≥3+) hematuria

Every renal laboratory trigger or renal event occurring after randomization as defined in Table 14-1 in Appendix 2 should be followed up by the investigator or designated personnel at the trial site as summarized in Appendix 2.

[redacted]

NOTE:

If you are unsure about how many doses to take each day, ask your physician or site personnel.

		
Capsule card (NOTE: Imprint on actual capsule card may look slightly different than above.)	**Inhaler** (T-326 Inhaler)	**Storage case**

How to inhale your medicine with the T-326 Inhaler

- **Only use the T-326 Inhaler contained in this pack.** Do not use the enclosed capsules with any other device, and do not use the T-326 Inhaler to take any other medicine
- When you start a new weekly pack of capsules, use the new T-326 Inhaler that is supplied in the pack. Each T-326 Inhaler is only used for 7 days
- **Do not swallow the capsules.** The powder in the capsules is for you to inhale. Please inform your study coordinator or nurse immediately, if you swallow the capsule by mistake
- Always keep the capsules in the capsule card until you need to use them. Do not take the capsules out of the card in advance
- Store the T-326 Inhaler in its tightly closed case when not in use

[redacted]