NOVARTIS

Global Clinical Development - General Medicine

TBM100/Tobramycin Inhalation Powder

Clinical Trial Protocol CTBM100G2202 / NCT02712983

A randomized, blinded, parallel group, multi-center dose-finding study, to assess the efficacy, safety and tolerability of different doses of tobramycin inhalation powder in patients with Non-Cystic Fibrosis Bronchiectasis and pulmonary *P. aeruginosa* infection

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List of abbreviations

ACR	Albumin-creatinine-ratio
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BE	Bronchiectasis
b.i.d.	twice a day
BSI	Bronchiectasis Severity Index
BUN	Blood urea nitrogen
CF	Cystic Fibrosis
CFR	US Code of Federal Regulations
CFU	Colony forming unit
Cmax	Maximum concentration
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CT	Computed Tomography
DMC	Data Monitoring Committee
DS&E	Drug Safety & Epidemiology
ECG	Electrocardiogram
EDC	Electronic Data Capture
FAS	Full Analysis Set
GCP	Good Clinical Practice
eGFR	Estimated Glomerular Filtration Rate
HRQoL	Health-related quality of life
HR-CT	High resolution computerized tomography
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
i.v.	Intravenous
IRB	Institutional Review Board
ISC	Independent Study Coordinator
KDIGO	Kidney Disease Improving Global Outcomes
[redacted]	[redacted]
LFT	Liver function test
MedDRA	Medical dictionary for regulatory activities
MDRD	Modification of diet in renal disease
MIC	Minimum inhibitory concentration
NIRT	Novartis Interactive Response Technology
NTM	Nontuberculosis mycobacterial
OC/RDC	Oracle Clinical/Remote Data Capture
o.d.	once a day
PCD	primary ciliary dyskinesia

[redacted]

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]

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.

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Protocol summary

Protocol number	CTBM100G2202
Title	A randomized, blinded, parallel group, multi-center dose-finding study, to assess the efficacy, safety and tolerability of different doses of tobramycin inhalation powder in patients with Non-Cystic Fibrosis Bronchiectasis and pulmonary *P. aeruginosa* infection
Brief title	Dose-finding study, to assess the efficacy, safety and tolerability of tobramycin inhalation powder in patients with Non-CF Bronchiectasis and pulmonary *P. aeruginosa* infection
Sponsor and Clinical Phase	Novartis, Clinical phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this Phase II study is to support the selection of a safe and tolerable TIP dose, and regimen that exhibits effective bacterial reduction of *P. aeruginosa* in non-CF BE patients with *P. aeruginosa* colonization.
Primary Objectives	• To evaluate the effect of different doses of TIP 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. • To assess the safety and tolerability with different doses of TIP and different regimens during the treatment epoch and during the follow-up epoch for each, as compared to placebo.
Secondary Objectives	• To assess the effect of different doses of TIP and different regimens on the frequency of pulmonary exacerbations • To assess the efficacy profile of different doses of TIP and different regimens, as measured by the use of anti-pseudomonal antibiotics • To assess the time to first hospitalization • To assess the pharmacokinetic concentrations of tobramycin in serum and in sputum from different doses of TIP and different regimens. • 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 impact of treatment with TIP on the Quality of Life Questionnaire for Bronchiectasis (QOL-B) by measuring change from baseline to all post-baseline visits.
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. The patients within each cohort will be randomized to blinded TIP (TIP continuous regimen or TIP/placebo cyclical regimen cohorts) or placebo. Total duration of the study is expected to be up to 196 days.
Population	The study population will consist of approximately 180 male and female BE patients ≥18 years old with clinical diagnosis of non-CF bronchiectasis

[redacted]

	confirmed radiologically by CT scan, a history of exacerbations and who had a history of positive culture for *P. aeruginosa* in sputum.
Key Inclusion criteria	• Written informed consent must be obtained before any assessment is performed. • Male and female patients of ≥ 18 years of age at screening (Visit 1). • Proven diagnosis of non-CF BE as documented by computed tomography or high-resolution computed tomography • 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. • FEV_1 ≥ 30% predicted at screening (Visit 1). • *P. aeruginosa*, must be documented in a respiratory sample at least 1 time within 12 months and also present in the expectorated sputum culture at Visit 1.
Key Exclusion criteria	• Patients with a history of cystic fibrosis. • Patients with a primary diagnosis of bronchial asthma. • Patients with a primary diagnosis of COPD associated with at least a 20 pack year smoking history. • 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. • 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 frequencies 0.5-4 kHz. The use of a hearing device is reflective of a clinically significant hearing loss; hence patients using hearing aids at screening are not eligible (revised per amendment 02). • Patients with active pulmonary tuberculosis. • Patients currently receiving treatment for nontuberculous mycobacterial (NTM) pulmonary disease. • Patients who are receiving inhaled anti-pseudomonal antibiotic within 28 days prior to study drug administration (Visit 101).
Study treatment	• Tobramycin inhalation powder (TIP) drug-device combination product consisting of tobramycin dry powder for inhalation in capsules (TBM100 28 mg inhalation powder hard capsule) administered by the T-326 Inhaler. • Matching placebo capsules to tobramycin inhalation powder administered by the T-326 Inhaler.
Key efficacy assessments	• *P. aeruginosa*: CFU (sputum) or semi-quantitative culture data (deep-throat cough swabs for non-sputum producing patients) • Other potentially pathogenic micro-organisms • MICs of tobramycin and other selected antibiotics for *P. aeruginosa* isolates • Anti-pseudomonal antibiotic use • Pulmonary exacerbations and related signs and symptoms • Pulmonary function by using spirometry

[redacted]

	• Patient reported outcomes [redacted]
Key safety assessments	• Adverse events, Serious adverse events • Physical examination and vital signs • Clinical chemistry, Hematology • Urinalysis and dipstick • Post-inhalation events • Bronchial hyperreactivity measured by change in FEV_1% predicted post-inhalation • Audiology (will be performed at selected sites and in patients with hearing events) • Serum pregnancy (females of child bearing potential) • Adverse events of special interest • Hospitalizations for respiratory-related AE
Other assessments	• Resource utilization • Pharmacokinetics [redacted]
Data analysis	The primary efficacy objective is to evaluate the effect of different daily doses of TIP 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. The comparisons of different TIP daily doses (combining TIP continuous or TIP/placebo cyclical regimens within a cohort) versus placebo will be evaluated by testing the following null hypothesis (H0) versus the alternative hypothesis (Ha): H0: TIP treatment group is equal to placebo group in bacterial load in sputum at Day 29 Ha: TIP treatment group is not equal to placebo group in bacterial load in sputum at Day 29 The primary efficacy endpoint will be analyzed using the analysis of covariance (ANCOVA) model. The model will contain treatment, cohort, baseline CFU, and baseline macrolide use. Pairwise comparisons of TIP dosing groups will be conducted versus placebo. To control the family-wise type-I error rate (three dose levels vs. placebo) at the two-sided 5% significance level, the step-wise Dunnett procedure will be used. The estimated adjusted treatment difference (TIP – placebo) will be displayed along with the associated standard error, 2-sided 95% confidence interval (CI), and p-value (2-sided).
Key words	Inhaled tobramycin; tobramycin inhalation powder; bronchiectasis; pulmonary *Pseudomonas aeruginosa* infection; dose-finding study

[redacted]

Amendment 3

Amendment rationale

The purpose of this protocol amendment is to revise:

Exclusion criterion 33b: To clarify the assessment of total abstinence as highly effective contraception method. Total abstinence has to be in line with the preferred and usual lifestyle of the subject. For consistency with the "Recommendations related to contraception and pregnancy testing" of the Clinical Trials Facilitation Group the wording has been reverted to the initial protocol wording.

In addition, this amendment includes the definition of personal data and modified withdrawal of study consent definition in accordance with the European Economic Area General Data Protection Regulation requirements.

This amendment also includes the following changes in planned statistical analysis:

- removing the cohort from the models due to confounding with treatment,
- including the multiple imputation technique as a sensitivity analysis and,
- dropping some exploratory analyses due to small sample size as outlined below.

Changes to the protocol

Glossary of terms

- Definition of personal data added and definition of withdrawal of consent modified.

4.2 Exclusion criteria

- Exclusion criterion 33b revised, as described above.

5.6.3 Withdrawal of informed consent.

- Section revised, as described above.

Section 9:

- Cohort is removed in the models for statistical analysis of primary and secondary variables due to confounding with treatment.
- Section 9.1. Information has been added to clarify that patients who are mistakenly randomized or who have not taken double blind study drug will be excluded from the full analysis set (FAS).
- Section 9.4.3 refers to a sensitivity analysis to account for patients who require treatment with anti-pseudomonal drugs for exacerbation: it was previously planned to exclude patient data from the start day of systemic anti-pseudomonal treatment for the relevant efficacy endpoints. This analysis will not be performed. Alternatively, for the primary endpoint only, multiple imputation will be implemented, as multiple imputation technique is more robust.

[redacted]

- Section 9.5.1.2 states that the proportion of patients with at least one pulmonary exacerbation, and the proportion of patients who permanently discontinue study drug due to pulmonary exacerbation will be analyzed using both logistic regression and time to event analysis. However, due to small sample size, these two endpoints will be evaluated using time to event analysis only. The annual rate of pulmonary exacerbations will be summarized only overall and not by exacerbations category due to small sample size.
- Section 9.5.1.3 refers to the use of anti-pseudomonal antibiotics. As anti-pseudomonal antibiotics used for treatment of pulmonary exacerbations are often used in combination, dose cannot be defined consistently. Therefore,the total amount (in doses) of anti-pseudomonal antibiotics used to treat pulmonary exacerbation during the treatment epoch and the study period will not be analyzed.

Summary of previous amendments

Amendment 2

Amendment rationale

The purpose of this protocol amendment is to revise the following enrolment criteria:

- Exclusion criterion 9a: The criterion was revised to reduce the number of disease-free survival years from 5 to 2 in patients with a history of cancer. Based on the tobramycin safety profile, there is no increased risk of cancer expected due to study medication.
- Exclusion criterion 10a: The exclusion criterion was revised to clarify that patients with clinically significant (in the opinion of the investigator) hearing loss that interferes with patients' daily activities (such as normal conversations) or chronic tinnitus should not be enrolled. The use of a hearing device is reflective of a clinically significant hearing loss; hence patients using hearing aids at screening are not eligible. Ototoxicity, manifested as both auditory toxicity (hearing loss) and vestibular toxicity, has been reported with parenteral aminoglycosides. Hearing loss and tinnitus were reported by patients in clinical trials with tobramycin inhalation powder. 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 frequencies 0.5-4 kHz.
- Exclusion criterion 18a: The renal exclusion criterion was updated with focus on the estimated glomerular filtration rate (eGFR, as per MDRD) and proteinuria, which are specific indicators to characterize the patient's renal function. Serum creatinine and blood urea nitrogen (BUN) have been removed as they are subject to significant diurnal variation based on the patients' hydration status and dependent on the meal composition taken. The mention of creatinine clearance is redundant as eGFR is measured.

[redacted]

- Exclusion criterion 21a: Patients with primary ciliary dyskinesia (PCD) were previously excluded from study participation because these patients frequently have hearing impairment secondary to chronic sinusitis and repeated otitis media episodes. The exclusion criterion was revised so that PCD patients may be enrolled, provided their hearing threshold at screening audiometry is 25dB or lower at frequencies 0.5-4 kHz.
- Exclusion criterion 33a: The criterion was revised to clarify the assessment of abstinence as highly effective contraception method.

The window for re-screening was revised to allow re-screening once for any patient until enrolment is completed. Bronchiectasis patients with *P.aeruginosa* infections may have several exacerbations a year. Therefore, patients who had an exacerbation during the screening period are now allowed to be re-screened twice until enrolment is completed.

Furthermore, the renal alert criteria and follow-up actions and the discontinuation criteria were amended in order to focus on the relevant renal function markers. To improve the renal function monitoring distinction is made between renal findings and confirmed renal events. Instructions for study treatment interruption/discontinuation have been clarified to distinguish events that mandate permanent study drug discontinuation as per protocol from those that are at investigators' discretion.

- Study treatment must be discontinued in patients who have a serum creatinine increase of 50% or more compared to baseline, as confirmed according to Appendix 2 Specific Renal Alert Criteria and Actions. The threshold of 50% is aligned with the definition of Stage 1 Acute Kidney Injury/Risk for Acute Kidney Injury in the KDIGO guideline (2012).
- Serum creatinine increase of up to 50% can reasonably be the result of patients' hydration status. Patients with serum creatinine increase of 25 – <50% will be monitored according to Appendix 2, which now includes also eGFR measurement as follow up action in patients with serum creatinine increase. Investigators should consider study treatment interruption or discontinuation based on clinical judgement.
- In patients with proteinuria ≥ 3+ urine microscopy, albumin-creatinine-ratio (ACR) and protein-creatinine-ratio (PCR) will be determined. Patients with confirmed proteinuria ≥ 3+ must discontinue study treatment.
- BUN has been removed from the discontinuation criteria because it is not specific enough to determine renal failure.

The pharmacokinetics (PK) sampling scheme was revised in order to maximize the number of samples for tobramycin exposure in particular in patients who are on alternating TIP/placebo treatment. Changing PK sampling from Day 29 to Day 8 is acceptable to assess the exposure. This is based on the short estimated terminal half-life of tobramycin in serum after inhalation of a single 112 mg dose of TIP which was approximately 3 hours (Ting 2014).

Additional minor clarifications were included, as summarized below in Changes to the protocol.

[redacted]

Changes to the protocol

3.1 Study design

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.

4.2 Exclusion criteria

- Exclusion criterion 9a. was amended to allow patients with a history of cancer (excluding lung cancer) and 2 years or more disease-free survival time to be included.
- Exclusion criterion 10a. was amended to clarify that patients with clinically significant (in the opinion of the investigator) hearing loss that interferes with patients' daily activities (such as normal conversations) or chronic tinnitus are not to be enrolled. 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 frequencies 0.5-4 kHz. The use of a hearing device is reflective of a clinically significant hearing loss; hence patients using hearing aids at screening are not eligible.
- Exclusion criterion 18a. was amended to remove serum creatinine and serum urea (BUN) from the panel of renal values relevant for enrolment.
- Exclusion criterion 21a. was revised: Patients with primary ciliary dyskinesia (PCD) may be enrolled, if their hearing threshold at screening audiometry is 25dB or lower at frequencies 0.5-4 kHz.
- Exclusion criterion 33a. was revised to clarify that women of child-bearing potential may participate in the study if the investigator assesses their abstinence compliance.

5.4 Section was amended to include unblinding requests from the Novartis study-independent safety review team.

5.5.7 Concomitant medication

Section was revised to clarify that short-term (maximum of 28 consecutive days) treatment with corticosteroids in case of an Adverse Event is permitted.

5.5.8 Prohibited medication

Section was revised to clarify that long-term treatment (more than 28 days) with corticosteroids >15mg/day is prohibited.

5.6.2 Discontinuation of Study Treatment

The discontinuation criteria were amended based on above rationale and aligned with Section 14 Appendix 2 Specific Renal Alert Criteria and Actions.

Table 6-1 Assessment schedule

A note was added to clarify that visits should occur on the designated day, or as close to it as possible, consistent with Section 6 Visit schedule and assessments.

The schedule was amended to account for changes in PK sampling and requirement for audiology assessments in patients with a past history of hearing loss or PCD according to the above rationale.

6.4.1 Microbiological assessment

[redacted]

The section was revised to clarify different options of obtaining sputum samples or swabs.

6.5.7 Audiology

The section was revised in alignment with exclusion criterion 10a.

6.6.2 Pharmacokinetics

The pharmacokinetics sampling scheme was aligned with the tobramycin exposure.

7.4 Renal safety monitoring

The section was revised to be aligned with Section 5.6.2 Discontinuation of Study Treatment and Section 14 Appendix 2

Section 14 Appendix 2

Specific Renal Alert Criteria and Actions were amended according to the above rationale and in alignment with Section 5.6.2 Discontinuation of Study Treatment.

Section 15 Appendix 3: Sputum/blood collection logs

The section was revised according to the amended PK collection schedule.

IECs

A copy of this amended protocol will be sent to the Independent Ethics Committee (IECs) and Health Authorities as appropriate.

The changes described in this amended protocol require IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 1

Amendment rationale

The purpose of this protocol amendment is to clarify specific elements in the protocol. First, the timing of the Data Monitoring Committee (DMC) interim review is removed, as this is detailed in the DMC charter.

Furthermore, the amendment clarifies that for the signs and symptoms characterizing the pulmonary exacerbations and which are required to last for more than 24 hours, additional information regarding duration will be collected to document if the reported signs and symptoms are present for more than 48 hours. The additional information is collected in line with the recently published consensus definition of pulmonary exacerbations for clinical research (Hill et al 2017).

In addition, thresholds and criteria for renal event monitoring are revised in accordance with the updated Novartis renal safety guideline and the safety profile of Tobramycin Inhalation Powder (TIP) obtained from clinical and post-marketing experience in cystic fibrosis (CF) patients. Based on the review of the most recent data cumulatively (until 30-June-2017), there is no evidence to suggest a causal relationship between use of TIP and the potential risk of

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nephrotoxicity. The risk for nephrotoxicity is expected to be very low considering the systemic levels of tobramycin after TIP administration (C_{max} is 1.02 ± 0.53 µg/mL) compared to the maximum systemic levels recommended for avoidance of the toxicity associated with intravenous tobramycin therapy (C_{max} greater than 12 µg/mL) (Sweetman 2011). The revised renal safety alert criteria have been designed to facilitate the early detection of a renal event.

Moreover, corrections on minor inconsistencies or clarifications are incorporated in this protocol amendment.

Changes to the protocol

- Section 4.1 Inclusion criteria: In inclusion criterion 4 'intravenous' has been replaced with 'parenteral' anti-pseudomonal antibiotic treatment. For consistency 'intravenous' has been replaced with 'parenteral' anti-pseudomonal antibiotics in sections 2.2 secondary objectives, 5.5.7 Concomitant medication and 9.5.1.3 Anti-pseudomonal antibiotics.
- Section 4.2 Exclusion criteria: exclusion criterion 26 has been clarified, in line with exclusion criterion 27.
- Table 6-1 and Section 6.4.6 Exit Interviews: The footnote on exit interviews is updated considering the timing of conduct of exit interviews.
- Section 6.4.4 Pulmonary exacerbations: additional time point of 48 hours is added to collect the presence of exacerbation symptoms, signs and findings lasting for more than48 hours. Furthermore, the protocol definition has been aligned to reflect the data collection in the Case Report Forms ('fever').
- Section 6.4.6 Health-related Quality of Life: The instructions were previously based on paper questionnaires and have been aligned with the electronic data collection used in this study.
- Section 6.5.4.3 Urinalysis: The assessments have been revised according to the updated renal event monitoring.
- Section 6.5.7 Audiology: The audiology assessment time window at visit 2 and following visits has been clarified.
- Section 7.4 Renal safety monitoring: Renal Alert criteria have been revised for consistency between sections 7.4 and Appendix 2 and in line with the revised Novartis guidelines. Thresholds and criteria for renal event monitoring are revised as follows:
    - Confirmed serum creatinine increase ≥ 25% from pretreatment baseline
    - New dipstick proteinuria ≥ 3+
    - Hematuria ≥ 3+ on urine dipstick

    In the event that any of the above is met, the renal markers will be repeated and the protein-creatinine ratio (PCR) and the albumin-creatinine-ratio (ACR) will be determined.

[redacted]

- Section 8.4 Data Monitoring Committee: The timing of the DMC review has been removed and referred to DMC charter for more details.
- Appendix 2: Revised Specific Renal Alert Criteria and Actions as indicated above.

IECs

A copy of this amended protocol will be sent to the Independent Ethics Committee (IECs) and Health Authorities as appropriate.

[redacted]

1 Introduction

1.1 Background

Bronchiectasis (BE) is defined as the irreversible dilatation of bronchi with destruction of elastic and muscular components of their walls. The gold standard method for diagnosis is via high resolution computerized tomography (HR-CT) scan. Bronchiectasis is frequently idiopathic in origin, or may be a result of a number of post-infectious causes, congenital diseases (e.g., immunodeficiency, primary ciliary dyskinesia, cystic fibrosis), inflammatory diseases (e.g., rheumatoid arthritis, inflammatory bowel disease) or anatomic obstruction, all of which predispose to a cycle of chronic infection and inflammation, and airways damage.

BE is often associated with bacterial infections that may be linked to higher morbidity. The cystic fibrosis population, who demonstrate significant bronchiectatic changes as a result of chronic lung infection and inflammation, experience a significant morbidity and mortality related to chronic *Pseudomonas (P.) aeruginosa* infection. The presence of bacterial colonization/infection in non–cystic fibrosis bronchiectasis (non–CF BE) has been associated with predictors of morbidity, such as exacerbations, and hospital admissions (Chalmers and Hill 2012). The pathogens most frequently associated with non-CF BE are: *Haemophilus influenzae* (30-47%), *Streptococcus pneumoniae* (7-11%), *Pseudomonas aeruginosa* (12-31%), *Staphylococcus aureus* (4-7%), and *Moraxella catarrhalis* (2-20%) (O'Donnell 2008). Wilson et al (2013) have published other potentially pathogenic microorganisms (PPMs) such as *Klebsiella spp* (7%) and *Proteus spp* (6%). However, the link between a specific bacterial colonization and exacerbation is often difficult to demonstrate. Several studies tried to identify the predictors of morbidity in non-CF BE patients. Among them colonization with *P. aeruginosa* may play a key role (Ho et al 1998, Angrill et al 2002, Loebinger et al 2009). Non-CF BE prevalence is not well defined; in a US cohort using a claims database (with the cohort definition having a combination of diagnostic criteria) estimates range from 4.2 cases per 100,000 persons aged 18-34 years up to 272 cases per 100,000 in those over 75 years (Weycker et al 2005) with a mean age of 61 years. Most subjects (68%) were women and common comorbidities included COPD (30.1%), ischemic heart disease (12.6%), malignant neoplasms (11.4%), diabetes mellitus (8.9%), and heart failure (8.1%).

At present, no specific treatment standards are available; some "best practice" recommendations have been developed such as the British Thoracic Society guidelines (Pasteur et al 2010); there are also review papers based mainly on the experience from CF. In stable lung disease (with or without chronic infection) the treatment aim is to reduce symptoms, limit exacerbations, preserve lung function and improve health-related quality of life (HRQoL). Antibiotic treatment is primarily recommended to treat exacerbations. Data on long-term treatment with antibiotics are sparse and evidence for clinical benefits remains limited: inhaled continuous therapy with gentamicin over 12 months was successful, however treatment effect was lost after 3 months off-treatment (Murray et al 2011). Recently Haworth et al (2014) have shown that 6 months therapy with inhaled colistin was successful, but only in the adherent subgroup.

A few pilot studies using inhaled tobramycin nebulised solution have been performed in non-CF BE patients, with variable treatment success rates (Barker et al 2000, Scheinberg and Shore 2005, Drobnic et al 2005). Other exploratory studies have assessed inhalation treatment as follow-up after intravenous (i.v.) therapy (Orriols et al 1999) or add-on treatment to oral ciprofloxacin during acute exacerbations (Bilton et al 2006); trends in improvements of clinical and/or microbiological outcomes have been noted in the arms with inhaled tobramycin. Eradication of *P. aeruginosa* infection has been noted in some of these studies, varying from less than 20% up to 40% (Barker et al 2000, Scheinberg and Shore 2005). Tolerability in these studies was noted to be lower than that seen with TOBI (tobramycin nebulised solution) registration trials in CF patients.

- Barker et al (2000): n= 74 patients double blind study TOBI 300 mg/5mL b.i.d. (37 patients) vs. placebo (37 patients), 4 weeks on/2 weeks off drug. Efficacy: significant microbiologic effect demonstrated – *P. aeruginosa* density reduction 4.54 $\log_{10}$ CFU/g sputum, P<0.01; *P. aeruginosa* eradicated in 35% of TOBI patients, more TOBI patients evaluated as having "improved" medical condition (investigators judgment). Safety: subset of patients appeared to have drug-related adverse events –increased cough, dyspnea, increased sputum, chest pain, wheezing.
- Scheinberg and Shore (2005): n=41 Open label; 3 cycles of 2 weeks on/2 weeks off nebulized TOBI 300 mg/5mL b.i.d.: 40 day follow-up. Result: microbiological benefit (decreased *P. aeruginosa* density) in addition to an improvement in pulmonary symptom scores.
- Orriols et al (1999): n=17 open label; nebulized ceftazidime 1000 mg + nebulized tobramycin solution 100 mg b.i.d. for 12 months vs. no inhaled antibiotics. Results: fewer hospitalizations, no improvement in pulmonary function (spirometry & arterial blood gas analysis).
- Drobnic et al (2005): n=30 double-blind, cross over; 300 mg/5mL nebulized TOBI b.i.d. or placebo, two 6 months treatment periods with 1 month wash out. Results: number of admissions and days of admissions reduced, decreased Pa density. No difference in exacerbation rate, pulmonary function and quality of life. No bacterial resistance.
- Bilton et al (2006): n=53 double-blind, randomized; ciprofloxacin oral plus either 300 mg/5mL nebulized TOBI b.i.d. or placebo, 2 weeks treatment, clinical outcome assessment at day 21. Results: consistent microbiological response but no statistical significant difference in clinical efficacy.

Tobramycin inhalation powder (TIP™) has been developed for the suppressive management of pulmonary infection due to *P. aeruginosa* in CF subjects aged 6 years and older. TIP is supplied in hard capsules at 28 mg dosage strength, to be administered via the T-326 dry powder inhaler. Phase III clinical studies have shown efficacy and safety comparable to nebulized tobramycin (TOBI) but with faster administration time and improved portability (Konstan et al 2011b). Bronchiectasis is a major component of the CF lung disease.

TIP is intended to be developed for the treatment of chronic lung infection with *P. aeruginosa* in symptomatic bronchiectasis patients, as documented by CT-structural changes. Given the benefits of inhaled tobramycin in CF patients and based on the preliminary results from pilot studies in BE patients with TOBI and also with inhaled gentamicin (Murray et al 2011), TIP is expected to show a reduction in bacterial load in BE patients which could translate into

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reduction of clinical symptoms, reduction in rates of exacerbation and reduction in use of systemic antibiotics.

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 et al 2013).

Based on the known concentration-dependent killing of bacteria and a post-administration antibiotic effect of aminoglycosides, once daily (o.d.) parenteral administration of tobramycin is well accepted (Smyth et al 2005). Concentration-dependent killing means that the bactericidal action of aminoglycosides is related to the peak concentration of antibiotic achieved. Greater bactericidal effect occurs at concentrations exceeding the minimum inhibitory concentration (MIC). The post-administration antibiotic effect is a phenomenon in which the bactericidal action of the aminoglycoside continues even after the antibiotic has been cleared and its concentration has fallen below the MIC. These pharmacological properties suggest that aminoglycosides can be administered o.d. Therefore in this study a once-daily regimen will be evaluated and compared to b.i.d regimen.

This study has been developed and will be executed as part of the iABC (inhaled Antibiotics in Bronchiectasis and Cystic Fibrosis) project. iABC, as an IMI (Innovative Medicines Initiative) project, [redacted] The scope of the iABC project is to advance the development of two inhaled antibiotics (one of them being TIP) for patients with CF and BE. Novartis retains the role of the sponsor and as such is responsible for the regulatory and pharmacovigilance activities, including clinical trial conduct.

1.2 Purpose

The purpose of this Phase II study is to support the selection of a safe and tolerable TIP daily dose, frequency of administration and regimen that exhibits effective bacterial reduction of *P. aeruginosa* in non-CF BE patients with a history of exacerbations and who had at least one positive culture of *P. aeruginosa* in sputum in the last 12 months, and a positive culture at screening for *P. aeruginosa*. Data from this study will be used to provide guidance on the dose selection and frequency of administration for subsequent [redacted] studies.

2 Study objectives and endpoints

2.1 Primary objectives

- 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.
- To assess the safety and tolerability with different doses of TIP administered o.d. and 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.

[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

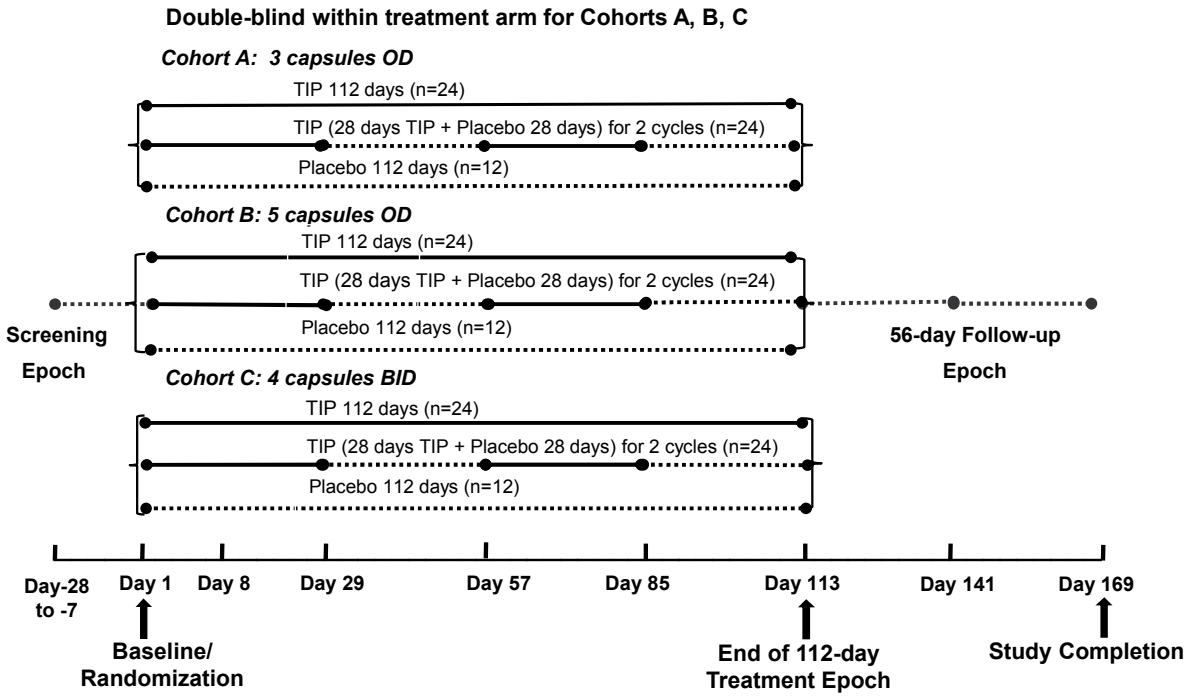
This is a blinded, randomized, dose and regimen finding trial utilizing a 3 treatment cohort design where active TIP doses or placebo in addition to the local standard care within each cohort are delivered once or twice daily. Approximately 180 eligible patients will be randomized to one out of the 3 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]

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]

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]

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]

frequencies 0.5-4 kHz. The use of a hearing device is reflective of a clinically significant hearing loss; hence patients using hearing aids at screening are not eligible.

11. Patients whose body mass index is less than 15 or greater than 40 kg/m^2.
12. Patients requiring long-term oxygen therapy for chronic hypoxemia. This is typically patients requiring oxygen therapy >15 h per day delivered by home oxygen cylinder or concentrator.
13. Patients who have had a pulmonary exacerbation requiring systemic glucocorticosteroid treatment and/or antibiotics in the 4 weeks prior to Visit 1. In the event of an exacerbation occurring during the screening epoch, the patient must discontinue from the study. The patient may be rescreened once the inclusion/exclusion criteria have been met.
14. Patients with active pulmonary tuberculosis.
15. Patients currently receiving treatment for nontuberculous mycobacterial (NTM) pulmonary disease.
16. Patients with one or more positive cultures in the last 12 months for *Mycobacterium. avium* complex, *M. abscessus* complex, *M. kansasii*, *M. malmoense*, *M. xenopi*, *M. simiae* or *M. chelonae*, unless all subsequent NTM cultures (at least two) are negative and in the opinion of the investigator the patient does not meet ATS criteria for NTM-pulmonary disease.
17. Hemoptysis of more than 60 mL at any time within 30 days prior to study drug administration (Visit 101).

18a. Estimated glomerular filtration rate (eGFR) of 50 mL/min/1.73m^2 or less, or an abnormal urinalysis defined as 2+ or greater proteinuria at screening (Visit 1).

19. Patients with clinically significant laboratory abnormalities (not associated with the study indication) at screening (Visit 1).
20. Patients with primary immunodeficiency receiving immunoglobulin therapy.

21a. Patients with primary ciliary dyskinesia (PCD) may be eligible if their hearing threshold at screening audiometry is 25dB or lower at frequencies 0.5-4 kHz.

22. Patients with active allergic bronchopulmonary aspergillosis.
23. Patients with an organ and bone marrow transplant/graft versus host disease.
24. Patients with haematological malignancies.
25. Patients with other clinically significant conditions (not associated with the study indication) at screening which might interfere with the assessment of this study.
26. Patients who are receiving inhaled anti-pseudomonal antibiotic within 28 days prior to study drug administration (Visit 101).
27. Any use of systemic anti-pseudomonal antibiotics within 28 days prior to study drug administration (Visit 101).
28. Use of loop diuretics, i.v. urea, i.v. mannitol within 7 days prior to study drug administration (Visit 101).
29. Patients receiving any medication that may influence the response to treatment. Prohibited medications: immunomodulators (cyclosporine, tacrolimus, anti-TNF alpha, steroids >15mg/day, alpha 1 antitrypsine, methotrexate, azathioprine, immune globulins (IV or subcutaneous), Prolastin, anti-cytokines).

[redacted]

30. Initiation of treatment with chronic macrolide therapy within 28 days prior to study drug administration (subjects may be taking chronic macrolide therapy at the time of enrollment into the study, but they must have initiated treatment more than 28 days prior to Visit 101, study drug administration).
31. Use of any other investigational drug within 30 days prior to screening (Visit 1) or 5 half-lives, whichever is longer.
32. 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 hCG laboratory test.

33b. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 1 day after stopping of study medication. Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject).
- Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment
- Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
- Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking investigational drug.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of child bearing potential.

34. Patients unable to successfully use a dry powder inhaler device or perform spirometry measurements.
35. Patients with a known history of non-compliance to medication or who are unable or unwilling to complete an electronic Patient Diary.
36. History or current diagnosis of ECG abnormalities indicating significant risk of safety for patients participating in the study such as:

[redacted]

- Concomitant clinically significant cardiac arrhythmias, e.g., sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

TIP is a drug-device combination product consisting of tobramycin dry powder for inhalation in capsules (TBM100 28 mg inhalation powder hard capsule) administered by the T-326 Inhaler. The test product consists of capsules of TIP at 28 mg dosage strength. The matching placebo is provided in hard capsules containing placebo particles consisting of DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine) and calcium chloride ($CaCl_2$). Three different dose regimens for the test product and placebo are investigated in this study.

A dose will always consist of sequential inhalation of the content of the number of prescribed capsules.

5.1.2 Additional treatment

No additional treatment beyond investigational treatment is requested for this trial. Patients will be allowed standard of care, as defined locally.

5.2 Treatment arms

Patients will be randomized to the following three cohorts in a ratio of 1:1:1. Blinding will be done within each cohort. Patients will be further randomized within each cohort to one of the three treatment arms: TIP, TIP/placebo cyclical, or placebo with a randomization ratio of 2:2:1.

Cohort A:

- TIP: Three capsules of blinded TIP at 28 mg dosage strength, inhaled o.d. via the T-326 Inhaler, for 112 days (on treatment). The total daily dose and each treatment therefore consists of 84 mg tobramycin (3 capsules of 28 mg each),
- TIP/placebo cyclical: patients will take same doses, i.e. 3 capsules o.d., by alternating TIP 28-days with placebo 28-days for two cycles for a total of 112 days.
- Placebo: The reference product consists of placebo capsules (DSPC/$CaCl_2$). The dose regimen for the reference product is three capsules blinded, inhaled o.d. via the T-326 Inhaler, for 112 days (on treatment).

[redacted]

Cohort B:

- TIP: Five capsules of blinded TIP at 28 mg dosage strength, inhaled o.d. via the T-326 Inhaler, for 112 days (on treatment). The total daily dose and each treatment therefore consists of 140 mg tobramycin (5 capsules of 28 mg each).
- TIP/placebo cyclical: patients will take same doses, i.e. 5 capsules o.d., by alternating TIP 28-days with placebo 28-days for two cycles for a total of 112 days.
- Placebo: The reference product consists of placebo capsules. The dose regimen for the reference product is five capsules blinded, inhaled o.d. via the T-326 Inhaler, for 112 days (on treatment).

Cohort C:

- TIP: Four capsules of blinded TIP at 28 mg dosage strength, inhaled b.i.d. in the morning and in the evening via the T-326 Inhaler, for 112 days of treatment. Each dose therefore consists of 112 mg tobramycin (4 capsules of 28 mg each), the total daily dose corresponds to 224 mg tobramycin (112 mg b.i.d.),
- TIP/placebo cyclical: patients will take same doses, i.e. 4 capsules b.i.d., by alternating TIP 28-days with placebo 28-days for two cycles for a total of 112 days.
- Placebo: The reference product consists of placebo capsules. The dose regimen for the reference product is four capsules blinded, inhaled b.i.d. via the T-326 Inhaler, for 112 days (on treatment).

The treatment epoch is followed by a 56-day follow-up epoch (no study treatment).

5.3 Treatment assignment and randomization

At Visit 101 (see Table 6-1), all eligible patients/subjects will be randomized via Novartis Interactive Response Technology (NIRT) to one of the treatment arms with the randomization stratum (use of macrolides as part of their standard of care therapy). The investigator or his/her delegate will contact the NIRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The NIRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of investigational treatment to be dispensed to the patient. The randomization number will not be communicated to the caller.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the Novartis IRT (NIRT) provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

Randomization by cohort and treatment arm will be stratified by use of macrolides.

The randomization scheme for patients/subjects will be reviewed and approved by a member of the Randomization Group.

[redacted]

5.4 Treatment blinding

The study will implement a within-cohort blinding approach (for details see Section 3.2).

Patients/subjects, investigator staff, persons performing the assessments, and data analysts will remain blind to the identity of the treatment from the time of randomization until database lock, using the following methods:

- Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study.
- The identity of the treatments within-cohort will be concealed by the use of study drug that are all identical in packaging, labeling, schedule of administration, appearance, taste, and odor.

The randomization codes associated with patients/subjects from whom PK samples are taken will be disclosed to PK bioanalysts who will keep PK results confidential until database lock.

Unblinding will only occur in the case of patient emergencies (see Section 5.5.9), request from the Novartis study-independent safety review team, request from the Data Monitoring Committee if needed for the safety interim analysis (Section 8.4) or as an outcome of their evaluation and at the conclusion of the study. Health authorities will be granted access to unblinded data if needed. Any patient whose treatment code has been broken inadvertently or for any non-emergency reason will be discontinued from treatment.

Each center shall identify individuals(s) called Independent Study Coordinators (ISC) responsible for dispensing study drug to the patient, assisting and supervising the patient with the first inhalation at the site during Visit 101, and supervising the patient whilst inhaling study drug at Visits 102 thru 106 (last inhalation). The ISC are independent of the study team in that they do not perform any patient assessments or study activities. The ISCs must not discuss the characteristics of the trial drug with the patients, the investigator(s) or any study staff responsible for evaluating patients, or Novartis personnel involved in conducting, monitoring, or analyzing data in this trial.

5.5 Treating the patient

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

5.5.1 Patient numbering

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

Upon signing the informed consent form, the investigator or his/her staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. The site must select the eCRF book with a matching Subject Number from the EDC system to enter data.

[redacted]

If the patient fails to be treated for any reason, the IRT must be notified within 2 days that the patient was not treated. The reason for not being randomized will be entered on the Screening epoch Study Disposition CRF.

5.5.2 Dispensing the study drug

Each study site will be supplied by Novartis with study drug in packaging of identical appearance specific for each dose level. Active and placebo packaging will be matching for each dose level.

The study drug packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the 9 treatment arms. Investigator staff will identify the investigational treatment package(s) to dispense to the patient by contacting the IRT and obtaining the medication number(s). Immediately before dispensing the package to the patient, the ISC or appropriate independent investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique subject number.

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

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

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

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Patients/subjects will be asked to return all unused study treatment and empty blisters from Visit 102, through Visit 106 or at the time of discontinuation of study treatment (TD).

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

5.5.3.2 Handling of additional treatment

Not applicable.

[redacted]

5.5.4 Instructions for prescribing and taking study treatment

The study drug (TIP or placebo) will be dispensed by the ISC at Visit 101 (start of treatment) and Visit 103 through Visit 106. Each patient will receive a kit of investigational treatment containing the medication for 28 days of treatment. For dosing visits 103, 104 and 105 study drug administered during the visit should be taken from the newly dispensed kit. At Visit 106, the study drug administered during the visit should be taken from the kit dispensed at Visit 105. Each kit contains five weekly boxes with each weekly box containing an inhaler and the required number of blister cards for one week dosing. The content of the fifth weekly box serves as a reserve in case a reserve inhaler is needed and provides supply until the next scheduled visit. Instructions for use for the T-326 Inhaler are given in Appendix 4 and will be handed out to the patient at Visit 101. Use of the reserve supply will be recorded on the appropriate CRF.

Patients will be provided with medication as described in Section 5.2.

The ISC will train the patient and assist and supervise the patient with the first inhalation at the site during Visit 101 by using instructions for use of T-326 Inhaler, describing in detail how to handle the drug-device combination. The ISC will also assist and supervise the patient's inhalation of the study drug at Visit 102 (Day 8) through Visit 106 (Day 113) or at the study treatment discontinuation visit (TD) if applicable. Detailed instructions for use are included in Appendix 4. In summary, each capsule containing the study medication has to be removed one at a time from the blister card, inserted into the T-326 Inhaler, the inhaler actuated and the study drug inhaled according to instructions. Patients are instructed to perform two inhalations and breath-hold maneuvers for each capsule by default, then verify that the capsule has been emptied completely and inhale again as necessary.

The last administration of study medication will be in the morning at Visit 106 (Day 113). Administration of any short-acting bronchodilator should occur 15 to 90 minutes prior to the spirometric assessments. Any other inhaled medications should have been taken prior to administration of study drug and any chest physiotherapeutic measures shall have been completed previously. If applicable, any long-acting bronchodilator prescribed to the patient should have been taken within the last 12 hours prior to the spirometric assessments; otherwise a short-acting bronchodilator shall be taken as described above. Also, the examinations which should be performed before study drug inhalation defined in Table 6-1 need to be completed prior to study drug administration. To ensure a robust and valid assessment of FEV_1 at each assessment it is important that these are done consistently at a similar time of day (to account for diurnal effects) and following consistent use (or not) of prior bronchodilator therapy.

All dosages prescribed and dispensed to the patient must be recorded on the Dosage Administration Record CRF.

All kits of investigational treatment assigned by the IRT will be recorded/databased in the IRT.

The investigator must promote compliance by instructing the patient to take the study treatment exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed.

[redacted]

If any faults or complaints are identified with the device, these should be returned to Novartis with a completed Device Return Form. The forms will be supplied to each investigator site by the Field Monitor.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Study drug dose adjustments are not permitted.

The patients with pulmonary exacerbations will continue in the study as scheduled once they have recovered and discontinued antibiotics administered for the exacerbation. If the patient continues in the study after the interruption of the study drug treatment, the schedule of visit/treatment cycle should be aligned with the original visit schedule.

Any interruption of the inhalation of study drug treatment must be recorded on the Dosage Administration Record CRF.

5.5.6 Rescue medication

Rescue medication for pulmonary exacerbations (including systemic antibiotics) and for bronchospasm is allowed. For concomitant treatments permitted see Section 5.5.7. Use of rescue medication must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

5.5.7 Concomitant medication

If a patient experiences a pulmonary exacerbation and/or worsening of the disease condition, he/she will be treated as deemed appropriate by the investigator. Following treatment for the pulmonary exacerbation and/or worsening of the disease condition, the patient will be expected to continue in the study as scheduled provided, in the opinion of the investigator, he/she can be safely returned to their pre-pulmonary exacerbation concomitant medications. In addition, if the patient requires any prohibited treatment listed in Table 5-1, then he/she should be withdrawn from the study medication.

The following treatments **are permitted** between Visit 101 and the completion of the study/termination visit and should be accurately documented in the CRF:

- Antibiotics (parenteral or by mouth) are allowed for the treatment of pulmonary exacerbations as dictated by the patient's condition.
    - Inhalation of study medication must be interrupted during i.v. aminoglycoside therapy. A window of 12 hours is recommended between stop of the study medication and initiation of i.v. aminoglycosides. Patients should restart inhalation of study medication within 24 hours after completing the i.v. treatment in order to complete the 112-day treatment epoch as close as possible to their initial study schedule, following completion of the course of i.v. aminoglycoside therapy.
    - Inhalation of study medication may continue upon physician's decision, if the antibiotics used are other than aminoglycosides.
- Pre-planned systemic antibiotics in the absence of an AE (prophylaxis of pulmonary exacerbation) are permitted only during the follow-up epoch.

[redacted]

- Short term treatment (of a maximum of 28 consecutive days) with corticosteroids for the treatment of pulmonary exacerbations or other adverse events
- Macrolides (anti-inflammatory regimen):
  - Patients should have been initiated on oral chronic macrolide therapy (i.e. macrolides prescribed for more than 14 days) more than 28 days prior to study drug administration (Visit 101) and should remain on treatment through the completion/termination visit.
- Bronchodilators:
  - Patients should have been kept on the same regimen more than 28 days prior to the first study drug administration (Visit 101) through the completion/termination visit. If patients are on short-acting bronchodilators, they should be consistently used prior to each assessment and inhaled 15 to 90 minutes prior to any spirometric assessments. Long-acting bronchodilators should be inhaled at least 12 hours prior to any spirometric assessments.
  - To ensure a robust and valid assessment of FEV_1 at each visit, it is recommended that these are done consistently at a similar time of day (to account for diurnal effects) and following consistent use (or not) of prior bronchodilator therapy.
- Inhaled corticosteroids:
  - Patients should have been initiated on therapy more than 28 days prior to study drug administration (Visit 101) and should remain on an unaltered regimen through the completion/termination visit.
- Use of oxygen is allowed for acute events, such as exacerbation. Long-term oxygen therapy for chronic hypoxemia over >15 h per day is not allowed.

Selected information for all antibiotics and macrolides, corticosteroids and bronchodilators administered within 12 months prior to screening will be recorded in the CRF.

Caution for concomitant use

Based on the interaction profile for tobramycin following intravenous and aerosolized administration, concurrent and/or sequential use of TIP 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, cefalothin, polymyxins (risk of increased nephrotoxicity);
- platinum compounds (risk of increased nephrotoxicity and ototoxicity);
- anticholinesterases, botulinum toxin (neuromuscular effects).

If the patient's condition/disease requires medications (including those listed above) which may potentially affect the systemic tobramycin levels (even the study drug is tobramycin inhalation powder), continuation of inhalation of study medication is at the investigator's discretion.

- If inhalation of study medication is continued during the following drug therapy, patients

[redacted]

will continue with the study schedule for the remainder of the study; however, therapeutic drug monitoring is strongly recommended.

- If inhalation of study medication is interrupted during the following drug therapy (either as a routine measure or due to elevated serum tobramycin levels), patients should restart inhalation of study medication in order to complete the 112-day treatment epoch as close as possible to their initial study schedule.

Caution should be exercised when prescribing TIP to patients with known or suspected neuromuscular disorders such as myasthenia gravis or Parkinson's disease. Aminoglycosides may aggravate muscle weakness because of a potential curare-like effect on neuromuscular function.

5.5.8 Prohibited medication

Use of the treatments displayed in Table 5-1 is NOT allowed after the start of the study treatment administration (Visit 101). If a prohibited medication is taken between start of study treatment administration and end of the treatment epoch, study drug must be discontinued. If taken during the follow-up epoch, the prohibited medication should be stopped as soon as possible. Use of the prohibited medication should be documented in the appropriate section of the CRF.

Some diuretics can enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue. TIP should not be administered concomitantly with ethacrynic acid, furosemide, urea, or intravenous mannitol.

Table 5-1 Prohibited medications requiring study drug discontinuation

Medication
Inhaled antibiotics except as per protocol
loop diuretics*
urea (intravenous)*
mannitol (intravenous)*
Cyclosporine
Tacrolimus
anti-TNF alpha
long-term treatment with corticosteroids >15mg/day (more than 28 days)
alpha 1 antitrypsine replacement therapy (Prolastin)
Methotrexate
Azathioprine
immune globulins (IV or subcutaneous)
anti-cytokines
Any other investigational treatments
Long-term oxygen therapy >15h per day

* Potential for nephrotoxicity

[redacted]

5.5.9 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the patient safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the Novartis (or CRO) monitor for the site and the Study Team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT at any time in case of emergency. The investigator will provide:

- protocol number
- study drug name (if available)
- patient number

In addition, oral and written information to the subject must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

Study drug must be discontinued after emergency unblinding. Study drug must also be discontinued for any patient whose treatment code has been inadvertently broken.

5.6 Study Completion and Discontinuation

5.6.1 Study completion and post-study treatment

A patient will be considered to have completed the study when the patient has completed the last visit planned in the protocol. Completion of the study will be when the last patient has completed Visit 202.

Continuing care should be provided by investigator and/or referring physician based on patient availability for follow-up. This care may include resuming of their standard of care treatment as deemed by their physician.

5.6.2 Discontinuation of Study Treatment

Discontinuation of study treatment for a patient occurs when study drug is stopped earlier than the protocol planned duration, and can be initiated by either the patient or the investigator.

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

Study treatment **must** be discontinued under the following circumstances:

- Patient wish
- Non-compliance of the patient with study procedures or investigator instructions, as per the investigator's judgment

[redacted]

- Emergence of AEs when worsened from baseline (Visit 2) or any newly occurring development of AEs with regards to the following:
  - If a patient is found to have a 20-dB or greater decrease in auditory acuity at one or more frequencies in 1 or both ears due to sensorineural deficit, the patient will be withdrawn from treatment and monitored until auditory acuity values return to the most recent pre-dose value (either at screening or baseline) or until study closure, whichever occurs first, i.e. the patient must be withdrawn from study treatment but should continue in the study. In case no pre-dose value is available for comparison, discontinuation of the study treatment and withdrawal of the patient from the study should be based on the investigator's best medical judgment.
- Any of the following laboratory abnormalities when worsened from baseline (Visit 101) or are a newly occurring AE:
  - Proteinuria ≥ 3+, as confirmed according to Section 14, Appendix 2 Specific Renal Alert Criteria and Actions
  - Serum creatinine increase ≥ 50% compared to baseline, as confirmed according to Section 14, Appendix 2 Specific Renal Alert Criteria and Actions
  - Estimated glomerular filtration rate (GFR) of ≤50 mL/min/1.73m^2
- Pregnancy (see Section 6.5.8 and Section 7.6)
- Use of any of the prohibited medications detailed in Table 5-1 and Section 5.5.8.
- Any situation in which study participation might result in a safety risk to the patient.

Any renal finding needs to be followed up according to Section 14 Appendix 2 Specific Renal Alert Criteria and Actions, which lists additional laboratory abnormalities that may require study treatment discontinuation based on clinical judgement. Confirmed renal events need to be followed up and documented according to Section 14 Appendix 2.

Patients who interrupted study medication based on the investigator's decision should continue in the study, as per the visits and assessment schedule (see Section 5.5.5) - interruption of study treatment does not necessarily mandate withdrawal from the study.

Patients who discontinue study medication should NOT be considered withdrawn from the study. The patient should return to the clinic as soon as possible, after discontinuation of study drug, for a study treatment discontinuation visit and then enter the 2-month follow-up epoch. Treatment discontinuation visit assessments detailed in the "treatment discontinuation visit" (TD) in Table 6-1 should be completed and recorded in the CRF. If they fail to return for these assessments for unknown reasons, every effort should be made to contact them as specified in Section 5.6.4. The investigator must determine the primary reason for the patient's premature discontinuation of study treatment and record this information on the Dosage Administration CRF.

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should to be collected at clinic visits or via telephone visits:

- new / concomitant treatments
- adverse events/Serious Adverse Events

[redacted]

If the patient cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the patient, or with a person pre-designated by the patient. This telephone contact should preferably be done according to the study visit schedule.

The investigator must also contact the IRT to register the patient's discontinuation from study treatment.

If study drug discontinuation occurs because treatment code has been broken, please refer to Section 5.5.9.

5.6.3 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study any longer, and
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

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

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

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in assessment table (Table 6-1.)

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law.

All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

The investigator must also contact the IRT to register the patient's withdrawal from the study.

Patients who prematurely discontinue study treatment or withdraw from the study will not be replaced.

5.6.4 Loss to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A patient cannot be considered as lost to follow-up until the time point of his/her scheduled end of study visit has passed.

5.6.5 Early study termination by the sponsor

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and treated for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

6 Visit schedule and assessments

The study will consist of a screening epoch, a 112-day treatment epoch and a 56-day follow-up epoch after the last treatment.

Table 6-1 lists all of the assessments and indicates with an "x" when the visits are performed. Patients/subjects must be seen for all visits on the designated day, or as close to it as possible. All data obtained for these assessments must be supported in the patients' source documentation. 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) as part of Visit 2 prior to being randomized and moving into the treatment epoch (Visit 101). Missed or rescheduled visits should not lead to automatic discontinuation.

Patients/subjects who prematurely discontinue 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 will be performed. At this final visit, all dispensed investigational product should be reconciled and the adverse event and concomitant medications reconciled on the CRF.

At a minimum, patients will be contacted for safety evaluations during the 30 days following the last administration of study treatment.

The PRO questionnaires should always be completed before any other assessments at a study visit. **The following assessments should be performed prior to dosing for applicable visits:**

- Physical examination
- Vital signs
- Body weight
- Serum specimen for Safety Laboratory
- Serum pregnancy test
- Urine pregnancy test
- Urinalysis
- Sputum specimens (2 separate specimens) for central analysis
- Pre-dose serum specimen for PK sub-study (if applicable)
- Audiology at Visit 2
- Pre-dose spirometry

[redacted]

[redacted]

[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**
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]

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]

[f] All subjects will have post-dose serum specimens collected during specified time windows. The time interval is measured from the completion of study drug administration. There must be a minimum of one hour difference between consecutive sampling points. Samples may be obtained from a peripheral site by phlebotomy or through a temporary i.v. site, but not through an existing central access or catheter. A patient who discontinues early and is on study medication will be asked to provide an extra serum specimen at the treatment discontinuation visit.

[g] All patients will have post-dose sputum specimens collected for PK testing during specified time windows. The time interval is measured from the completion of study drug administration. 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. A patient who discontinues early and is on study medication will be asked to provide an extra sputum specimen at the treatment discontinuation visit.

[h] Subjects in the serum PK sub-study will have a pre-dose serum specimen collected prior to administration of study drug. A patient who discontinues early and is on study medication will be asked to provide a pre-dose serum specimen at the treatment discontinuation visit.

[i] Audiological assessments will be conducted at selected study sites or in patients with oto-toxic events. Auditory acuity will be measured at frequencies from 250 to 8000Hz using a standard dual-channel audiometer. Audiology can be performed within 3 days of the assigned visit.

[j] If audiology is normal up to and including the end of the treatment epoch (Visit 106), audiological examination is not needed at Visits 201 and 202.

[k] Spirometric measurements shall be conducted at approximately the same time of day to minimize effects of diurnal variability in lung function.

[l] PROs to be completed for whom a validated version in a language well understood by the patient is available. [redacted] 1. QOL-B, [redacted]

[m] Identical training regardless of treatment arm.

[n] The ISC will assist subjects in conducting the first study drug inhalation (Visit 101), while the inhalation of the study drug at Visits 102, 103, 104,105 and 106 (last study drug inhalation) at the study site is performed by the subject in the presence of the ISC.

[n] If a patient prematurely discontinues study drug , study drug administration in the presence of the ISC, study drug accountability, post-dose spirometry and post-inhalation events should be assessed at the TD visit provided the patient agrees to inhale study medication during the visit.

[o] Exit interviews should be conducted by telephone at the last follow-up visit after completion of the PRO questionnaires and preferably prior to other assessments. Approximately 25 patients are planned to be recruited.

[p] Patients with a past history of clinically significant hearing loss in the opinion of the investigator and patients with primary ciliary dyskinesia (PCD) may be eligible only if their hearing threshold at screening audiometry is 25dB or lower at frequencies 0.5-4 kHz.

[redacted]

6.1 Information to be collected on screening failures

All patients/subjects who have signed informed consent but not entered into the next epoch will have the study completion page for the screening epoch, demographics, inclusion/exclusion, and serious adverse event (SAE) data collected. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

6.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all patients include: date of birth, age, sex, race, ethnicity, and source of patient referral. Relevant medical history or current medical condition data include data present before signing informed consent. Where possible, diagnoses and not symptoms will be recorded. History of pulmonary exacerbations will be collected on a specific medical history CRF.

A standard 12 lead ECG will be performed at screening (Visit 1). For eligibility in the study the interpretation of the tracing must be made by a qualified physician and documented. The original ECGs, appropriately signed, should be collected and archived at the study site.

ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection is ECG collection first, followed by vital signs, blood sampling, and spirometry. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

Each ECG tracing should be labeled with study number, subject initials, subject number, date and time, and filed in the study site source documents. For any ECGs with subject safety concerns, two additional ECGs should be performed to confirm the safety finding. If the ECG findings are clinically relevant and would prevent the patient from participating in the study (taking into account the overall status of the patient as well as the medication profile), the patient should be recorded as a screen failure, should NOT be randomized and should not receive treatment.

Clinically significant abnormalities should be recorded on the relevant section of the medical history/Current medical conditions/AE CRF page as appropriate.

Investigators will have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

Conditions associated with bronchiectasis disease and signs or symptoms including etiology and age at diagnostic will be captured by using a specific BE-related Medical History CRF page.

Baseline data (using a specific CRF as necessary) such as spirometry, previous hospital admissions and exacerbations, baseline Medical Research Council (MRC) breathlessness score, colonization with *P. aeruginosa* and other organisms, and radiological changes will be collected for calculation of the Bronchiectasis Severity Index (BSI) for all patients. The BSI will serve as a disease-specific severity assessment tool (Chalmers et al 2014).

[redacted]

Previous medication to be listed includes information for all antibiotics and macrolides administered within the last 12 months prior to Visit 1.

A sputum sample is required to be collected at Visit 1, cultured locally at the site and tested for the presence of *P. aeruginosa*, to ensure patients meet the inclusion criteria.

6.2.1 Chest CT-scan

For each patient all reconstructed series from the most recent available digital computed tomography (CT) chest scan images will be sent to the Central Reader for advanced centralized image analysis. Before sending CT images to the Central Reader by secure file transfer protocol (SFTP) server, courier or eRoom, all images will be de-identified. For each patient CT images will be scored for the presence or absence of BE. Furthermore, all CT images will be scored using the Bauman and Hartmann scoring systems to quantify the presence and extend of key lung disease features including BE, airway wall thickening, trapped air, parenchymal abnormalities and nodules. In addition for a subset of random selected CT images, advanced image analysis of the most appropriatie series for each CT scan will be executed in random order to develop the PRAGMA-BE scoring system.

For the development of the Airway Artery (AA) method for objective measurement of airway dimensions CT images from a subset of approximately 30 patients will be used. The following structures will be manually measured: airway lumen area (A_{inner}), airway outer area (A_{outer}) and the area of the accompanying vessel (A) for all visible airway vessel pairs (100-300 per scan) (de Jong et al 2005). From these measurements the following ratios will be computed: Aouter/A; Ainner/A; Airway wall Area (AWA)/A. The automated airway and artery extraction algorithm as developed by the central reader imaging group will subsequently be tuned to match these manual annotations. Automated measurement will be further validated by determining agreement with the same measures derived from manual annotation in this patient cohort. Furthermore, the manual and automated AA-method will be compared to BE and airway wall thickness sub-scores [redacted] and spirometry outcomes.

Through image analysis quantitative image analysis parameters will be allocated for each patient to CT images that will be included into the clinical database. The annotated images will be stored within the secured hospital environment on the data storage facility of the Central Reader.

Results from the Phase II study will be used to select the best image analysis strategy to phenotype BE CT images and to fine-tune the automated AA method to be used [redacted].

6.3 Treatment exposure and compliance

Assessment of compliance will be based on the electronic patient diary to capture the number of inhaled capsules in every morning and evening if applicable, and the number of unused capsules returned per patient assessed by the ISC. The ISC will then inform the investigator and/or study personnel who will then record the data in the CRF accordingly.

6.4 Efficacy

The following efficacy assessments will be performed:

[redacted]

- *P. aeruginosa*: CFU (sputum) or semi-quantitative culture data (deep-throat cough swabs for non-sputum producing patients)
- Anti-pseudomonal antibiotic use (other than study drug)
- Pulmonary exacerbations (total count, rate, severity and time of onset) and related signs and symptoms
- Pulmonary function by using spirometry
- Patient reported outcomes (QOL-B,)

6.4.1 Microbiological assessment

Sputum will be collected in sterile containers before study drug administration at all treatment epoch and follow-up epoch visits. The sputum specimen will be used to culture for the presence of *P. aeruginosa* (quantitative test) Following alternatives can be chosen, if a patient is unable to expectorate during the visit:

- Sputum will be induced at the baseline visit (Visit 2) as the specimen.
- At the other visits, a deep-throat cough swab will be collected for non-sputum producing patients for microbiology specimens. Deep-throat cough swab specimens will be evaluated semi-quantitatively.
- Patients may undergo a short physiotherapy session at any visit, if feasible, to enable to expectorate spontaneously.

Microbiological analyses, , will be performed centrally at a qualified microbiology laboratory. Details on the collection and shipment of samples, generation of data and reporting of results by the microbiology laboratory are provided in a separate laboratory manual.

[redacted]

6.4.3 Anti-pseudomonal antibiotic use

The proportion of patients having anti-pseudomonal antibiotic and duration of treatment (other than study drug) will be determined from the collection of concomitant medications during the study.

A list of anti-pseudomonal antibiotics can be found in Appendix 12.

6.4.4 Pulmonary exacerbations

The rate, duration and primary precipitating factors of pulmonary exacerbations will be assessed during the study. Pulmonary exacerbation episodes will be collected on a specific CRF.

Pulmonary exacerbations are defined as: events for which it is clinically determined by the site investigator that antibiotic therapy is required AND at least 3 of the following 6 symptoms, signs, or findings were present outside of normal variation:

1. Increased sputum volume, or change in viscosity / consistency or purulence for more than 24 hours;
2. Increased shortness of breath at rest or on exercise for more than 24 hours;
3. Increased cough for more than 24 hours;
4. Fever of ≥38° Celsius within the last 24 hours;
5. Increased malaise / fatigue / lethargy for more than 24 hours;
6. A reduction in forced expiratory volume in the first second of expiration (FEV_1) or forced vital capacity (FVC) of least 10% from screening;

A worsening of symptoms that either does not meet the above symptom definition but is treated by the investigator with antibiotics, or that meets the symptom definition but is not treated with antibiotics, is not considered a pulmonary exacerbation for the study.

[redacted]

For the above reported signs and symptoms, additional information will be collected to document if the reported signs and symptoms last for more than 48 hours.

Patients should be advised to contact the site when experiencing a pulmonary exacerbation for advice. An unscheduled visit should occur within 2 working days of the event to confirm the diagnosis, unless the patient is hospitalized and thus unable to attend the site. AEs/SAEs, concomitant medications, and safety laboratory exams should be captured, as appropriate.

The start date for a pulmonary exacerbation recorded in the CRF should be the first day of symptom worsening of at least 3 of the 6 symptoms, as defined above. The end of a pulmonary exacerbation episode is marked by the return to pre-exacerbation symptom status.

An exacerbation might result in missed or rescheduled visit(s) and missing associated CRF data in some circumstances.

Patients who develop a pulmonary exacerbation between screening and prior to treatment will be screen failed but will be permitted to be re-screened once the inclusion/exclusion criteria have been met (see exclusion criteria).

6.4.5 Pulmonary function tests

Pulmonary function testing will be performed locally at the site using locally available spirometry equipment. FEV_1, [redacted] values will be recorded on the CRF as absolute volume measurements. The pre-dose values will be used as efficacy measurements.

Please refer to the Spirometry Guidance, in Appendix 5 for full details on scheduling and performing spirometry.

6.4.6 Health-related Quality of Life

The PROs QOL-B, [redacted] questionnaires should always be completed before any other assessments [redacted]

All patients/subjects will complete the PRO questions via a handheld electronic device or an electronic tablet. Patients/subjects should be given sufficient space and time to complete all study PROs. If patients/subjects experience any difficulties with submission after they complete the PROs, the study staff should assist them with submitting their PRO responses. Attempts should be made to collect responses to all PROs for all patients/subjects, including from those who prematurely discontinue prior to the study evaluation completion visit, however, if patients/subjects refuse to complete PROs, this should be documented in study source records. Patient's refusal to complete study PROs are not protocol deviations.

Completed questionnaires will be reviewed and examined by the investigator, before the clinical examination, for responses that may indicate potential adverse events (AEs) or serious adverse events (SAEs). The investigator should review not only the responses to the questions in the questionnaires but also for any unsolicited comments written by the patient. If AEs or SAEs are confirmed, then the physician must record the events as per instructions given in Section 7.1 and Section 7.2 of the protocol. Investigators should not encourage the patients to change the responses reported in the completed questionnaires.

[redacted]

Quality of Life Questionnaire-Bronchiectasis (QOL-B)

The QOL-B is a bronchiectasis specific PRO instrument that has been recently developed according to the principles in FDA 2009 PRO guidance (Quittner et al 2014). The QOL-B consists of 8 domains (Respiratory Symptoms, Physical, Emotional, Social, and Role Functioning, Vitality, Treatment Burden, and Health Perceptions), all have been developed based on patient interviews and went through preliminary validation, its validity and reliability has been confirmed. The respiratory domain is of particular interest. The minimal important difference (MID) has been found to be 8 on this domain and have shown to be responsive to treatment (Quittner et al 2015). The recall period is one week, and the responses are graded on a 4-point Likert scale.

The instrument will be administered at each of the following study visits: baseline (Visit 2) and each of the post-baseline visits. It must be administered at the beginning of each study visit, before any measurements are taken (i.e., weight, lung function).

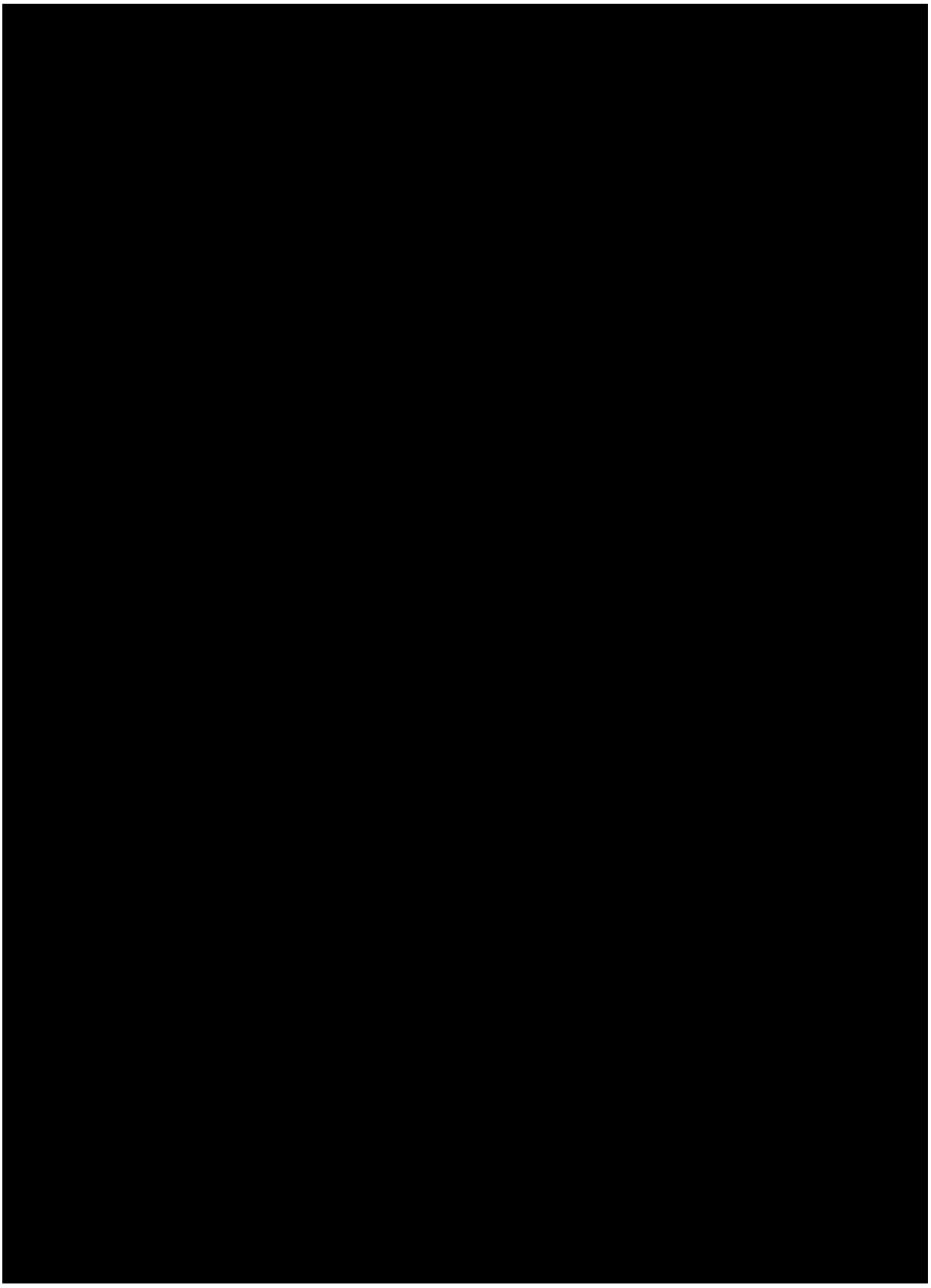
The appropriate language version(s) of the questionnaire will be used in each participating country. The same language version of the questionnaire should be used by a particular patient throughout the study.

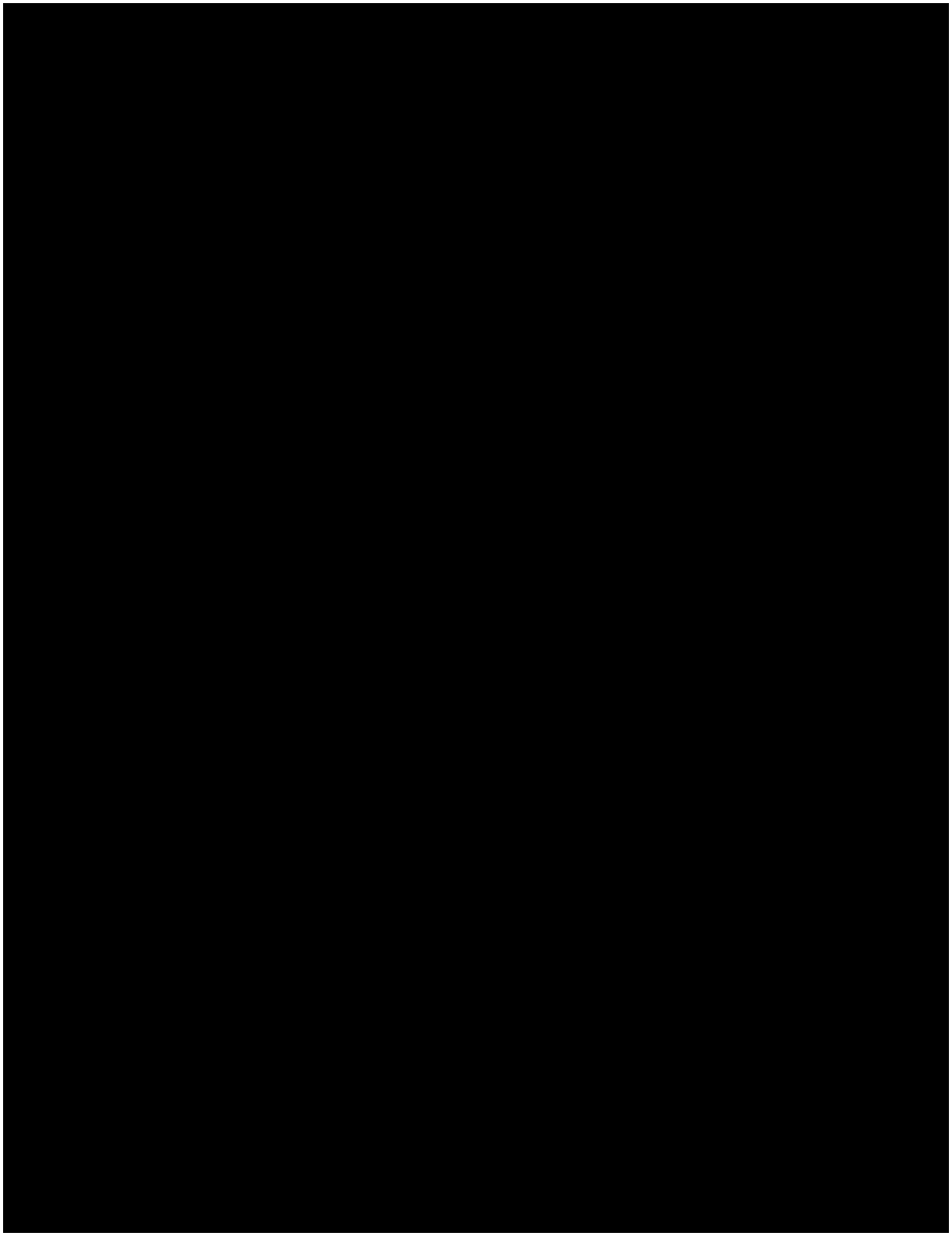
The study coordinator should be familiar with the instrument and the associated user guides and training materials provided. The patient should complete the questionnaire on his/her own (no family members present) in a quiet area and be allowed to ask questions; however site staff should take care not to influence the patient's responses. The patient will be instructed to provide the truest and for them best response.

While completing the PROs, the electronic device will prompt patients at appropriate intervals to ensure that they respond to all questions to minimize missing data. At later visits patients are not allowed to review their previous responses. The original questionnaire will be kept with the patient's file as the source document.

Exit Interviews

Novartis will conduct (by an entrusted external vendor) exit interviews with a subset of patients completing this trial to evaluate the content validity of the QOL-B, with particular emphasis on the Respiratory Symptoms subscale, as recommended in the feedback received from the FDA. Exit interviews will be conducted in the United Kingdom only and the planned recruitment is approximately 25 patients. Telephone interviews with the patients should be conducted at the last follow-up visit after completion of the PRO questionnaires and preferably prior to other assessments. The results will be independently reported.





6.4.8 Appropriateness of efficacy assessments

The efficacy variables selected (see Section 6.4.1 through [redacted]) are commonly used for studies investigating the efficacy of antibiotics and/or the indication of BE, [redacted]. Microbiological data will assess the direct impact of the drug on the pathogens, while spirometric data and pulmonary exacerbations are representative for the control of BE overall.

6.5 Safety

The following assessments will be performed to assess study treatment safety:

- Adverse events, Serious adverse events
- Physical examination and vital signs
- Clinical chemistry, Hematology
- Urinalysis and dipstick
- Post-inhalation events
- Bronchial hyperreactivity measured by change in FEV_1% predicted post-inhalation
- Audiology (will be performed at selected sites and in patients who have oto-toxic AEs during the study)
- Serum pregnancy (females of child bearing potential)
- Adverse events of special interest (ototoxicity/hemoptysis/renal)
- Hospitalizations for respiratory-related AE

6.5.1 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. Clinically relevant findings that are present prior to signing informed consent must be included in the Medical History part of the CRF. Significant findings made after first administration of investigational drug which meet the definition of an Adverse Event must be recorded on the Adverse Event section of the CRF.

6.5.2 Vital signs

Systolic/diastolic blood pressure, radial pulse rate (over a 30 s interval), respiratory rate and body temperature will be recorded at Visit 1 (screening), start of treatment epoch (Visit 101), end of the treatment epoch (Visit 106), and end of the follow-up epoch (Visit 202). Single measurements will be performed before inhalation of study medication in the case of a dosing visit.

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

[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).

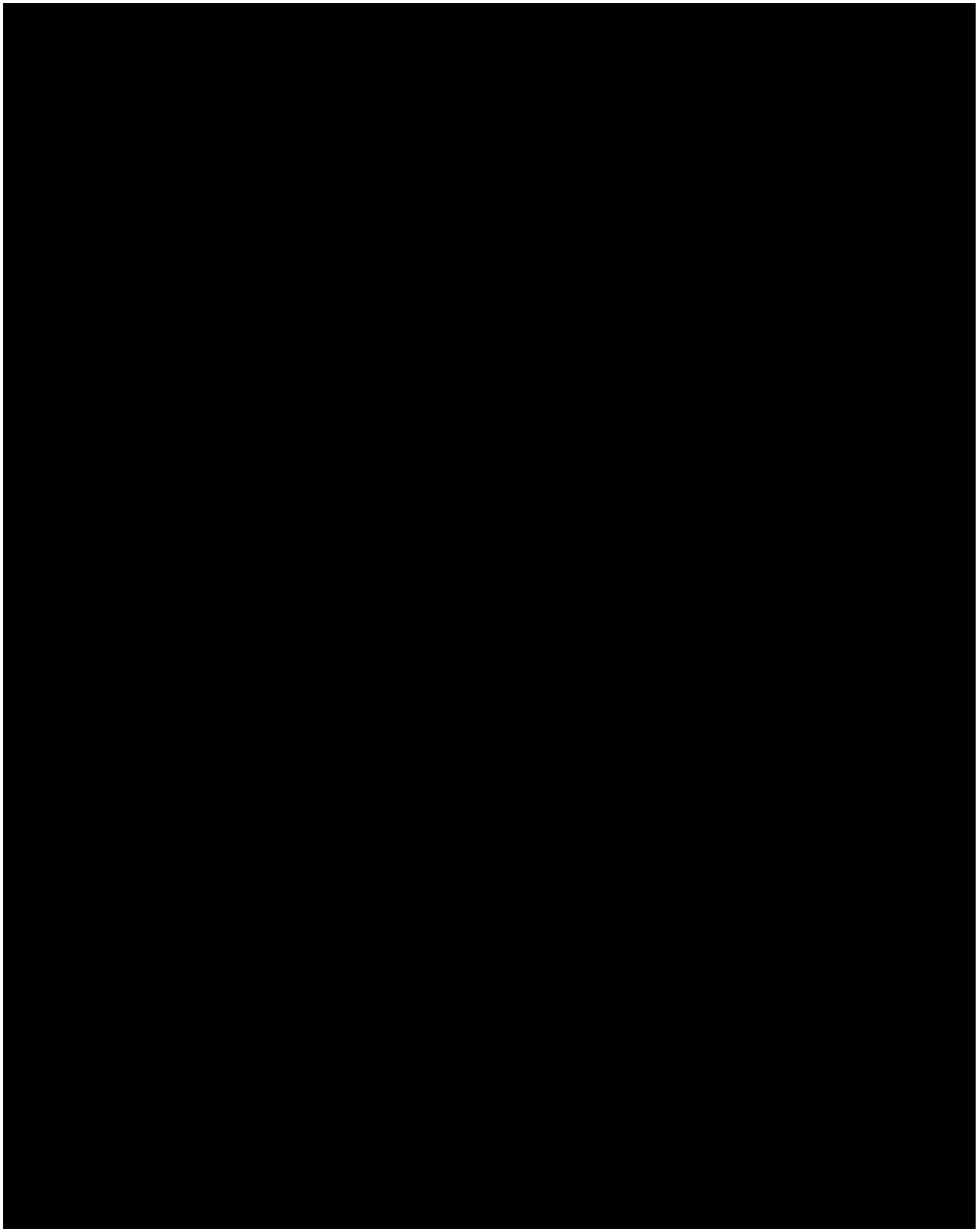
To evaluate serum PK in approximately 16 patients on active treatment, at least 20-22 patients from each cohort (at least 60 total patients) will participate in a PK sub-study. All patients will be asked to participate in the sub-study until enrollment is fulfilled for each cohort. Patients in this PK 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).



6.6.5 Patient diaries

All patients will be provided with an electronic Patient Diary to record dosing of study treatment (number of inhaled capsules every morning and evening during the treatment epoch).

7 Safety monitoring

7.1 Adverse events

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

In addition, all reports of intentional misuse and abuse of the product are also considered an adverse event irrespective if a clinical event has occurred.

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

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

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

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

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

- the severity grade
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities
- its relationship to the study treatment (no/yes)
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.

[redacted]

- 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]

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]

7.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the DAR (dose administration record) CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE.

Treatment error type	Document in Dose Administration (DAR) CRF (Yes/No)	Document in AE CRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes,	Yes, even if not associated with a SAE

7.6 Pregnancy reporting

To ensure patient safety, each pregnancy occurring after signing the informed consent 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.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis or CRO representative will review the protocol and CRFs with the investigators and their staff. During the study, Novartis and CRO employ several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to

[redacted]

check the completeness of patient records, the accuracy of entries on the (e)CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

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 also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis or CRO monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the CRFs using fully validated software that conforms to US CFR 21 Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the CRO working on behalf of Novartis. The Investigator must certify that the data entered into the CRFs are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

Novartis staff (or CRO working on behalf of Novartis) review the data entered into the CRFs 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. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff that will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

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

[redacted]

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Patients/subjects will fill in their PRO data via a handheld electronic device or an electronic site based tablet. The system will be supplied by a vendor(s), who will also manage the database. The database will be sent electronically to Novartis personnel (or designated CRO).

Randomization codes and data about all study drug(s) dispensed to the patient and all dosage changes will be tracked using an Interactive Response Technology (IRT).

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis Development management.

8.4 Data Monitoring Committee

An independent data monitoring committee (DMC) will be set-up to review AE / SAE data and provide the Sponsor with guidance on safety issues.

SAEs will be reviewed on a regular basis. The DMC will also perform a pre-planned review of AE and additional pre-defined safety data as described in the DMC charter.

The membership of the DMC and the responsibilities of the DMC and Novartis will be defined in a separate ‘DMC Charter’ document. The DMC Charter will include information about data flow, purpose and timings of DMC meetings, communication strategy, procedures for ensuring confidentiality, procedures to address conflicts of interest and statistical monitoring guidelines.

8.5 Adjudication Committee

Not required.

9 Data analysis

The study is characterized by 3 cohorts. Each of them consists of TIP, TIP/placebo cyclical, or placebo in a ratio of 2:2:1 for blinding purposes. For the efficacy analysis the placebo patients will be pooled from the three cohorts. For the safety analysis, placebo patients across the three cohorts will not be pooled. Data will be summarized and analyzed by treatment groups.

9.1 Analysis sets

The full analysis set (FAS) will include all randomized patients who received at least one dose of study drug. Following the intent-to-treat principle, patients will be analyzed according to the treatment they are assigned to at randomization, which may be different from the actual treatment received. Patients who are mistakenly randomized or who have not taken double blind study drug will be excluded from the FAS.

The per-protocol set (PPS) population will include all patients in the FAS without any major protocol deviations.

The safety set is defined as patients who received at least one dose of study drug. In all safety analyses patients will be analyzed according to the actual treatment received.

The analysis of the primary objective will be performed on the FAS. The PPS will be used for the supportive analysis of the primary variable. The FAS will also be used for the analysis of all other efficacy variables. The safety set will be used in the analysis of all safety variables.

9.2 Patient demographics and other baseline characteristics

Descriptive statistics for patient demographics data including age, weight, height, gender, and other baseline characteristics will be provided to describe the study population both for overall population and by treatment groups. Categorical variables will be summarized with the number and percentage of patients in each category. Continuous variables will be summarized using descriptive statistics including number of patients, mean, standard deviation (SD), median, minimum and maximum.

9.3 Treatments

The prescribed dosing regimens are two o.d. (3, and 5 capsules per day) and one b.i.d. (4 capsules twice per day) for TIP, TIP/placebo cyclical and placebo. Descriptive statistics will be provided by treatment group for the duration of treatment and the percent compliance to study drug by treatment groups. The reasons for dose changes and interruptions will be tabulated with number and percentage.

The number and percentage of patients taking concomitant medications will be summarized by treatment and by ATC classes and preferred terms. Each concomitant medication could be classified by more than one ATC class and will be counted for each. Summary tables will be created for concomitant medications started prior to study drug, started on or after start of study drug and for non-CF BE related medications started on or after start of study drug.

Duration of exposure (days) will defined as end date of study medication in on-treatment phase minus start date of study medication in on-treatment phase plus 1 day. The total

[redacted]

duration of exposure in the TIP/placebo cyclical arm will be the sum of duration from the two treatment cycles. The duration of exposure will be presented with standard descriptive statistics (n, mean, SD, minimum, median and maximum) and with number and percentage for pre-defined categories (≤28 days, 29-56 days, 57-84 days, 85-112 days and ≥113 days.

Discontinuations of study (yes/no) will be summarized with number and percentage of patients by treatment groups.

Treatment compliance with study medication over the study period will be summarized.

9.4 Analysis of the primary variable(s)

The analysis of the primary efficacy variable will be based on the FAS.

9.4.1 Variable(s)

The primary efficacy variable is the absolute change in the bacterial load in sputum as assessed by the change in log10 colony forming units (CFUs) of *P. aeruginosa* from baseline to Day 29 of treatment.

Baseline is defined as the last measurement prior to the first dose of blinded study medication.

9.4.2 Statistical model, hypothesis, and method of analysis

The comparisons of TIP 3 capsules o.d, 5 capsules OD, and 4 capsules b.i.d versus placebo will be evaluated by testing the following null hypothesis (H0) versus the alternative hypothesis (Ha):

H0: TIP treatment group is equal to placebo group in bacterial load in sputum at Day 29

Ha: TIP treatment group is not equal to placebo group in bacterial load in sputum at Day 29

The primary efficacy endpoint will be analyzed using the analysis of covariance (ANCOVA) model. The model will contain treatment, baseline CFU, and baseline macrolide use. Pairwise comparisons of TIP dosing groups will be conducted versus placebo. To control the family-wise type-I error rate (three dose levels vs. placebo) at the two-sided 5% significance level, the step-wise Dunnett procedure will be used.

For the primary efficacy analysis, patients from treatment arms TIP and TIP/placebo cyclical regimen will be pooled for each cohort. This is possible because all patients within the same cohort on the TIP treatment arms (cyclical or continuous) are receiving the same treatment during the first 28 days. Placebo patients will be pooled across the 3 cohorts, as the number of placebo capsules is not expected to influence the change in *P. aeruginosa* bacterial counts.

The estimated adjusted treatment difference (TIP – placebo) will be displayed along with the associated standard error, 2-sided 95% confidence interval (CI), and p-value (2-sided).

9.4.3 Handling of missing values/censoring/discontinuations

No missing value imputation will be implemented for the primary efficacy analysis. Various imputation methods will be explored to handle missing values due to censoring or discontinuations in the sensitivity analyses.

[redacted]

To account for patients who require treatment with anti-pseudomonal drugs for exacerbation, a sensitivity analyses will be performed using multiple imputations for the relevant efficacy endpoints.

Details of the sensitivity analyses will be specified in the statistical analysis plan prior to database lock.

9.4.4 Supportive analyses

The non-parametric Mann-Whitney-Wilcoxon test will be carried out as a sensitivity analysis due to the potential non-normality of the CFU data.

The primary efficacy analysis will be repeated in the PP population as a supportive analysis.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

For efficacy analysis, patients assigned to placebo arms will be pooled across the 3 cohorts, as the number of placebo capsules is not expected to impact the efficacy assessments. Unless otherwise specified, the following analysis will be conducted both over the treatment epoch (through Day 113) and over the study period (through Day 169).

9.5.1.1 *P. aeruginosa* colony forming units (CFU)

Anti-microbial efficacy of TIP versus placebo 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 visit, other than Visit 103, will be assessed by biotype and sum of all biotypes with the same ANCOVA model as specified for the primary efficacy variable.

9.5.1.2 Pulmonary exacerbation

The following pulmonary exacerbation-related parameters over the treatment epoch (through Day 113) and the study period will be summarized by treatment (pulmonary exacerbation is defined in Section 6.4.4). The analysis will be performed by exacerbation category wherever specified in the analysis plan. The following analysis will also be repeated in the subgroup of patients who had 3 or more pulmonary exacerbations within 12 months prior to screening, if data permit.

- Time to first pulmonary exacerbation by exacerbation category
- The annual rate of pulmonary exacerbations overall
- Duration of pulmonary exacerbations in days by exacerbation category
- The percentage of patients with at least one pulmonary exacerbation
- Time to permanent study drug discontinuation due to pulmonary exacerbation
- The percentage of patients who permanently discontinued study drug due to pulmonary exacerbation

Time-to-event variables will be analyzed using a Cox regression model stratified by baseline macrolide use. The model will include treatment, as fixed-effect factor, and number of pulmonary exacerbation in the 12 months prior to screening as covariate. The estimated

[redacted]

adjusted hazard ratio for TIP over placebo will be displayed along with the associated two-sided 95% confidence interval and corresponding p-value.

Kaplan-Meier analysis stratified by treatment group will be also presented and displayed graphically.

Number of the pulmonary exacerbation will be analyzed using a generalized linear model assuming the negative binomial distribution including treatment, baseline macrolide use as fixed-effect factors, and number of pulmonary exacerbation in the 12 months prior to screening as covariate. The log exposure in years will be included as an offset variable in the model. The estimated rate ratio along with two-sided 95% interval and corresponding p-value will be provided.

The duration of pulmonary exacerbation is defined as the sum of the duration of days recorded as an exacerbation for all exacerbations recorded per patient. This will be analyzed using an ANCOVA model. The model will include treatment, as fixed-effect factors, and number of pulmonary exacerbation in the 12 months prior to screening as covariate

9.5.1.3 Anti-pseudomonal antibiotics

Time to first use (overall, oral, and parenteral) of anti-pseudomonal antibiotics will be analyzed using Cox regression model stratified by baseline macrolide use. The model will include treatment, cohort as fixed-effect factors, and number of pulmonary exacerbation in the 12 months prior to screening as covariate.

Rate of usage (overall, oral, and parenteral) of anti-pseudomonal antibiotics will be analyzed using a generalized linear model assuming the negative binomial distribution including treatment, cohort, baseline macrolide use as fixed-effect factors, and number of pulmonary exacerbation in the 12 months prior to screening as covariate. The log exposure in years will be included as an offset variable in the model.

9.5.1.4 Hospitalization

Time to first hospitalization and the rate of hospitalization due to serious respiratory-related AEs will be analyzed using the same models as specified for the pulmonary exacerbation.

[redacted]

9.5.1.6 Patient reported outcomes

Quality of Life Questionnaire-Bronchiectasis (QoL- B)

QOL-B Respiratory Symptom domain contains 9 items, and each of the 37 items is scored from 1 to 4, and the overall score is standardised on a 0-100 point scale, with higher scores representing fewer symptoms or better functioning.

Items in the questionnaire are expressed either "negatively" or "positively," therefore a number of items must be recorded before the scores for each of the domains are calculated. The score is calculated by adding the score obtained for each item of a domain (scale), after any necessary recoding. Scoring for each domain can be computed only if at least half the items have been completed. If not, then the domain should not be scored and should be considered missing for that particular person who filled out the questionnaire.

The minimum or maximum score always corresponds to the highest QOL and the minimum score always corresponds to the lowest QOL.

Change from baseline in QOL-B Respiratory Symptom Score (RSS) will be analyzed using a linear repeated measure model. The model will contain treatment, baseline macrolide use, visit (visits 102 to 202), and treatment-by-visit interaction as fixed effects with baseline QOL-B RSS, baseline-by-visit interaction as covariates. The within-patient correlation will be modeled using the unstructured covariance matrix in the mixed model. If the model does not converge, then the compound symmetry covariance structure will be used Restricted maximum likelihood method will be used.

[redacted]

[redacted]

9.5.2 Safety variables

All safety analyses will be performed using the safety population, and will be presented by treatment groups. Baseline for safety analyses is defined as the last measurement prior to the first dose of study medication in the study.

Appropriate summary statistics will be provided for laboratory test results, audiology, bronchial hyperreactivity and vital signs.

AEs will be deemed treatment-emergent if the onset date is on or after the date of first study drug and until study completion. Treatment emergent AEs will be summarized by MedDRA primary SOC and preferred term for each cycle and overall. The actual MedDRA version in effect at the time of the clinical study report will be used for coding AEs.

Audiology testing will be performed at selected centers and in patients with hearing events. Audiology function data will be analyzed via summary statistics by treatment and visit.

Clinical laboratory parameters will be summarized using means and mean changes from baseline to each post-baseline visit by treatment group. Shift-from-baseline summaries (shift tables) will be presented for the last available measurement (Termination Visit).

Vital sign parameters will be summarized using means and mean changes from baseline by treatment group and visit.

Analysis of post-inhalation events will be conducted for the two types of events (post-inhalation clinical events/post-inhalation adverse events). The number of patients with post-inhalation events will be summarized by treatment. In addition, the number of these events and the event rate adjusted for exposure will be displayed by treatment.

Post-inhalation events occurring at a site visit within 5 minutes (yes/no), post-inhalation events that are ongoing at completion of the site visit (yes/no) and for which are an action taken to reduce the event (yes/no), the time-point of an event and the time of onset (≤30 sec, >30 sec-1min, >1-2min, >2-5min, >5min) will be summarized with the number and percentage overall and for each cycle. Descriptive statistics including mean, standard deviation, minimum, median and maximum will be provided for the duration of the event in seconds.

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 indicative of bronchospasm/ bronchial hyperreactivity. This change will be summarized with the number and percentage of patients who experienced no change, a decrease/increase of >0-<10%, a decrease/increase of 10-<20% or a decrease/increase ≥20%. Both analyses will also be done for the patients who did the post-dose spirometry test in a 60 minutes time window.

9.5.3 Resource utilization

Data relating to resource utilization will be used for the purpose of economic evaluation which will be carried out and reported as a separate activity.

9.5.4 Pharmacokinetics

The serum and sputum pharmacokinetic properties of tobramycin will be assessed by evaluating tobramycin concentrations in serum and sputum collected from non-CF BE population post administration of o.d. or b.i.d. doses of TIP. Descriptive statistics will be provided for tobramycin serum concentrations by scheduled visit and time of collection. Serum and sputum pharmacokinetics of tobramycin after TIP inhalation will be characterized by population non-linear mixed effects modeling techniques.

[redacted]

9.5.7 PK/PD

An exploratory analysis of the relationship of sputum concentrations (for efficacy) and/or systemic exposures (for safety) pooled across the arms may be conducted with endpoints including CFU changes from baseline, certain laboratory and clinical safety parameters, change in bacterial susceptibility, PROs, and exacerbations. This analysis will depend on performing a graphical analysis and visual inspection of the data to determine whether the data collected in TBM100G2202 permits a modeling approach. Longitudinal data will be pooled across the study cohorts, including the patients randomized to placebo.

[redacted]

PK modeling of serum and sputum concentration data will be considered to characterize the population PK in BE patients. If a model can be constructed then the effect of covariates (such as age, weight, baseline creatinine clearance, CFU/g of sputum) will also be explored in describing the inter-subject variability.

Exploratory exposure-response modeling of the time course of CFU data collected during the treatment period in addition to the data collected post treatment may be performed if supported by the data. The CFU modeling will explore the relationship between exposure, most likely based on the sputum PK model, and CFU reduction from baseline.

The results of these exposure-response analyses will be combined with the results from complementary data analyses of these same data, as well as analyses of data on other efficacy and safety endpoints, to support dose and regimen selection.

9.6 Interim analyses

No interim analysis for efficacy is planned. It is planned that the independent DMC will review semi-blinded safety data (see Section 8.4).

9.7 Sample size calculation

Sample size estimation was based on a difference of 2.0 $\log_{10}$ CFU/g, with standard deviations of 2.0 $\log_{10}$ CFU/g. The assumptions were based on conservative estimates from published results (Konstan et al 2011a, Konstan et al 2011b, Barker et al 2000, and Wilson et al 2013). As there are three primary comparisons between the three doses versus placebo, the Bonferroni multiplicity adjustment has been used (0.05/3) for sample size calculation. Using α=1.67% (two-sided) and 90% power, the sample size estimation yielded n = 36 subjects per treatment group as valid for ITT analyses. This takes into account an approximate 20%-discontinuation rate. For the primary efficacy analysis, patients from TIP continuous and TIP cyclical regimen within the same cohort will be pooled as they receive exactly the same treatment during the first 28 days. Placebo patients will be pooled across the 3 cohorts, as the number of placebo capsules is not expected to influence the change in *P. aeruginosa* bacterial counts. With the current study design, the power is 94% to detect a reduction of 2.0 $\log_{10}$ CFU/g for each dose level versus placebo.

For calculation of sample size, NQuery Advisor version 7.0 module MTTO-1 was used.

10 Ethical considerations

10.1 Regulatory and ethical compliance

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

[redacted]

10.2 Informed consent procedures

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

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. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

Women of child bearing potential must be informed that taking the study treatment 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. If there is any question that the patient will not reliably comply, they must not be entered in the study.

[redacted]

10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to patients/subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis 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.

[redacted]

10.4 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

11 Protocol adherence

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

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

11.1 Protocol Amendments

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

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13 Appendix 1: Clinically notable laboratory values

The central laboratory will flag laboratory values falling outside of the normal ranges on the central laboratory reports. Investigators are responsible for reviewing these abnormal values for clinical significance, signing the laboratory reports to indicate their review, and reporting values considered clinically significant in the appropriate CRF.

Any clinically significant abnormal laboratory value should be evaluated and followed-up by the investigator until normal or a cause for the abnormality is determined.

14 Appendix 2: Specific Renal Alert Criteria and Actions

Table 14-1 Specific Renal Alert Criteria and Actions

Serum Finding	
Serum creatinine increase 25 – <50% compared to baseline	Confirm 25 – <50% increase after 24-48h if possible and determine albumin-creatinine-ratio (ACR), protein-creatinine-ratio (PCR) and eGFR. If <u>any</u> of the below • serum creatinine increase is confirmed OR • eGFR ≤ 50mL/min/1.73m^2 OR • ACR ≥30 mg/g or ≥3 mg/mmol OR • PCR ≥150 mg/g or ≥15 mg/mmol: - Follow up within 2-5 days to determine serum creatinine and eGFR. If values do not show improvement of renal function, consider study treatment interruption / or discontinuation based on clinical judgment
Acute Kidney Injury: Serum creatinine increase ≥ 50% compared to baseline	Follow up within 24-48h to confirm serum creatinine value. If serum creatinine is increased 25 – <50% compared to baseline, - Follow-up within 2-5 days to determine serum creatinine and eGFR. - If values are not improving consider study treatment interruption / or discontinuation based on clinical judgment. If serum creatinine increase ≥ 50% is confirmed - Discontinue study treatment - Consider patient hospitalization / specialized treatment
Urine Finding	
New dipstick proteinuria ≥3+	Confirm test result within 7 days, perform urine microscopy and determine ACR and PCR. If proteinuria ≥ 3+ confirmed - Discontinue study treatment. - Consider patient referral for specialized treatment
New dipstick hematuria* ≥3+ * not due to menstruation, infection, extreme exercise, or trauma	Perform urine sediment microscopy and determine ACR and PCR on the same sample. If ACR ≥30 mg/g or ≥3 mg/mmol OR PCR ≥150 mg/g or ≥15 mg/mmol: - Perform serum creatinine within 5 days and follow up, as described above
Serum and urine findings that have been confirmed according to this appendix are considered renal serum and urine events. **For all renal events:** <u>Document contributing factors in the CRF</u>: co-medication, other co-morbid conditions, and additional diagnostic procedures performed Monitor patient regularly (frequency at investigator's discretion) until either: Event resolution: serum creatinine within 10% of baseline or protein-creatinine ratio within 50% of baseline, or Event stabilization: serum creatinine level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ± 50% variability over last 6 months.	

15 Appendix 3: Sputum/blood collection logs

Sputum sampling for pharmacokinetic assessments

At study visits 101, 102, and 104, post-dose sputum samples at specified time intervals are collected for pharmacokinetic analyses.

Table 15-1 Time schedule for sputum sampling for sputum pharmacokinetic assessments

Visit number	Study day	Scheduled time	Sample number
101	1	0-1 h post-dose	101
101	1	1-2 h post-dose	102
~~102~~	~~8~~	~~0-2 h post-dose~~	~~103~~
102	8	5-6 h post-dose	107
~~103~~	~~29~~	~~5-6 h post-dose~~	~~104~~
104	57	3-4 h post-dose	108
~~105~~	~~85~~	~~3-4 h post-dose~~	~~105~~
TD*	N/A		106

*For patients who discontinue early and are on study drug, an extra sputum 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 and from visit 105 to visit 104.

Blood sampling for pharmacokinetic assessments

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

Table 15-2 Time schedule for blood sampling for serum pharmacokinetic assessments

Visit number	Study day	Scheduled time	Sample number
101	1	0-1 h post-dose	201
101	1	1-2 h post-dose	202
102	8	0-1 h post-dose	206
102	8	1-2 h post-dose	207
~~103~~	~~29~~	~~0-1 h post-dose~~	~~203~~
~~103~~	~~29~~	~~1-2 h post-dose~~	~~204~~
TD*	N/A		205

*For patients who discontinue early and are on study drug, 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.

[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

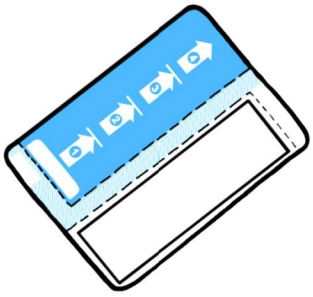
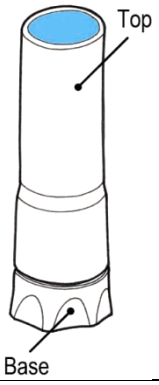
If your capsule cards contain 4 capsules each:

- 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]

NOTE:

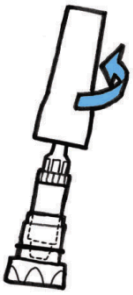
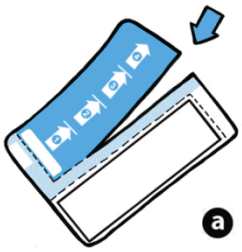
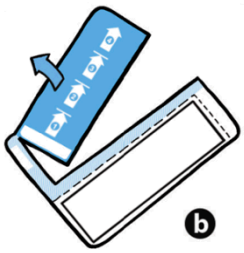
If you are unsure about how many doses to take each day, ask your physician or site personnel.

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

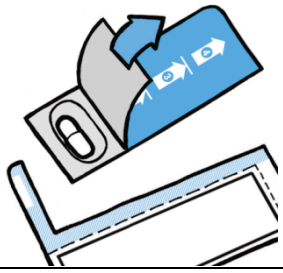
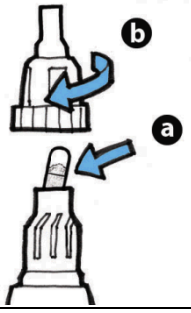
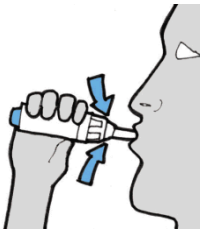
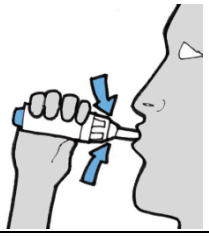
How to inhale your medicine with the T-326 Inhaler

- **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

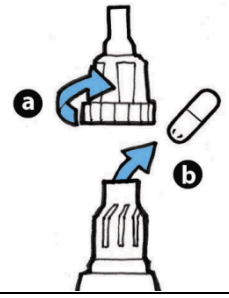
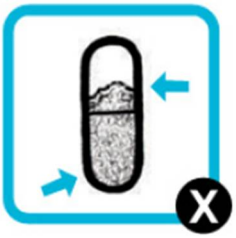
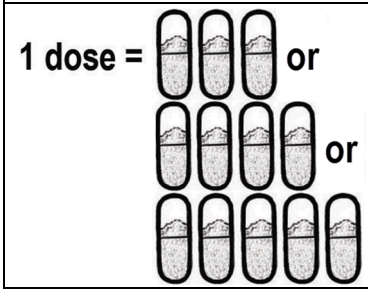
[redacted]

	1. Wash and **fully dry your** hands.
	2. • Just before use, remove the Inhaler from its case by holding the base and twisting off the top of the case in an anti-clockwise direction. • Set the top of the case aside. • Look at the Inhaler to make sure it is not damaged or dirty. • Stand the Inhaler upright in the base of the case.
	3. • Hold the body of the Inhaler and unscrew the mouthpiece in an anti-clockwise direction. • Set the mouthpiece aside on a clean, dry surface.
 	4. • Tear along the perforations on the capsule card lengthwise then widthwise, as indicated in pictures (a) and (b). (Note: Actual imprint on the capsule card may look slightly different than the illustration.)

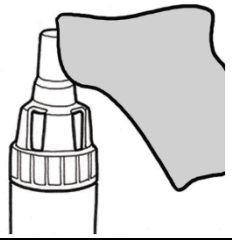
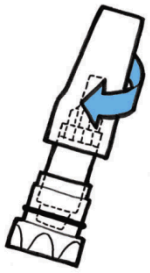
[redacted]

	5. • Peel back the foil from the capsule card to reveal one capsule only. • Remove that capsule from the card. (Note: Actual capsule card may look slightly different than the illustration.)
	6. • Put the capsule into the Inhaler chamber straightaway (a). • Replace the mouthpiece. • Screw the mouthpiece on firmly until it stops. Do not overtighten (b).
	7. • Hold the Inhaler **with the mouthpiece pointing down**. • Pierce the capsule by pressing firmly the blue button with your thumb as far as it will go, then release the button. • You are now ready to inhale from the capsule in 2 separate breaths (Steps 8 and 9).
	8. **Inhale the capsule – 1st breath:** • Before putting the mouthpiece in your mouth, breathe out fully, away from the Inhaler. • Place your mouth over the mouthpiece – to make a tight seal. • Inhale the powder deeply with a single breath, while keeping your head horizontal. • Remove the Inhaler from your mouth, and hold your breath for about 5 seconds. • Then breathe out normally, away from the Inhaler.
	9. **Inhale the capsule – 2nd breath:** • Take a few normal breaths away from the Inhaler. When you are ready, take your 2nd breath by repeating Step 8, using the same capsule.

[redacted]

	10. Unscrew the mouthpiece (a) and remove the capsule from the chamber (b).
	11. **Look at the used capsule. It should appear pierced and empty**. If it is empty, discard the capsule.
	If the capsule is pierced but still contains some powder: • Put the capsule back into the Inhaler chamber (Step 6). Put the pierced side of the capsule in first. • Replace the mouthpiece and repeat Steps 8, 9 and 10.
	If the capsule does not look pierced: • Put the capsule back into the Inhaler chamber (Step 6) • Replace the mouthpiece and repeat Steps 7, 8 and 9. • After this if the capsule is still full and appears not to be pierced, replace the Inhaler with the reserve Inhaler (from your 5th weekly carton) and repeat Steps 2, 3, 6, 7, 8, 9 and 10.
	12. Take the other capsules (to complete a single dose) in the same way. If you are unsure about how many doses to take each day, ask your physician or site personnel. • So for each remaining capsule, repeat Steps 5, 6, 7, 8, 9, 10 and 11.

[redacted]

	13. • Replace the mouthpiece and screw it on firmly until it stops. When the full dose has been inhaled, wipe the mouthpiece with a clean dry cloth. • **Do not wash the inhaler with water.**
	14. • Place the inhaler back in its storage case. • Twist the top of the case in a clockwise direction until it is closed tightly.

REMEMBER:

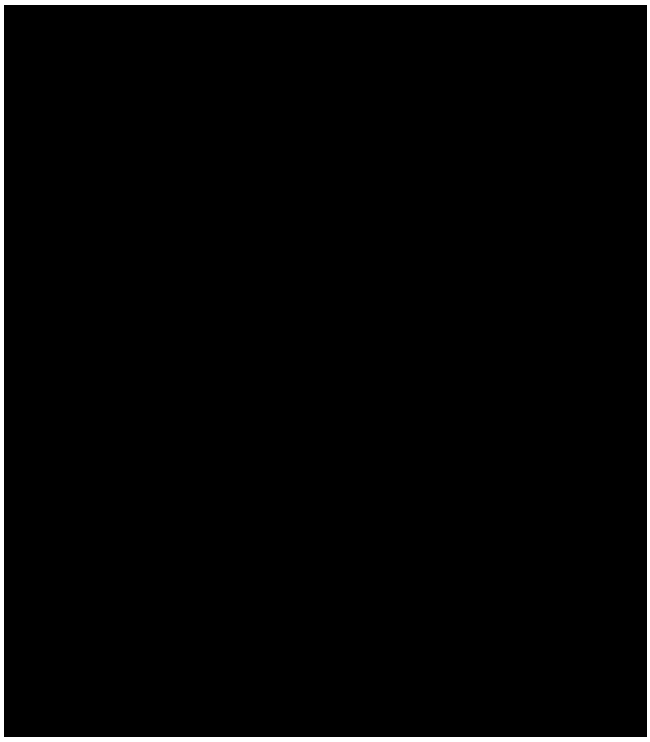
- **Do not swallow the enclosed capsules.** Please inform your study coordinator or nurse immediately, if you swallow the capsule by mistake
- Only use the Inhaler contained in this pack
- Always keep the capsules in the capsule card. Only remove a capsule just before you are going to use it. Do not store the capsules in the Inhaler
- Always keep the capsules and the T-326 Inhaler in a dry place
- Never place a capsule directly into the mouthpiece of the T-326 Inhaler
- Always hold the T-326 Inhaler with the mouthpiece pointing down when piercing the capsule
- Do not press the piercing button more than once at a time to pierce the capsule
- Never blow or breathe into the mouthpiece of the T-326 Inhaler
- Never wash the T-326 Inhaler with water. Keep it dry and store it in its case

[redacted]

Additional information

Occasionally, very small pieces of the capsule can get past the screen and get into your mouth.

- If this happens, you may be able to feel these pieces on your tongue
- It is not harmful if these pieces are swallowed or inhaled
- The chances of the capsule breaking into pieces will be increased if the capsule is accidentally pierced more than once or if the T-326 Inhaler is not held with the mouthpiece pointing down during step 7



17 Appendix 5: Spirometry Guidance

Equipment

Spirometers must meet the specifications and performance criteria recommended in the American Thoracic Society (ATS)/European Respiratory Society (ERS) Standardization of Spirometry[1]. Spirometers must have the capacity to print FVC tracings. All spirometry values should be reported at BTPS by the method established by the manufacturer.

Calibration

The spirometer should be calibrated every morning before any spirometric measurements for the study are performed. Calibration reports should be printed and stored as source data at the site.

Preparing the test subject

On study days when spirometry will be performed, patients should refrain from the following:

- Coffee, tea, chocolate, cola and other caffeine-containing beverages and foods and ice-cold beverages for 4 hours prior to spirometry
- Alcohol for 4 hours prior to spirometry
- Strenuous activity for 12 hours prior to spirometry
- Smoking within at least 1 hour of testing
- Exposure to environmental smoke, dust or areas with strong odors

Every effort should be made to assure consistent testing conditions throughout the study. A seated position with nose clips is recommended to reduce risks related to dizziness or syncope. When possible, spirometry should be conducted by the same technician using the same spirometer. To minimize the effects of diurnal variation on lung function, spirometry visits should start at approximately the same time of day at each visit.

Performing Spirometry

The subject's age, height and gender will be entered into the spirometer. It is important that the height is measured accurately at the study site. Spirometry, an effort-dependent test, requires careful instruction and cooperation of the subject. The technician should ensure a good seal around the mouthpiece, and confirm that the subject's posture is correct. The subject should be instructed to perform a maximal inspiration, followed by maximum forced expiration until no more air can be exhaled or for at least 6 seconds. Expiration must be rapid with exertion of maximal effort. The results of spirometry should meet the ATS/ERS criteria for acceptability and repeatability. Acceptability criteria should be applied before repeatability is determined.

Number of trials

A minimum of 3 acceptable forced vital capacity (FVC) maneuvers should be performed. If a subject is unable to perform a single acceptable maneuver after 8 attempts, testing may be discontinued.

Acceptability

An acceptable maneuver has the following characteristics:

- No hesitation or false start;
- A rapid start;
- No cough, especially during the first second of the maneuver;
- No glottic closure or obstruction by tongue or dentures
- No early termination of exhalation (minimum exhalation time of 6 seconds is recommended, or no volume change for at least 1 second) or the subject cannot continue to exhale further

Repeatability

The 2 largest FVC and FEV_1 values from 3 acceptable maneuvers should not vary by more than 0.150 L.

Recording of data

[redacted]

The greatest FEV_1 and FVC from any of the acceptable curves are recorded. (The greatest FEV_1 and FVC may not necessarily result from the same acceptable curve).

Predicted normal

For subjects 3 years of age or greater, this study will utilize the spirometric predication equation standards from the ERS Global Lung Function Initiative [2] or Japanese Respiratory Society [3] for Japanese subjects 17 years of age or greater.

References

[1] Miller MR et al, Standardization of Lung Function Testing. Eur Resp J 2005; 26:153-161.

[redacted]

[3] Kubota, Kobayashi, Quanjer PH, et al. Reference values for spirometry, including vital capacity, in Japanese adults calculated with the LMS method and compared with previous values. Clinical Pulmonary Functions Committee of the Japanese Respiratory Society. Respiratory Investigations 2014, 242-250.

[redacted]

18 Appendix 6: QOL-B

QOL-B QUALITY OF LIFE QUESTIONNAIRE – BRONCHIECTASIS

Understanding the impact of your illness and treatments on your everyday life can help your doctor monitor your health and adjust your treatments. For this reason, we have developed a quality of life questionnaire specifically for people who have bronchiectasis. Thank you for your willingness to complete this questionnaire.

Instructions: The following questions are about the current state of your health, as you perceive it. This information will allow us to better understand how you feel in your everyday life.

Please answer all the questions. There are **no** right or wrong answers! If you are not sure how to answer, choose the response that seems closest to your situation.

Demographics *Please fill-in the information or check the box indicating your answer.*

A. What is your date of birth?
Date ☐☐/☐☐/☐☐☐☐
Mo Day Year

B. What is your gender?
☐ Male ☐ Female

C. During the **past week**, have you been on vacation or out of school or work for reasons **NOT** related to your health?
☐ Yes ☐ No

D. What is your current marital status?
☐ Single/never married
☐ Married
☐ Widowed
☐ Divorced
☐ Separated
☐ Remarried
☐ With a partner

E. Which of the following best describes your racial background?
☐ Caucasian
☐ African American
☐ Hispanic
☐ Asian/Oriental or Pacific Islander
☐ Native American or Native Alaskan
☐ Other (please describe) _____
☐ Prefer not to answer this question

F. What is the highest grade of school you have completed?
☐ Some high school or less
☐ High school diploma/GED
☐ Vocational school
☐ Some college
☐ College degree
☐ Professional or graduate degree

G. Which of the following best describes your current work or school status?
☐ Attending school outside the home
☐ Taking educational courses at home
☐ Seeking work
☐ Working full or part time (either outside the home or at a home-based business)
☐ Full time homemaker
☐ Not attending school or working due to my health
☐ Not working for other reasons/ Retired

Continue to Next Page

[redacted]

QOL-B QUALITY OF LIFE QUESTIONNAIRE – BRONCHIECTASIS

Section I. Quality of Life *Please check the box indicating your answer.*

During the past week, to what extent have you had difficulty:	A lot of difficulty	Moderate difficulty	A little difficulty	No difficulty
1. Performing vigorous activities, such as gardening or exercising	☐	☐	☐	☐
2. Walking as fast as others (family, friends, etc.)	☐	☐	☐	☐
3. Carrying heavy things, such as books, groceries, or shopping bags	☐	☐	☐	☐
4. Climbing one flight of stairs	☐	☐	☐	☐

During the past week, indicate how often:	Always	Often	Sometimes	Never
5. You felt well	☐	☐	☐	☐
6. You felt tired	☐	☐	☐	☐
7. You felt anxious	☐	☐	☐	☐
8. You felt energetic	☐	☐	☐	☐
9. You felt exhausted	☐	☐	☐	☐
10. You felt sad	☐	☐	☐	☐
11. You felt depressed	☐	☐	☐	☐

Are you currently on any treatments (such as oral or inhaled medications, PEP or Flutter® device, chest PT, or Vest) for bronchiectasis?

☐ Yes ☐ No (Go to Question 15 on the next page)

Please circle the number indicating your answer. Please choose only one answer for each question.

12. To what extent do your treatments for bronchiectasis make your daily life more difficult?
    1. Not at all
    2. A little
    3. Moderately
    4. A lot

13. How much time do you currently spend each day on your treatments for bronchiectasis?
    1. A lot
    2. A moderate amount
    3. A little
    4. Almost none

14. How difficult is it for you to fit in your treatments for bronchiectasis each day?
    1. Not at all
    2. A little
    3. Moderately
    4. Very

Continue to Next Page

[redacted]

QOL-B QUALITY OF LIFE QUESTIONNAIRE – BRONCHIECTASIS

Please circle the number indicating your answer. Please choose only one answer for each question.

15. How do you think your health is now?
1. Excellent
2. Good
3. Fair
4. Poor

Please select a box indicating your answer.

Thinking about your health during the past week, indicate the extent to which each sentence is true for you.	Completely true	Mostly true	A little true	Not at all true	
16. I have to limit vigorous activities, such as walking or exercising	☐	☐	☐	☐	
17. I have to stay at home more than I want to	☐	☐	☐	☐	
18. I am worried about being exposed to others who are sick	☐	☐	☐	☐	Doesn't apply
19. It is difficult to be intimate with a partner (kissing, hugging, sexual activity)	☐	☐	☐	☐	☐
20. I lead a normal life	☐	☐	☐	☐	
21. I am concerned that my health will get worse	☐	☐	☐	☐	
22. I think my coughing bothers others	☐	☐	☐	☐	
23. I often feel lonely	☐	☐	☐	☐	
24. I feel healthy	☐	☐	☐	☐	
25. It is difficult to make plans for the future (vacation, attending family events, etc.)	☐	☐	☐	☐	
26. I feel embarrassed when I am coughing	☐	☐	☐	☐	

Please circle the number or check the box indicating your answer.

During the past week:

27. To what extent did you have trouble keeping up with your job, housework, or other daily activities?
1. You have had no trouble keeping up
2. You have managed to keep up but it's been difficult
3. You have been behind
4. You have not been able to do these activities at all

	Always	Often	Sometimes	Never
28. How often does having bronchiectasis get in the way of meeting your work, household, family, or personal goals?	☐	☐	☐	☐

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[redacted]

QOL-B QUALITY OF LIFE QUESTIONNAIRE – BRONCHIECTASIS

Section II. Respiratory Symptoms *Please check the box indicating your answer.*

Indicate how you have been feeling during the past week:	A lot	A moderate amount	A little	Not at all
29. Have you felt congestion in your chest?	☐	☐	☐	☐
30. Have you been coughing during the day?	☐	☐	☐	☐
31. Have you had to cough up mucus?	☐	☐	☐	☐

32. Has your sputum been mostly: ☐ Clear ☐ Clear to yellow ☐ Yellowish-green ☐ Brownish-dark ☐ Green with traces of blood ☐ Don't know

How often during the past week:	Always	Often	Sometimes	Never
33. Have you had shortness of breath with greater activity, such as housework or yardwork?	☐	☐	☐	☐
34. Have you been wheezing?	☐	☐	☐	☐
35. Have you had chest pain?	☐	☐	☐	☐
36. Have you had shortness of breath when talking?	☐	☐	☐	☐
37. Have you woken up during the night because you were coughing?	☐	☐	☐	☐

Please be sure you have answered all the questions.

THANK YOU FOR YOUR COOPERATION!

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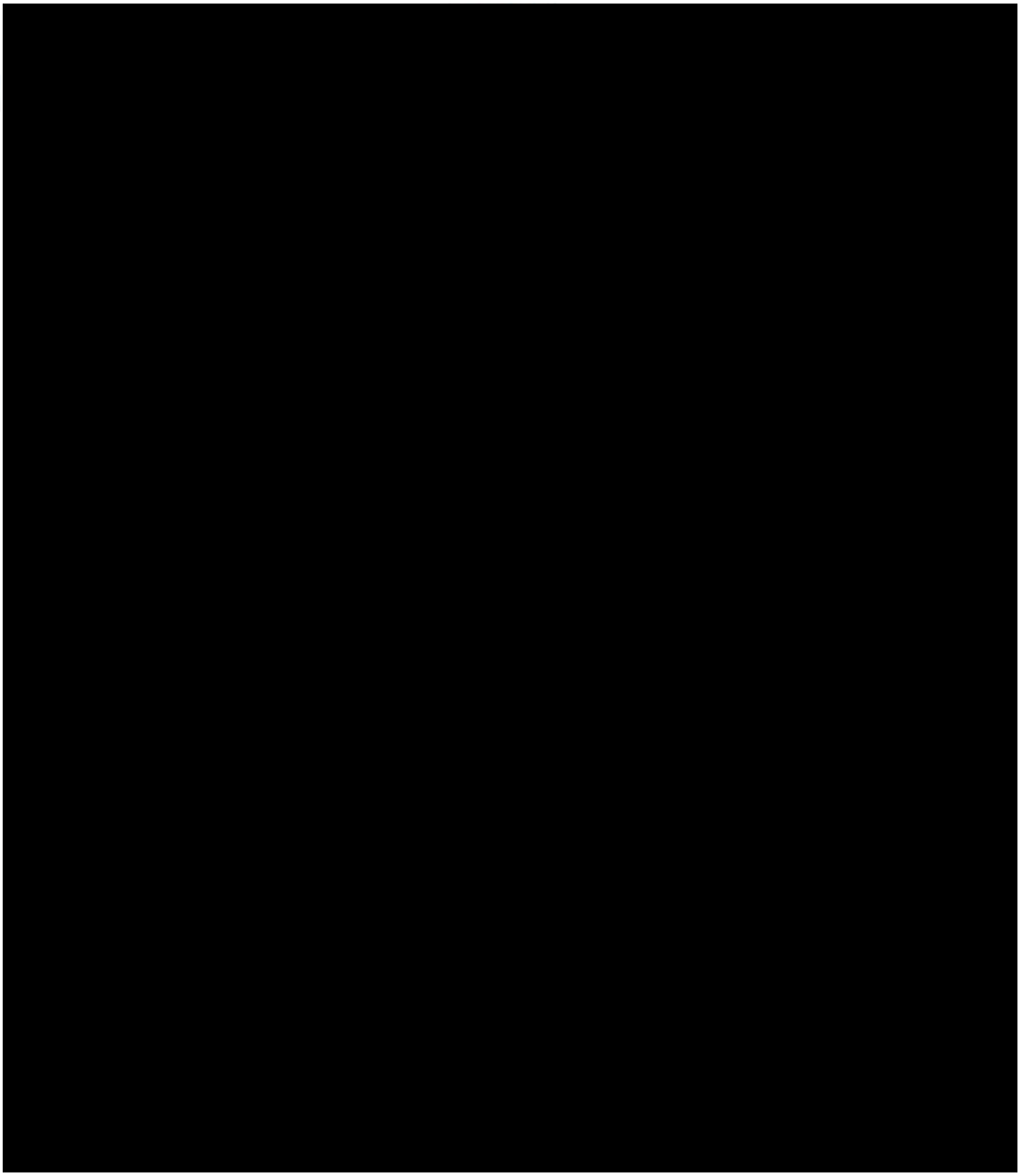

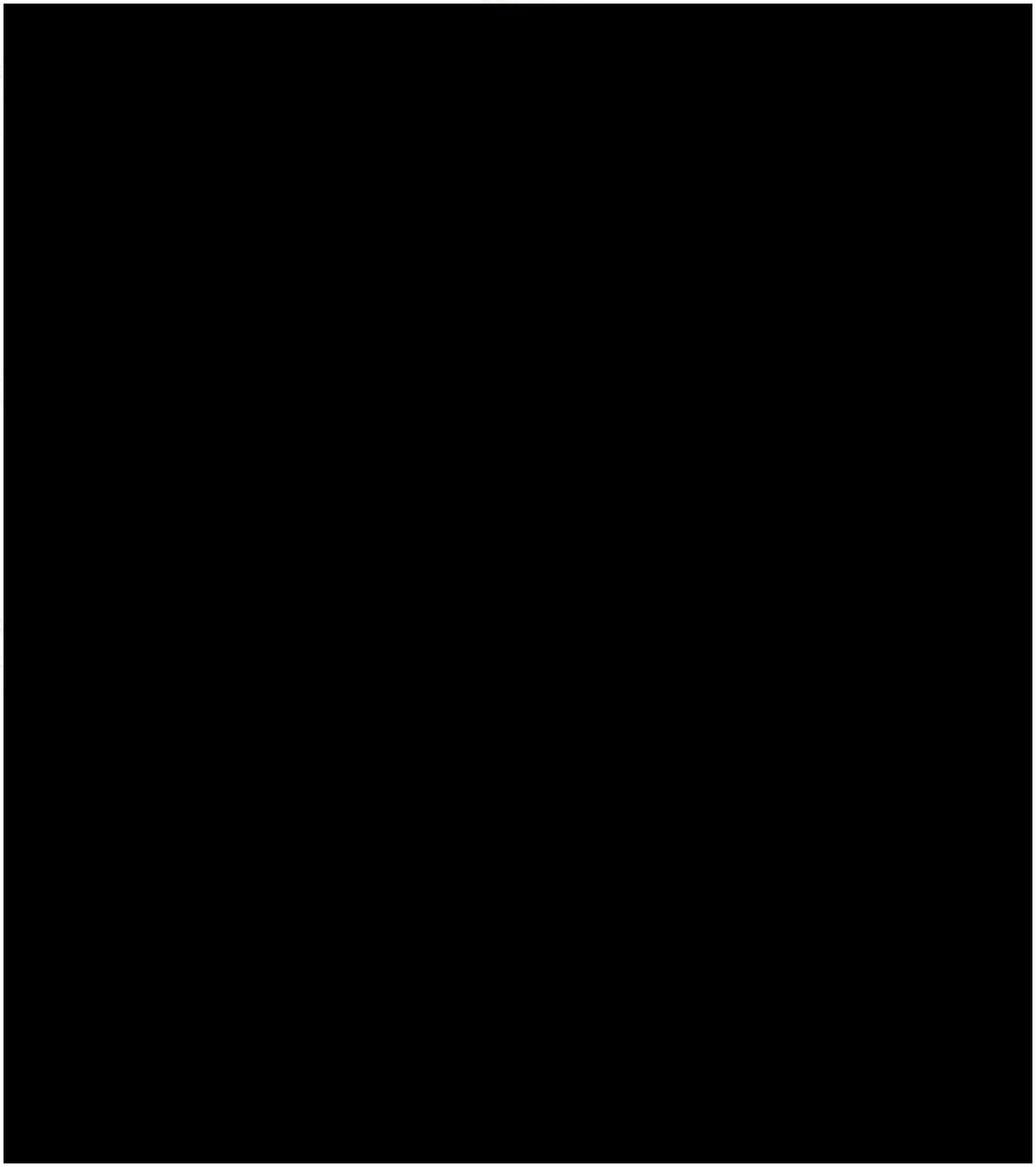

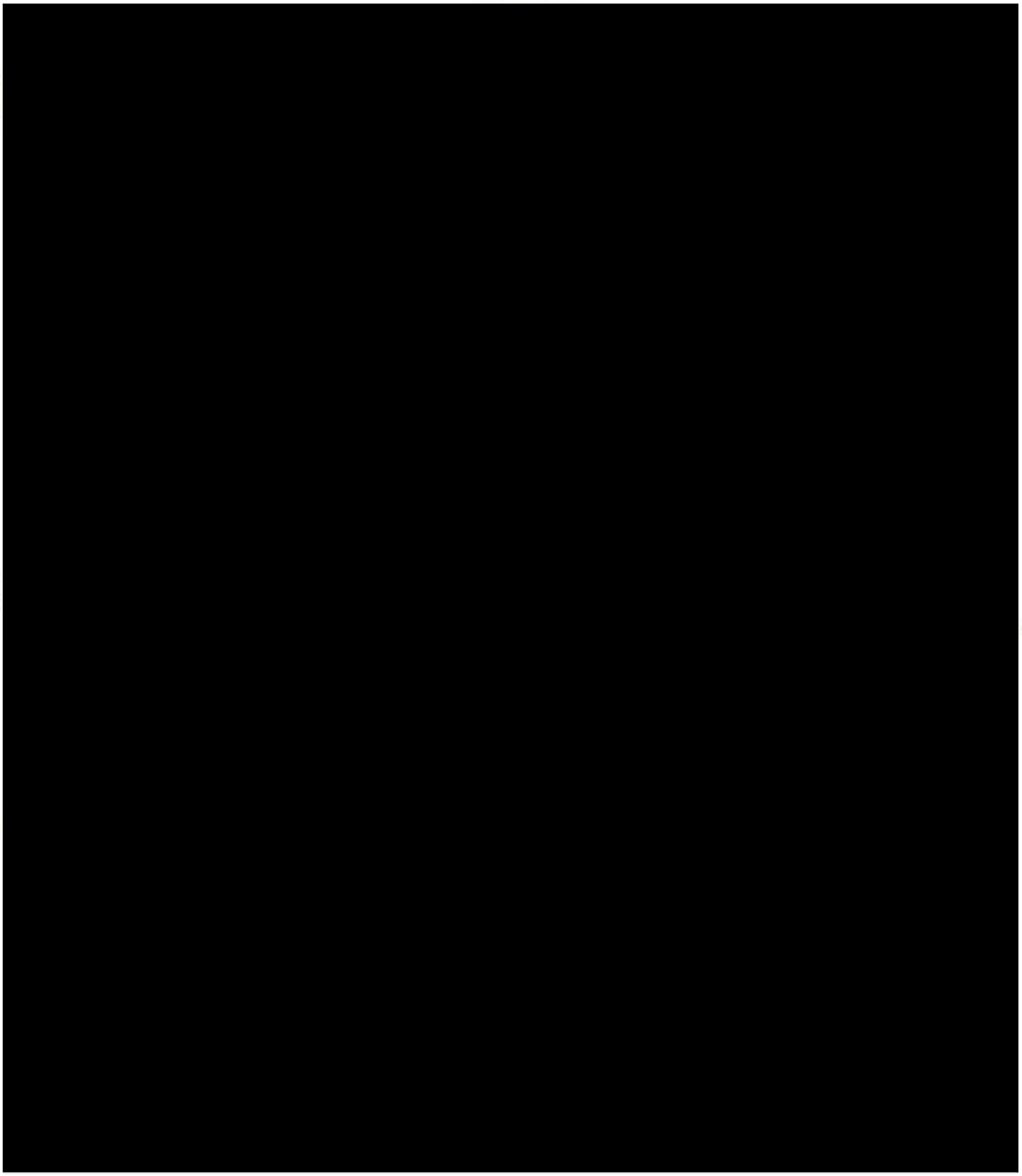

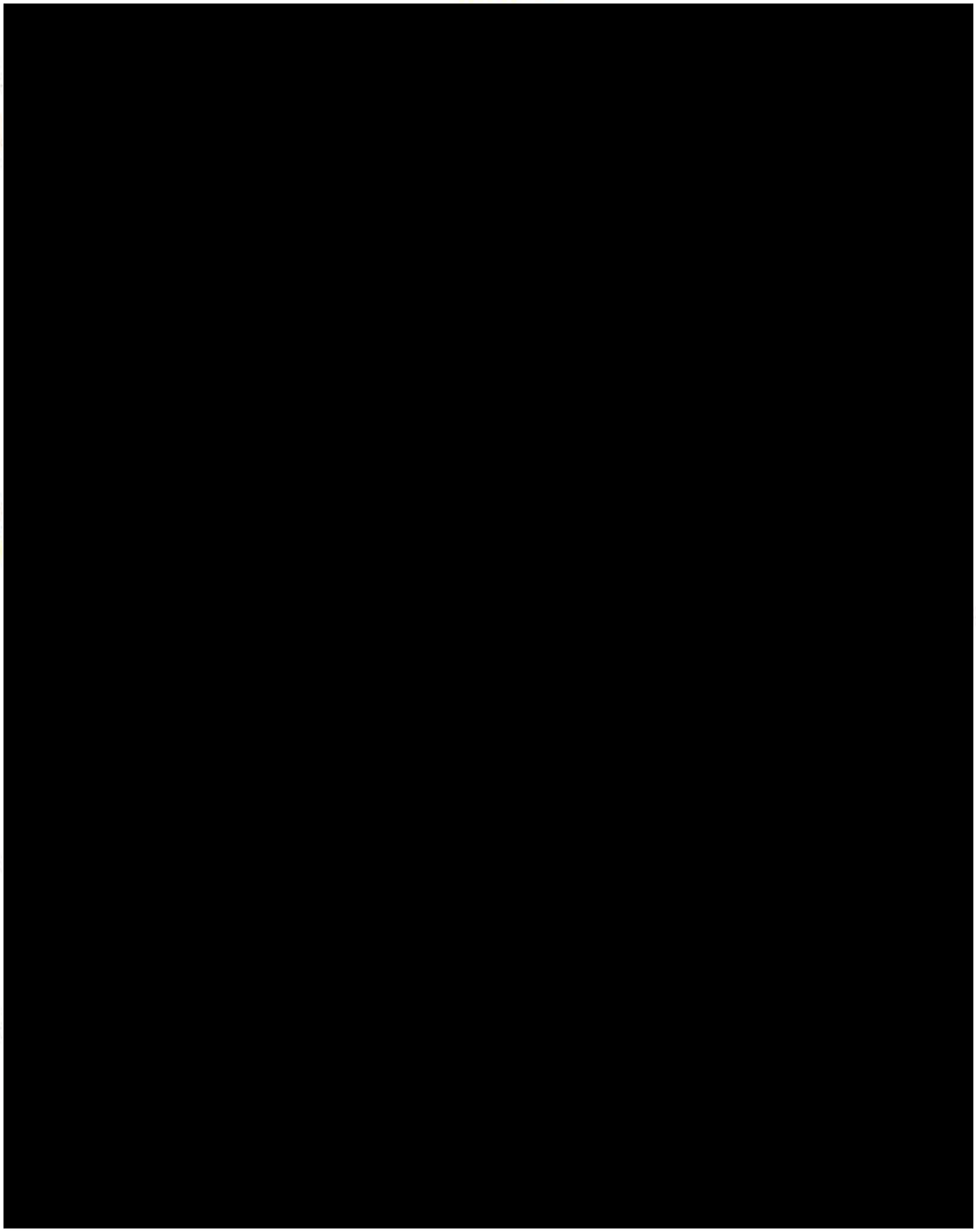

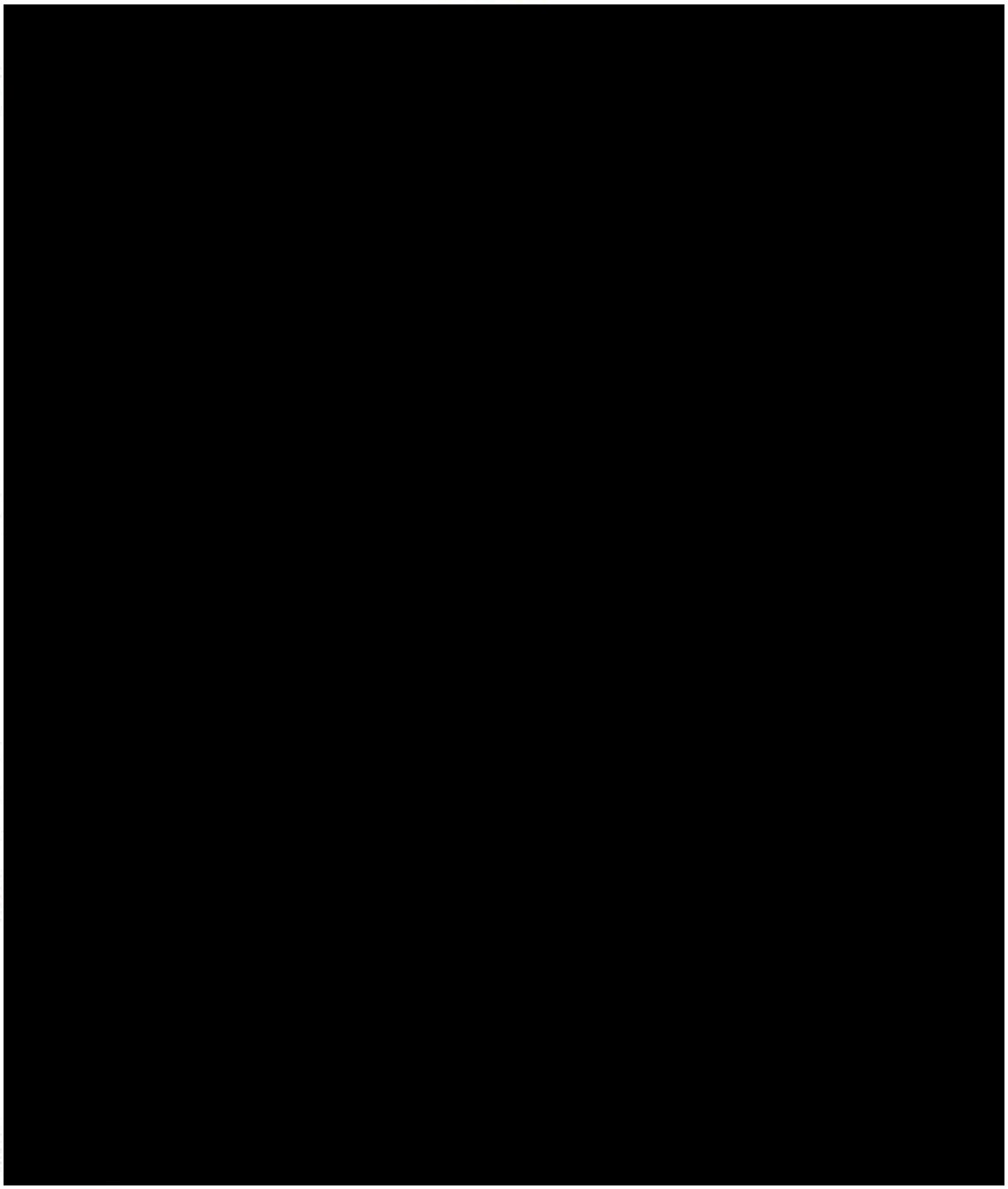

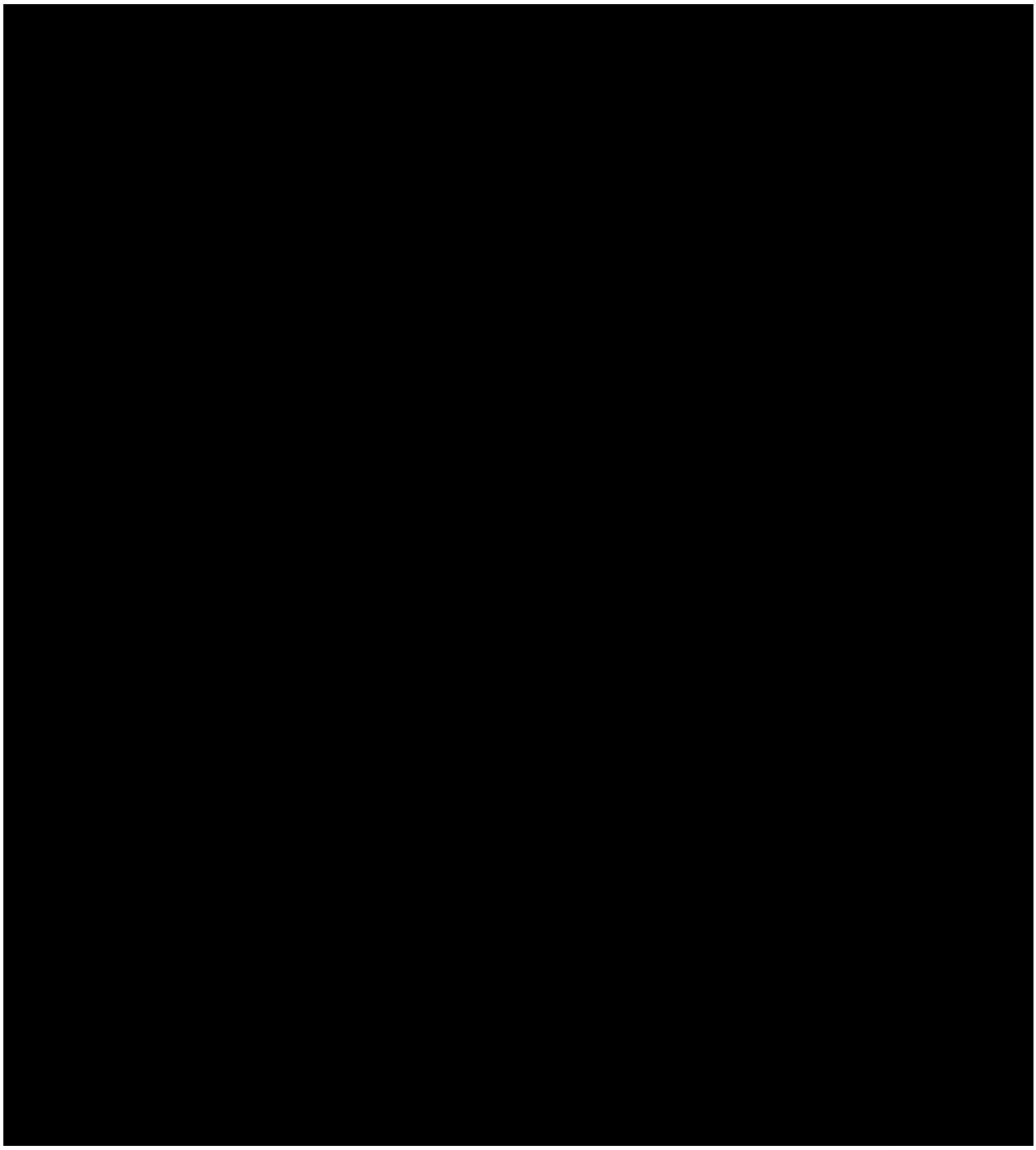

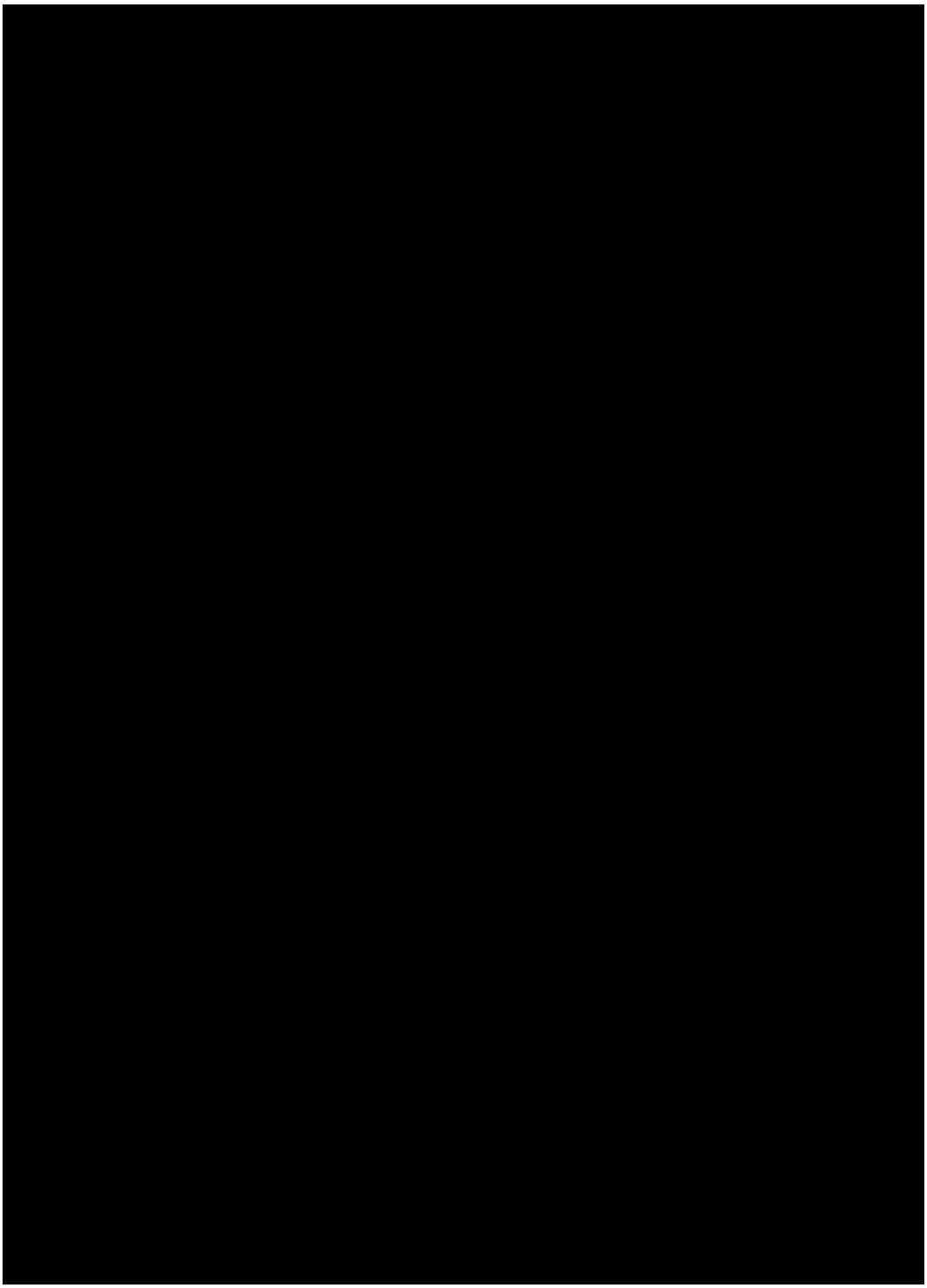

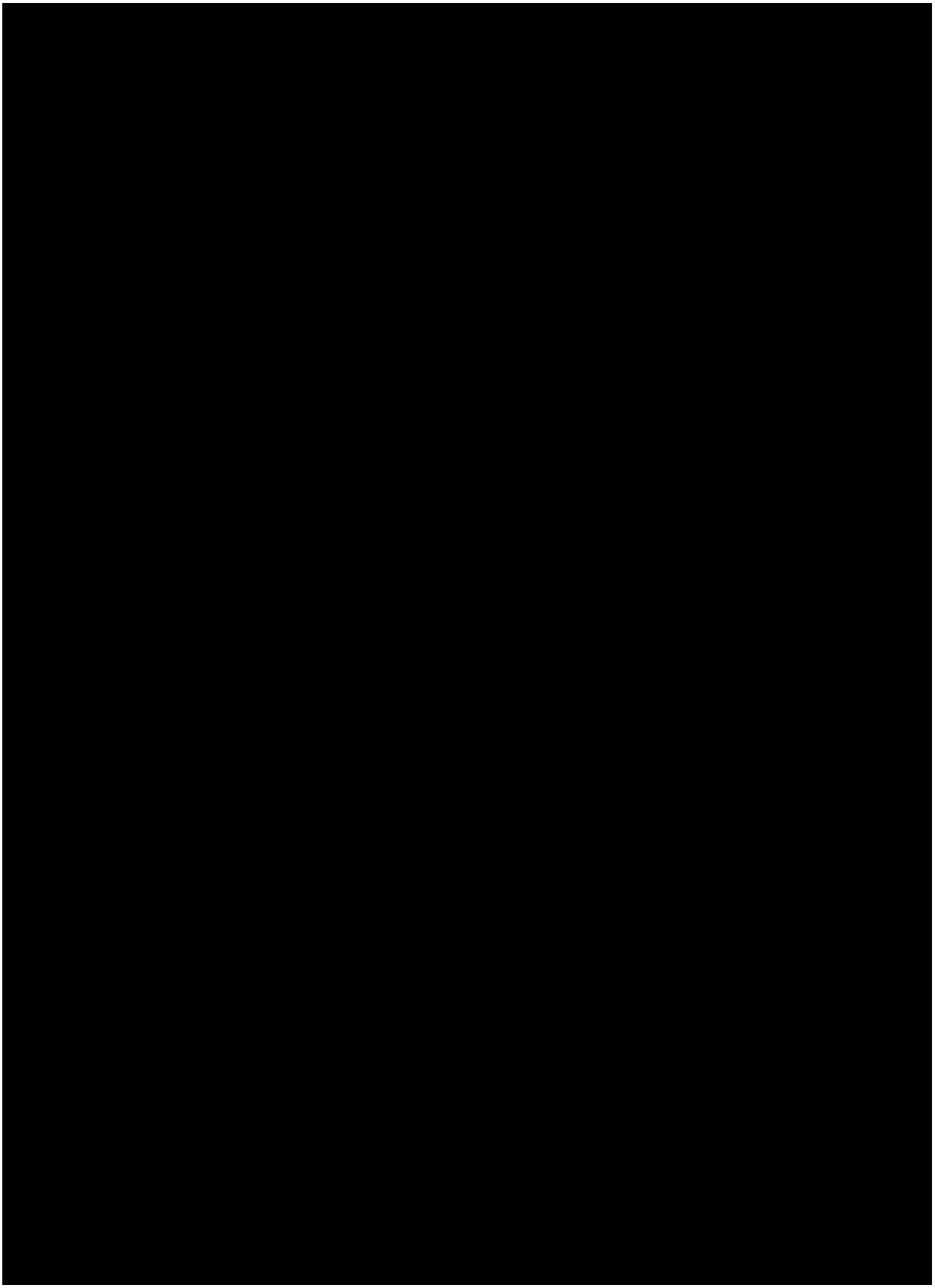

24 Appendix 12: Anti-pseudomonal medications

This table is not considered all-inclusive.

Table 24-1 Anti-pseudomonal medications

Drug class	Generic name
Aminoglycosides	Amikacin
	Gentamicin
	Netilmicin
	Streptomycin
	Tobramycin
Penicillins extended spectrum	Carbenicillin
	Mezlocillin
	Piperacillin
	Ticarcillin

Drug class	Generic name
	ticarcillin, combination potassium clavulanate
	piperacillin, combination tazobactam
	Azlocillin
Fluoroquinolones	Ciprofloxacin
	Enoxacin
	Levofloxacin
	lomefloxacin
	Moxifloxacin
	Norfloxacin
	Oflofloxacin
	Trovafloxacin
	Alatrofloxacin
	Gatifloxacin
Cephalosporins	Cefepime
	Cefdinir
	Cefoperazone
	cefoperazone, combination sulbactam
	Cefotaxime
	Cefpirome
	Ceftazidime
	Ceftizoxime
	Ceftriaxone
	ceftriaxone, combination tazobactam
Carbapenems	Meropenem
	Dorepenem
	Imipenem
	imipenem, combination cilastatin
Polymixins	Colistimethate
	polymixin B
Miscellaneous	Aztreonam

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