PROTOCOL TITLE:

Effects of long term ToBrAmycin InhalaTion SoluTion (TIS) once daiLy on Exacerbation rate in patients with non-cystic fibrosis bronchiectasis. A double blind, randomized, placebo controlled trial. The BATTLE study.

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	Adverse Event
ABPA	Allergic Bronchopulmonary Aspergillosis
BAT trial	Bronchiectasis and long term Azithromycin Treatment trial
CRF	Case Record Form
CF	Cystic Fibrosis
CFU	Colony Forming Units
DSMB	Data Safety Monitoring Board
EudraCT	European drug regulatory affairs Clinical Trials
FEV1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GP	General Practitioner
HRCT	High Resolution Computed Tomography
IB	Investigator's Brochure
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
LTRI-VAS	Lower Respiratory Tract Infection Visual Analogue Scale
METC	Medical research ethics committee (MREC); in Dutch: Medisch Ethische Toetsing Commissie (METC)
MIC	Minimum Inhibitory Concentration
Non-CF bronchiectasis	Non-Cystic Fibrosis bronchiectasis
Non-PDPE	non- protocol-defined pulmonary exacerbation
PDPE	protocol-defined pulmonary exacerbation
QoL	Quality of Life
QoL-B	Quality of Life Bronchiectasis
SAE	Serious Adverse Event
SPC	Summary of Product Characteristics (in Dutch: officiële productinfomatien IB1-tekst)
SUSAR	Suspected unexpected serious adverse reaction
TIS	Tobramycin Inhalation Solution
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen)

SUMMARY

Rationale: Patients with bronchiectasis often have exacerbations of their disease. These exacerbations influence the quality of life. In patients with cystic fibrosis (CF) longterm inhaled antibiotics lower the bacterial load in bronchial secretions and have positive effect on the number of exacerbations, lung function and quality of life (QoL). In patients with non-CF bronchiectasis colonized with *Pseudomonas aeruginosa* studies with tobramycin inhalation solution (TIS) are limited, however with only five trials to date[3,10,21,22,45]. In present study the value of maintenance TIS will be investigated in patients with non-CF bronchiectasis colonized by different bacterial species sensitive for tobramycin.

Objective: The primary outcome of the study is a 50% reduction in exacerbation rate in patients using maintenance TIS (OD). Secondary outcome parameters are lung function (FEV1, FVC), QoL (QOL-B), LTRI-VAS, Leicester cough score, bacterial load in sputum and tobramycin resistant pathogens.

Study design: A randomised, double blind placebo controlled, multicenter study.

Study population: Patients aged ≥ 18-year-old with confirmed bronchiectasis by (HR)CT and at least two exacerbations during previous 12 months.

Intervention (if applicable): During the study each group (placebo, intervention) receives TIS or placebo, once daily 300mg/5ml for at least 9 months and up to 12 months.

Main study parameters/endpoints: The primary endpoint is a reduction of exacerbations that patients suffer during the treatment period. Next to this parameter we expect to show a significant beneficial effect on lung function parameters, QoL, bacterial load of pathogens in sputum and tobramycin resistance.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: After informed consent patients have 3 monthly visits. During the visits patients have to deliver a sputum sample, fill in the QoL questionnaires and a spirometry will be performed according the study schedule. Also a blood sample will be taken during the visits. All patients are instructed to use the nebulizer adequately. The whole procedure of TIS (preparation, inhalation and cleaning) takes approximately 15 minutes. Adverse effects consist of cough, wheezing and dyspnoea. In general practice salbutamol is used before nebulizing TIS, to relieve these symptoms. TIS has already been used by a number of patients with bronchiectasis and is well tolerated. Safety of TIS will be assessed during each contact.

1. INTRODUCTION AND RATIONALE

Non-cystic fibrosis (non-CF) bronchiectasis is a chronic disorder of the major airways characterized by permanent dilation and destruction[1]. The origin of bronchiectasis varies, but the presence of microbial infection and a persistent inflammatory response are characteristic for the disease[2;3]. Colonization of the airway by bacteria stimulates an inflammatory response, which can become chronic if the infection is not eradicated[4]. Chronic inflammation causes host-mediated lung damage leading to a vicious cycle of events and decline in lung function[5]. This vicious cycle of infection and inflammation periodically develops into pulmonary exacerbations that are characterized by the following symptoms: changes in sputum production and purulence, increased dyspnoea, cough, wheezing, fever and fatigue. These exacerbations maybe associated with changes in chest sounds, radiographic abnormalities, but also lead to a decreased exercise tolerance and spirometer values[6]. Bacteria isolated from the sputum of patients with bronchiectasis include *Streptococcus pneumoniae, Staphylococcus aureus*, *Haemophilus influenzae,* and other gram-negative bacteria including *Pseudomonas aeruginosa*[7]. *P. aeruginosa* may appear later in the disease and causes more extensive and severe symptoms than the other bacteria[8]. Non-CF bronchiectasis patients with *P. aeruginosa* infection have more hospitalizations, a worse quality of life (QoL), and a more rapid decline in lung function than patients with other lung infections[9-11]. For other Gram-negative bacteria the progression of bronchiectasis as disease is less well known. Treatment of patients with non-CF bronchiectasis consists of postural physiotherapy, therapy with bronchodilators if reversible airflow obstruction is present, sometimes inhaled corticosteroids as a local anti-inflammatory agent, and antimicrobial therapy including immunomodulating therapy[12]. Treatment of recurrent respiratory infections is the cornerstone in patients with chronic suppurative lung disease. It has been reported that long-term systemic antibiotic treatment results in significant improvements in respiratory symptoms, pulmonary exacerbations, and health-related QoL in patients with severe bronchiectasis[8;13-16]. However, systemic antibiotics frequently fail to eradicate lung infections despite intensive therapy. In addition, relapse may occur when the antibiotics are stopped, and resistance frequently occurs with long-term use of systemic antibiotics[8]. An attractive alternative is the use of an inhaled antibiotic that delivers drug in high concentrations directly to the site of infection, eliminating the need for high systemic concentrations and reducing the risk of systemic toxicity or gastrointestinal side effects. Tobramycin inhalation solution (TIS) has been introduced for the long-term management of chronic *P. aeruginosa* infection, with a Cochrane review suggesting some benefit from TIS in terms of lung function and pulmonary exacerbation rate but also concern regarding an increase in antibiotic resistance[17]. The rationale for intermittent administration of tobramycin was based on the observation that during the treatment-free period tobramycin sensitive pathogens may repopulate the lower airways[18]. A recent registry study examining data from the Cystic Fibrosis Foundation's Patient Registry has suggested that TIS use is associated with reduced mortality[19]. TIS has also been demonstrated to be effective in delaying re-infection in those with early *P. aeruginosa* infection[20]. Because secretions in the non-CF bronchiectatic airways are similar to the purulent mucus found in the CF airways, and because pulmonary complications and progression of disease in non-CF bronchiectasis is similar to CF bronchiectasis, many centers treat patients with bronchiectasis using aerosolized TIS. There have been only a few small studies of aerosolized antibiotics to treat

pseudomonas infection in subjects with non-CF bronchiectasis[3;10;21]. The study of Drobnic[22] showed that TIS has effect on the rate of hospitalization and bacterial density of sputum. However, pulmonary function and QoL were not influenced. In another study symptoms and QoL were improved[3;10;22]. Furthermore, the risk of adverse events such as bronchospasm may be more common in adults with non-CF bronchiectasis than reported in the CF population[3;10]. No data is available of the effect of maintenance use of TIS in non-CF bronchiectasis colonized by *non Pseudomonas aeruginosa* Gram negative bacteria.

It is known that the antibiotic pharmacokinetics of CF-bronchiectasis differs from non-CF bronchiectasis. The twice-daily TIS dosing regimen in CF is based in large part on studies of tobramycin concentrations in expectorated sputum after administration of a single dose to adolescents and adults with CF[23-25]. No data are available of the sputum half-life of TIS in non-CF bronchiectasis. Most of these studies used the 4 weeks on-off protocol[26-29] . In this study we intend to establish the efficacy of once daily dosing of tobramycin. This is supported by knowledge that its bactericidal activity is concentration-dependent with a long post-exposure antibiotic effect[30-32]. Studies of intravenous administration of tobramycin and other aminoglycosides have shown that once daily dosing is equivalent in terms of antimicrobial efficacy compared to more frequent dosing [33-36]. Therefore a strong body of evidence supports once daily administration of tobramycin.

The present study has been designed to answer the question whether maintanance treatment with TIS once daily may reduce the number of exacerbations in non-CF bronchiectasis compared to placebo. As written above, the previous studies in patients with non-CF bronchiectasis are limited, small and open label. Next to this argument, it is unknown if extrapolation of the data collected in patients with CF bronchiectasis is justified. That is the reason why the British and Dutch guideline research recommendation mention that randomised controlled trials are needed to investigate the efficacy of nebulised antibiotics in patients with bronchiectasis chronically colonised with P. aeruginosa and other organisms. This study is designed as a randomized controlled trial, and TIS wil be compared to placebo.

2. OBJECTIVES

Primary Objective:
The primary objective of the study is to determine whether maintenance use of TIS once daily (OD) as compared to placebo may reduce the number of exacerbations per year in patients with non-CF bronchiectasis.

Secondary Objective:
The secondary objective of this study is to evaluate the effect of TIS treatment on time to next exacerbation, airflow limitation (FVC% predicted, FEV1% predicted), LRTI-VAS, Quality of Life-Bronchiectasis (QOL-B), Leicester cough score, bacterial load in sputum and tobramycin resistance, including MIC values, depending on the capabilities of the microbiological laboratory.

3. STUDY DESIGN

This study will be set up as a randomized, placebo controlled, multicenter study to evaluate the efficacy and safety of Tobramycin Inhalation Solution (TIS) compared to placebo. The target group are patients with non-CF bronchiectasis with recurrent exacerbations (≥ 2 per year) and colonized by Gram-negative bacteria (including *Haemophilus influenzae*) and/or *Staphylococcus aureus* in sputum. A sufficient number of subjects across 6 sites will be enrolled to ensure 58 patients. These patients are randomized in a 1:1 ratio of TIS OD (29 patients) to placebo OD (29 patients). The study will compare the number of exacerbations for 52 weeks, as well as the other secondary endpoints.
During the study patients visit the outpatient ward. During these visits' actual medical history, physical examination and questionnaires are obtained. Next to these sputum examination, spirometry and safety tests (lab examination, diary card) are performed. Study medication starts after the run-in period.
This study will consist of an up to 30-day screening phase, a treatment phase of 52 weeks, and a washout phase of 4 weeks.
Participating patients are randomized to one of the two study arms and will be treated for at least 9 months and up to 12 months in a double-blind fashion with placebo or TIS 300mg OD. Sputum samples will be collected from each subject for culture. At the Screening Visit (Visit 0) subjects will review and sign the informed consent form (ICF) and the screening procedures will be completed. Subjects meeting all study eligibility criteria will be randomized 1:1 to receive once daily inhaled treatment with either TIS OD or placebo. Subjects will have a screening visit and 6 additional scheduled visits during the study. Subjects will receive their first dose of study drug at the study site on day 1 during visit 1, and on day 7 they will be contacted by phone for the assessment of compliance and tolerance with study drug. Further visits are scheduled with 12-week intervals. Visit 7, which is the final visit of the study, will be conducted 4 weeks after the end of treatment period (see figure 1).
At visit 1, subjects will be instructed on daily study drug administration by self-administering study drug under the supervision of study personnel at the site; subjects will self-administer study drug during the complete study period.
Efficacy parameters will include assessment of pulmonary exacerbations, spirometry, LTRI-VAS, QOL-B and Leicester cough questionnaires. Microbiological response measurements will include semi-quantitative density of pathogens in sputum, including the tobramycin minimum inhibitory concentration (MIC) for isolated pathogens. Safety parameters will include assessment of AEs, serial spirometry findings, clinical laboratory test results, vital signs measurements, physical examination. Study drug is dispended on the regular visits. The first patients will be enrolled in the summer of 2016, with a treatment period of 12 months, we expect to terminate the study 31-01-2020.

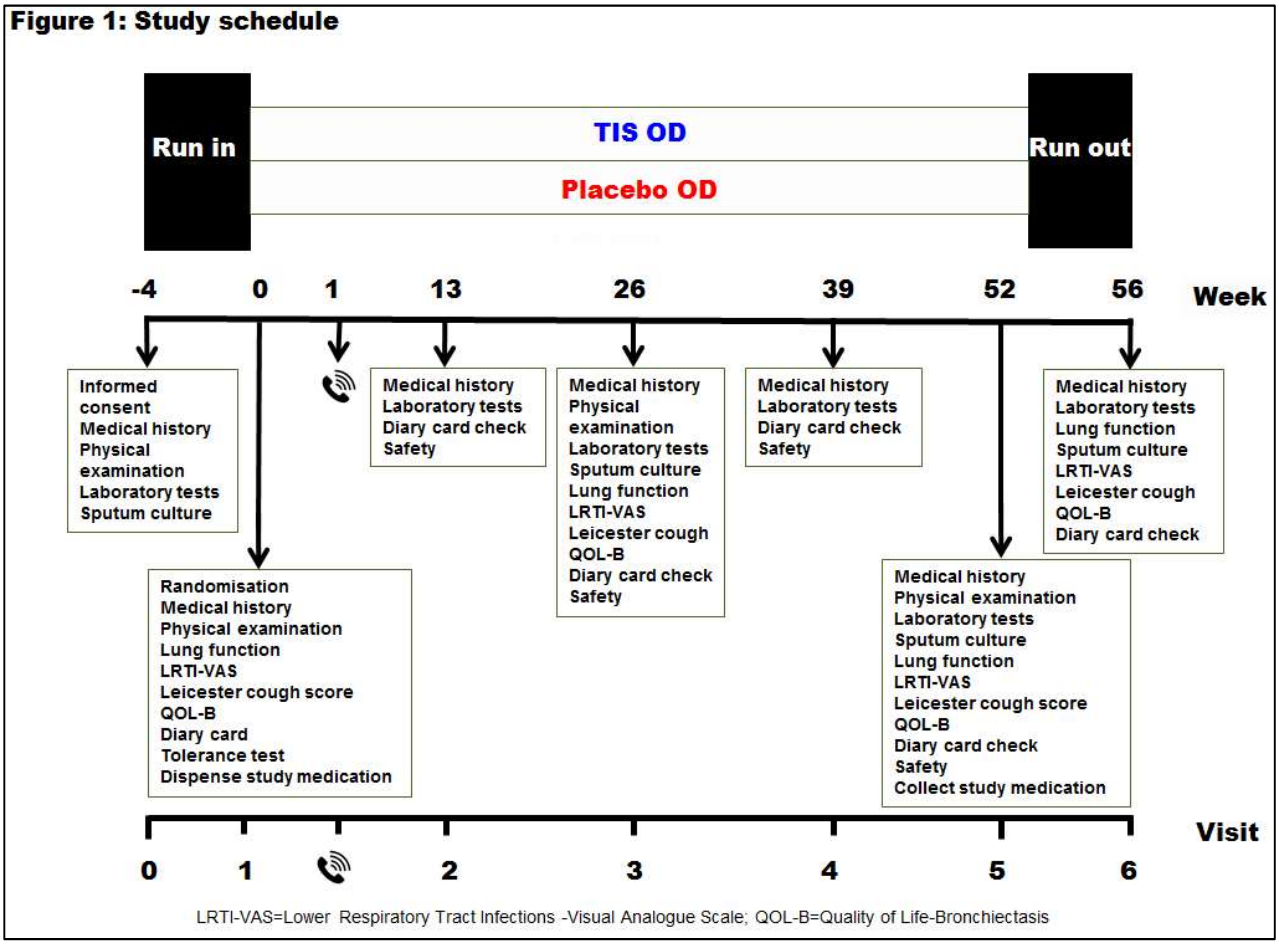
In subjects who experience a pulmonary exacerbation, every effort should be made to continue their allocated inhaled study drug, unless the study drug is not tolerated, or the pulmonary exacerbation is believed to be related to study drug. All subjects who receive any study drug need to complete the visit 7 assessments. Subjects who are prematurely withdrawn from study drug will be encouraged to

remain in the study and attend subsequent study visits; at a minimum, they should complete the visit 7 assessments as an early termination visit.

An independent expert will be established to conduct periodic reviews of subject safety for this protocol. The independent expert will also perform a blinded analysis of the pulmonary exacerbation data to check whether the assumptions for sample size estimation are valid, and if they are not, the sample size may be increased.

This study will be conducted in the Noordwest Ziekenhuisgroep, Canisius ZH Nijmegen, Spaarne Gasthuis Hoofddorp, Zuyderland MC Heerlen, VU Medical Center Amsterdam and UMC Utrecht.

Figure 1: Study schedule



LRTI-VAS=Lower Respiratory Tract Infections -Visual Analogue Scale; QOL-B=Quality of Life-Bronchiectasis

4. STUDY POPULATION

4.1 Population (base)

Non-cystic fibrosis bronchiectasis remains an important cause of chronic respiratory morbidity with a considerable healthcare. The prevalence and incidence of bronchiectasis are not known accurately, however in the last years, there is an increase in prevalence. In this study a total of 58 patients with clinically significant and radiological proven bronchiectasis are recruited from the outpatient clinic. Patients have at least two pulmonary exacerbations in the past year, for further inclusion and exclusion criteria see 4.2 and 4.3. The patients will be enrolled in the study and will be divided into two equally groups of 29 patients.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

1. Age ≥ 18 years
2. The presence of chronic respiratory symptoms such as cough, dyspnoea, expectoration of sputum
3. Confirmed non-CF bronchiectasis by (HR)CT
4. Documented history of at least 2 pulmonary exacerbations treated with courses of antibiotics within 12 months before inclusion.
5. No course of antibiotics or maintenance antibiotics (except for macrolides) 1 month prior to the start of the study.
6. Minimal one documented sputum or BAL-fluid culture with gram-negative bacteria or *S. aureus* within 12 months.
7. Growth of protocol defined pathogens in sputum

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

1. Any exacerbation within the month prior to the start of the study
2. Diagnosis of cystic fibrosis
3. Active allergic bronchopulmonary aspergillosis (ABPA)
4. Any oral, IV or inhaled antibiotics (except for macrolides) within 1 month prior to the start of the study
5. Any IV or IM corticosteroids or change in oral corticosteroids (> 10 mg) within 1 month prior to the start of the study
6. Any change/start treatment regimens macrolides, hypertonic saline, inhaled mannitol or other mucolytics, corticosteroids within 1 month prior to the start of the study
7. Severe immunosuppression or active malignancy
8. Active tuberculosis
9. Chronic renal insufficiency (eGFR < 30 ml/min)
10. Use of loopdiuretics, urea or mannitol
11. Earlier diagnosed hearing impairment, balance disorders or neuromuscular disorders

12. Serious active haemoptysis
13. Have received an investigational drug or device within 1 month prior to the start of the study
14. Serious or active medical or psychiatric illness
15. Pregnancy and child bearing
16. History of poor cooperation or non-compliance
17. Unable to use nebulizers
18. Allergic for tobramycin or NaCl 0.9%

4.4 Sample size calculation

The hypothesis is that prolonged treatment with tobramycin reduces the number of exacerbations per patient by 50%. This reduction seems clinically relevant and is based on the assumption that maintenance treatment with TIS OD as well as intermittent TIS BID is comparable to that of azithromycin treatment. This assumption is derived from the data of the BAT trial (placebo: mean 2,1 exacerbations (sd 1.6); azithromycin: mean 0,8 exacerbations (sd 1.1) [49]. The reduction in percentage is used for the determination of trial size.

We used a poisson regression model to determine group size[39]. For type I error and type II error 0.05 and 0.2 were used respectively. The hypothesis will be tested two sided. With a baseline exacerbation rate of 2.1 in the placebo group and an expected response rate ratio of 0.5 with an exposure time of 1 year a total of 18 evaluable patients are required to be on each treatment arm.

With a drop-out percentage of 30% we must include totally 48 (24 patients per group) patients[10;22]. Due to unforeseen reasons we initially include two extra patients per group. But after the interim analysis three extra patients will be included in the study, because the drop-off percentage is higher as expected in advance. Reason for discontinuation of the study is the intensive treatment and cleaning schedule of the inhaled study medication. So, with a total of 58 patients (29 per group) with bronchiectasis, and not the initially 52 patients (26 per group), we expect to achieve the intended effect size.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

Tobramycin inhalation solution (TIS)

This medication is used to treat people with cystic fibrosis (CF) and non-CF bronchiectasis who have a persistent lung infection with Gram-negative bacteria *(H. influenzae, Klebsiella spp, E. coli, P. aeruginosa, e.g.).* People with bronchiectasis often produce thick, sticky mucus that can plug up the tubes, ducts and passageways in the lungs. This can result in serious breathing problems and infections in the lungs. Tobramycin belongs to a class of drugs known as aminoglycoside antibiotics. Tobramycin inhalation solution works by stopping the growth of Gram-negative bacteria and *S. aureus* that commonly infects the lungs of people with bronchiectasis. This effect decreases lung infections and damage and helps to improve breathing.

Placebo: Sodium chloride inhalation solution 0.9% (NaCl 0.9%)

This medication is frequently used as a placebo. Each single-use plastic ampule contains sterile, non-pyrogenic, preservative-free sodium chloride. There is no bacteriostatic agent or other preservative added. Sodium chloride inhalation solution 0.9% is well tolerated and no severe adverse effects or side effects were recorded.

5.2 Use of co-intervention

All co-medications are allowed, except for any oral (except for macrolides), IV or inhaled antibiotics within 1 month prior to the start of the study and any IV or IM corticosteroids or change in oral corticosteroids (> 10 mg) within 1 month prior to the start of the study. Immunosuppressive agents such as azathioprine, chemotherapeutic agents, and TNFα inhibitors are prohibited. Also, any change/start treatment regimens of macrolides, hypertonic saline, inhaled mannitol or other mucolytics, within 1 month prior to the start of the study are prohibited. Also, the use of loopdiuretics, mannitol or urea are prohibited.

5.3 Escape medication

In consultation with the own GP or respiratory physician the patient may use extra bronchodilators for relief of dyspnoea. In subjects who experience a pulmonary exacerbation, every effort should be made to continue their allocated inhaled study drug, unless the study drug is not tolerated, or the pulmonary exacerbation is believed to be related to study drug. All subjects who receive any study drug need to complete the visit 7 assessments. Subjects who are prematurely withdrawn from study drug will be encouraged to remain in the study and attend subsequent study visits; at a minimum, they should complete the visit 7 assessments as an early termination visit.

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational product(s)

Tobramycin Inhalation Solution USP[37]

This medication is used to treat people with (CF) and non-CF bronchiectasis who have a persistent lung infection with Gram-negative bacteria (e.g*., H.influenzae, Klebsiella spp, E.coli, P. aeruginosa*). People with bronchiectasis often produce thick, sticky mucus that can plug up the tubes, ducts and passageways in the lungs. This can result in serious breathing problems and infections in the lungs. Tobramycin belongs to a class of drugs known as aminoglycoside antibiotics. Tobramycin inhalation solution works by stopping the growth of a Gram-negative bacteria and *S. aureus* that commonly infects the lungs of people with bronchiectasis. This effect decreases lung infections and damage and helps to improve breathing.

Sodium chloride inhalation solution 0.9% (NaCl 0.9%)

This medication is frequently used as a placebo. Each single-use plastic ampule contains sterile, non-pyrogenic, preservative-free sodium chloride. There is no bacteriostatic agent or other preservative added. Sodium chloride inhalation solution 0.9% is well tolerated and no severe adverse effects or side effects were recorded.

6.2 Summary of findings from non-clinical studies

6.2.1 Pharmacokinetics

Tobramycin inhalation solution contains tobramycin, a cationic polar molecule that does not readily cross epithelial membranes[38]. The bioavailability of tobramycin inhalation solution may vary because of individual differences in nebulizer performance and airway pathology[25]. Following administration of tobramycin inhalation solution, tobramycin remains concentrated primarily in the airways.

6.2.2 Sputum Concentrations

Ten minutes after inhalation of the first 300 mg dose of tobramycin inhalation solution, the average concentration of tobramycin was 1237 mcg/g (ranging from 35 to 7417 mcg/g) in sputum[37]. Tobramycin does not accumulate in sputum; after 20 weeks of therapy with the tobramycin inhalation solution regimen, the average concentration of tobramycin at ten minutes after inhalation was 1154 mcg/g (ranging from 39 to 8085 mcg/g) in sputum. High variability of tobramycin concentration in sputum was observed. Two hours after inhalation, sputum concentrations declined to approximately 14% of tobramycin levels at ten minutes after inhalation.

6.2.3 Serum concentrations

The average serum concentration of tobramycin one hour after inhalation of a single 300 mg dose of tobramycin inhalation solution by cystic fibrosis patients was 0.95 mcg/mL. After 20 weeks of therapy

on the tobramycin inhalation solution regimen, the average serum tobramycin concentration one hour after dosing was 1.05 mcg/mL[37].

6.2.4 Elimination

The elimination half-life of tobramycin from serum is approximately 2 hours after intravenous (IV) administration. Assuming tobramycin absorbed following inhalation behaves similarly to tobramycin following IV administration, systemically absorbed tobramycin is eliminated principally by glomerular filtration. Unabsorbed tobramycin, following tobramycin inhalation solution administration, is probably eliminated primarily in expectorated sputum.

6.3 Summary of findings from clinical studies

In present table all studies using TIS (all preparations) and outcomes are documented.

TABLE 1. PUBLISHED CLINICAL TRIALS USING AEROSOL ANTIBIOTICS TO TREAT NON-CF BRONCHIECTASIS IN ADULT SUBJECTS WHO WERE CHRONICALLY INFECTED WITH *PSEUDOMONAS AERUGINOSA*

Study	*Design*	*Number of subjects*	*Therapy given*	*Outcomes*
Orriols et al., 1999	RCT PG	15 completed, 7 on active treatment	Aerosol ceftaz and tobra for 12 months	Significantly fewer admissions in the active group. Decrease in FEV_1 while on active therapy compared with placebo (p = NS)
Barker et al., 2000;[19] Couch, 2001[20] NB: same study was reported twice	RCT	74: 37 TSI 37 placebo	TSI or placebo 4 weeks	Decrease in P.a. density on TSI but 11% developed P.a. resistance. Improved "general health" Decrease in FEV_1 while on TSI compared with placebo (p = NS) and 32% developed dyspnea on TSI.
Drobnic, et al., 2005[23]	RCT COT	30: 20 finished 5 died	6 months of TSI or placebo then cross after 1 month washout	Decrease in FEV_1 while on TSI compared with placebo (p = NS) Ni change in antibiotic use or QOL 10% of subjects had bronchospasm while on TSI.
Scheinberg and Shore, 2005[32]	OLT	41	3 × 14 days On and off cycles	Eradication of Pa in 22% and resistance developed in 7%. Nine withdrawals due to cough and wheezing.
Bilton et al., 2006[21]	RCT PG	53 enrolled 43 finished	TSI added to ciprofloxacin vs. cipro alone for 14 days	Significant decrease of P.a. in sputum. Decrease in FEV_1 while on TSI compared with placebo (p = NS). 50% on TSI developed wheeze vs. 15% on placebo.

All studies used tobramycin solution for inhalation (TSI) 300 mg b.i.d. as active drug except Orriols[24] used aerosol ceftazidime 1 g every 12 h and tobramycin injection solution 100 mg every 12 h. *Abbreviations:* PG, parallel group trial; RCT, randomized controlled trial; OLT, open label trial; COT, crossover trial, NS, not signficant; P.a., *Pseudomonas aueroginosa;* SGRQ, St George Respiratory Questionnaire; ceftz, ceftazidime; tobra, tobramycin; TSI, tobramycin solution for inhalation.

TIS USP (TEVA) has only been studied in CF patients (two studies, unpublished)[37]. In each study, tobramycin inhalation solution therapy resulted in a significant reduction in the number of *P.*

aeruginosa colony forming units (CFUs) in sputum during the on-drug periods. Sputum bacterial density returned to baseline during the off-drug periods. Reductions in sputum bacterial density were smaller in each successive cycle. Patients treated with longterm tobramycin inhalation solution were hospitalized for an average of 5.1 days compared to 8.1 days for placebo patients. Patients treated with tobramycin inhalation solution required an average of 9.6 days of parenteral anti-pseudomonas antibiotic treatment compared to 14.1 days for placebo patients. During the 6 months of treatment, 40% of tobramycin inhalation solution patients and 53% of placebo patients were treated with parenteral anti-pseudomonas antibiotics.

The relationship between in-vitro susceptibility test results and clinical outcome with tobramycin inhalation solution therapy is not clear. However, 4 tobramycin inhalation solution patients who began the clinical trial with *P. aeruginosa* isolates having MIC values ≥ 128 mcg/mL did not experience an improvement in FEV1 or a decrease in sputum bacterial density.

Treatment with longterm tobramycin inhalation solution did not affect the susceptibility of the majority of *P. aeruginosa* isolates during the 6-month studies. However, some *P. aeruginosa* isolates did exhibit increased tobramycin MICs. The percentage of patients with *P. aeruginosa* isolates with tobramycin MICs ≥ 16 mcg/mL was 13% at the beginning, and 23% at the end of 6 months of the tobramycin inhalation solution regimen.

6.4 Summary of known and potential risks and benefits

Maintenance use of TIS UPS is generally well tolerated as shown during two clinical studies in 258 cystic fibrosis patients ranging in age from 6 to 48 years. Patients received tobramycin inhalation solution in alternating periods of 28 days on and 28 days off drug in addition to their standard cystic fibrosis therapy for a total of 24 weeks. No severe adverse effects were recorded. The most common side effects are coughing, sore throat, dysphonia and bronchospasm. Tinnitus (3%) was transient, resolved without discontinuation of the tobramycin inhalation solution treatment regimen, and were not associated with loss of hearing in audiograms.
Nine (3%) patients in the tobramycin inhalation solution group and nine (3%) patients in the placebo group had increases in serum creatinine of at least 50% over baseline. In all nine patients in the tobramycin inhalation solution group, creatinine decreased at the next visit.

6.5 Description and justification of route of administration and dosage

TIS UPS is produced and packed by TEVA Pharmaceuticals in accordance to the principles and the detailed guidelines of Good Manufacturing Practice for Medicinal Products and will be delivered at the pharmacy of Stichting Haarlemse Ziekenhuizen. All the public information about the investigational product is written in the SPC-document. TIS is packaged in small plastic ampules (miniplasco's) of 5 ml; each ampule contains one full dose of tobramycin (300mg). These ampules are packed in identical sealed boxes. The investigators will be blinded for the content of the boxes. The placebo is a plastic ampule of NaCl 0.9% 5ml. These ampules are also called miniplasco's. The placebo is produced by Centrafarm B.V in accordance to the principles and detailed guidelines of Good Manufacturing

Practice for Medical Products. Also, these ampules will be delivered at the pharmacy of Haarlemse Ziekenhuizen. The shape of the ampules of the placebo (NaCl 0.9%) is different form the ampules of TIS, therefore the ampules will be packed in identical sealed boxes. The investigators will be blinded for the content of the boxes, in this way the blind will remain existent.
Labelling will be done at the pharmacy of Haarlemse Ziekenhuizen. The ampules remain intact, and a new label is printed on the package in accordance with the guidelines Good Manufacturing Practice. The expiration date, reference code and batch code are printed on the ampules and sealed boxes.
The 300mg dose of tobramycin inhalation solution (or placebo) is the same for patients regardless of age or weight. Doses should be inhaled as close to 12 hours apart as possible and not less than 6 hours apart. In this study TIS is used once daily in the morning. The pharmacy of Haarlemse Ziekenhuizen is responsible for the labelling and packaging of the sealed boxes for both TIS and placebo. These labelled and sealed boxes are sent to the pharmacy of the Noordwest Ziekenhuisgroep, location Alkmaar. The transportation is under refrigeration at 2-8ºC/36-46ºF. The storage of the investigational product (TIS or placebo) is under refrigeration at 2-8ºC/36-46ºF with 2-year shelf life at these circumstances. Temperature will be monitored continuously.
Upon removal from the refrigerator, tobramycin inhalation solution USP pouches (opened or unopened) may be stored at room temperature (up to 25ºC/77ºF) for up to 28 days. Tobramycin inhalation solution USP should not be used beyond the expiration date stamped (totally of two years) on the ampule when stored under refrigeration (2-8ºC/36-46ºF) or beyond 28 days when stored at room temperature (25ºC/77ºF). TIS USP ampules should not be exposed to intense light. The solution in the ampule is transparent but may darken with age if not stored in the refrigerator; however, the color change does not indicate any change in the quality of the product

The investigational product (TIS or placebo) is especially formulated to be used with an InnoSpire Deluxe compressor (Philips Respironics) with a SideSteam Plus nebulizer with mouthpiece. This compressor is produced by Philips Respironics and delivered by Mediq Romedic Netherlands. The air compressor is used with a nebulizer to turn the medicine into a fine spray. Before inhalation of TIS salbutamol is administered at a dose of 200mcg to prevent bronchial constriction. TIS (or placebo) while breathing through the mouthpiece the spray is inhaled into the airways. The nebulizer is used for about 5 minutes. The whole procedure; preparation of the nebulizer, inhalation and cleaning takes about 15 minutes to complete. Afterwards the patient should rinse their mouth three times.

6.6 Dosages, dosage modifications and method of administration

See 6.5

6.7 Preparation and labelling of Investigational Medicinal Product

Randomisation will be done by the statistician at the Noordwest Ziekenhuisgroep. The randomisation list will be sent to the pharmacy of Haarlemse Ziekenhuizen. Labelling takes place at the pharmacy of the Haarlemse Ziekenhuizen in accordance to this randomisation list. This labelled and sealed boxes

are sent to the pharmacy of the Noordwest Ziekenhuisgroep. Storage will be done in the refrigerator at the department of pulmonology in accordance to the GCP guidelines. See also 6.5.

6.8 Drug accountability

Medication will be provided by TEVA Pharmaceuticals and delivered at the pharmacy of the Haarlemse Ziekenhuizen. After labelling and packaging, the investigational medication will be delivered at the pharmacy of the Noordwest Ziekenhuisgroep location Alkmaar. All medication is coded. The medication will be delivered by the investigator at all participating centres. Transportation will be at refrigeration at 2-8ºC/36-46ºF in special boxes. The medication will be stored at the participating centres under refrigeration at 2-8ºC/36-46ºF, according to the local arrangements. Medication will be provided at the patients during each out-patient visit, with the explanation to store the investigational product in the refrigerator at 2-8ºC/36-46ºF. Used ampules are returned in opaque sealed plastic bags during the out-patient visit. The used ampules are counted by an independent research nurse and will be recorded in an excel file. In this way the blind will remain existent and nevertheless compliance can be checked. The ampules will be destroyed by the local pharmacy of the relevant hospital.

7. METHODS

7.1 Study parameters/endpoints

7.1.1 Main study parameter/endpoint

The primary objective of the study is to determine whether maintenance use of TIS once daily (OD) as compared to placebo may reduce the number of exacerbations per year in patients with non-CF bronchiectasis.

7.1.2 Secondary study parameters/endpoints (if applicable)

The secondary objective of this study is to evaluate the effect of TIS treatment on time to next exacerbation, airflow limitation (FVC% predicted, FEV1% predicted), LRTI-VAS, Quality of Life-Bronchiectasis (QOL-B), Leicester cough score, bacterial load in sputum and tobramycin resistance, including MIC values, depending on the capabilities of the microbiological laboratory.

7.1.3 Other study parameters (if applicable)

Other objectives of the study are age of the patients, sex, tobacco and alcohol use, number of patients with COPD or other etiologies, and the biomarkers like C-reactive protein level and leukocytes in serum, liver function and renal function. In addition to these objectives, it is also interesting how much patients withdrew from the study because of bronchospasm or other adverse effects, supplementary use of oral antibiotics due to an exacerbation, azithromycin maintenance and pseudomonas carriage. An exacerbation will be noticed bij using the diary card weekly. If there are any changes in medical

condition and compliance with medication, this will be noticed by using the diary card. In subjects who experience a pulmonary exacerbation, the own GP or respiratory physician will assess the severity of pulmonary symptoms and signs and prescribes antibiotics and/or medication e.g prednisolone, bronchodilators) . If so, the investigator will be informed. At least also an objective of the study is hospitalization and duration of the hospitalization.

7.2 Randomisation, blinding and treatment allocation

Randomisation will be done by Excel and SPSS statistics 20 with an allocation ratio of 1:1 between groups. Once a number is assigned to a patient, the investigator will open the treatment regimen assignment and the subject will receive treatment according to the assigned strategy. The numbers are anonymous dispensed in closed envelopes and stored at department of pulmonary diseases of the Noordwest Ziekenhuisgroep location Alkmaar. The main-investigator will be responsible for maintaining the storage and allocation of the envelopes.

7.3 Study procedures

Patients with bronchiectasis and who fulfil the inclusion and exclusion criteria will be asked to participate in the study. After a run-in period of 4 weeks' patients will be randomized to receive one of the two possible treatment regimens: TIS OD 300 mg daily or placebo. Administration will be continuous for the full 12 months. According to the parallel group design patients will be treated for 52 weeks. After completing the intervention period patients will have a follow-up (wash out period) of 4 weeks. This wash-out period was considered to be one month, in which time the antimicrobial effect of the antibiotic supposedly disappears, as suggested in earlier studies[22].

Subjects will be evaluated at run-in = visit 0 (week -4), visit 1 (day 1- start of the study), visit 2 (week 13), visit 3 (week 26), visit 4 (week 39), visit 5 (week 52: end of treatment) and visit 6 (run-out; week 56: end of the study). One week after start of treatment a phone call will be scheduled. Clinical, laboratory, and bacteriology evaluations will be determined according the schedule (Figure 1: study schedule). Subjects who terminate treatment should be followed for the same period as those who complete the study, according to the study schedule.

During the study any changes in medical condition and compliance with medication will be filed in the diary card.

At visit 1, after randomisation, a tolerance test with either TIS or placebo (blinded acccording randomisation) will be performed. Before nebulizing TIS patients are treated with salbutamol 200mcg using an aerochamber. During tidal breathing patients inhale 300mg TIS or placebo (at room temperature) by using the Innospire Deluxe nebulizer with mouthpiece during approximately 5 minutes. If patients develop a moderate-severe bronchial obstruction, patients are excluded from the study. The severity of bronchial obstruction and coughing is assessed by a specialized nurse, the respiratory physician or the own GP. An exacerbation is defined as the presence of three or more of the following symptoms or signs for at least 24 hours: increased cough, increased sputum volume, increased sputum purulence, haemoptysis, increased dyspnoea, increased wheezing, fever (>38.5°C)

or malaise, and the treating physician agreed that antibiotic and/or prednisolone therapy was required.
All participants are provided with 24-hour contact details (phone and mail) and invited to contact their respiratory physician or general practitioner and study staff at any time (including after hours) in the event of exacerbation symptoms, to ensure that these symptoms are evaluated prospectively. Participants will be instructed to ensure that antibiotic prescriptions will be provided by the own respiratory physician of the centres or the general practitioner.
Criteria for protocol-defined pulmonary exacerbation (PDPE) will be adjudicated prospectively by the treating respiratory physician. Antibiotic and/ or prednisolone prescriptions are also directed by the treating respiratory physician or the general practitioner, and standardized according to microbiology and antibiotic tolerance. Deteriorations in respiratory symptoms that do not meet criteria for PDPEs will be termed non–protocol-defined PEs (non-PDPEs). In these circumstances, participants were advised that they did not require antibiotics and only if clinically indicated, determined by the treating physician or the general practitioner.

Run-in (Visit 0, week -4)

At the baseline visit (- 4 weeks), subjects will be deemed eligible for the study after the clinical diagnosis bronchiectasis has been made, and the study has been explained to them. The following procedures will be completed:

- Verify inclusion/exclusion criteria
- Obtain written informed consent (alternatively at visit 1)
- Record medical history
- Collection of demographic information, concurrent disease, concomitant medication use, and previous course(s) of antibiotic therapy in the preceding year
- Physical examination (including sputum characteristics, cough, dyspnoea, pleuritic chest pain, chills or rigors, and lung sounds) and vital signs (respiratory rate, heart rate, blood pressure, body temperature and oxygen saturation)
- Laboratory examination (CRP, Hb, WBC, Sodium, Potassium, Creatinin, eGFR, Liver Function Tests, extra blood sample(s) will be taken and frozen for future research)
- Sputum culture (semi-quantitative)
- Randomisation (or at visit 1)

Day 1 (Visit 1)

- Record medical history
- Assessment of LRTI-VAS
- Quality of Life-Bronchiectasis (QOL-B) questionnaire
- Leicester cough score
- Physical examination (including sputum characteristics, cough, dyspnoea, pleuritic chest pain, chills or rigors, and lung sounds) and vital signs (respiratory rate, heart rate, blood pressure, body temperature and oxygen saturation)

- Collection of demographic information, concurrent disease, concomitant medication use, and previous course(s) of antibiotic therapy in the preceding year
- Spirometry according to the standard criteria of the European Respiratory Society
- Concomitant medication monitoring
- Study drug and Innospire deluxe dispensation
- Inhalation tolerance test with either TIS or placebo (depending on randomisation) and first dose of study drug administered under supervision of study staff
- Instructions on proper administration and return of study drug and proper care of the nebulizer
- Diary card instruction

Week 1 (Phone call)
- AE assessment of site effects of study medication
- Assessment compliance with medication and potential problems with nebulizer
- Diary card check

Week 13 (Visit 2)
- Record medical history (exacerbation, antibiotics?)
- Diary card check
- Repeat laboratory examination (CRP, Hb, WBC, Sodium, Potassium, Creatinin, eGFR, Liver Function)
- Potential side effects will be recorded
- Dispense study medication
- Remaining study drug is collected and/or is sent to Noordwest Ziekenhuisgroep, location Alkmaar

Week 26 (Visit 3)
- Record medical history (exacerbation, antibiotics?)
- Assessment of LRTI-VAS
- Quality of Life-Bronchiectasis (QOL-B) questionnaire
- Leicester cough score
- Physical examination (including sputum characteristics, cough, dyspnoea, pleuritic chest pain, chills or rigors, and lung sounds) and vital signs (respiratory rate, heart rate, blood pressure, body temperature and oxygen saturation)
- Diary card check
- Repeat laboratory examination (CRP, Hb, WBC, Sodium, Potassium, Creatinin, eGFR, Liver Function)
- Sputum examination for microbiologic assessment
- Spirometry according to the standard criteria of the European Respiratory Society
- Potential side effects will be recorded
- Dispense study medication
- Remaining study drug is collected and/or is sent to Noordwest Ziekenhuisgroep location Alkmaar

Week 39 (Visit 4)

- Record medical history (exacerbation, antibiotics?)
- Diary card check
- Repeat laboratory examination (CRP, Hb, WBC, Sodium, Potassium, Creatinin, eGFR, Liver Function)
- Potential side effects will be recorded
- Dispense study medication
- Remaining study drug is collected and/or is sent to Noordwest Ziekenhuisgroep location Alkmaar

Week 52 (Visit 5)

- Record medical history (exacerbation, antibiotics?)
- Assessment of LRTI-VAS
- Quality of Life-Bronchiectasis (QOL-B) questionnaire
- Leicester cough score
- Physical examination (including sputum characteristics, cough, dyspnoea, pleuritic chest pain, chills or rigors, and lung sounds) and vital signs (respiratory rate, heart rate, blood pressure, body temperature and oxygen saturation)
- Diary card check
- Repeat laboratory examination (CRP, Hb, WBC, Sodium, Potassium, Creatinin, eGFR, Liver Function Tests, extra blood sample(s) will be taken and frozen for future research)
- Sputum examination for microbiologic assessment
- Spirometry according to the standard criteria of the European Respiratory Society
- Potential side effects will be recorded
- Remaining study drug, nebulizer, and compressor are collected

Week 56 (run out, Visit 6)

- Record medical history (exacerbation, antibiotics?)
- Assessment of LRTI-VAS
- Quality of Life-Bronchiectasis (QOL-B) questionnaire
- Leicester cough score
- Diary card check
- Repeat laboratory examination (CRP, Hb, WBC, Sodium, Potassium, Creatinin, eGFR, Liver Function)
- Sputum examination for microbiologic assessment
- Spirometry according to the standard criteria of the European Respiratory Society

7.4 Withdrawal of the individual subjects

Subjects can quit the study at any time for any reason if they wish to do so without any consequences. The investigator/treating physician can decide to withdraw a subject from the study for urgent medical reasons.

7.5 Replacement of individual subjects after withdrawal

We estimate a drop-out of 30% patients. The number of potentially lost patients has been added to the number patients required by sample size calculation.

7.6 Follow-up of subjects withdrawn from treatment

Follow-up of patients withdrawn from treatment have an out-patient visit following the study schedule. These patients will be evaluated the same as the patients who complete the study. Subjects will be evaluated at run-in = visit 0 (week -4), visit 1 (day 1- start of the study), visit 2 (week 13), visit 3 (week 26), visit 4 (week 39), visit 5 (week 52: end of treatment) and visit 6 (run-out; week 56: end of the study). One week after start of treatment a phone call will be scheduled. During an exacerbation the patient will contact his/her own GP or specialist.

7.7 Premature termination of the study

With the expertise of maintenance treatment in CF patients and non-CF patients it is not likely that side effects may be a reason for termination of the study. If the independent expert sees any issues with safety regarding this clinical trial the study may be suspended or terminated for further/interim analysis by an independent statician. If he has serious concerns about safety of study subjects he will report these to the METC.

8. SAFETY REPORTING

8.1 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except in so far as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

8.2 AEs, SAEs and SUSARs

8.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational product / the experimental intervention. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded. Only AE's related to study procedures or medication will be recorded and reported once a year.

8.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that at any dose: Results in death; is life threatening (at the time of the event); requires hospitalisation or prolongation of existing inpatients' hospitalisation; results in persistent or significant disability or incapacity; is a congenital anomaly or birth defect.
Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardise the subject or may require an intervention to prevent one of the outcomes listed above.

SAE will be reported by the participating centres, preferably by mail, as soon as possible to the coordinating investigator.
The coordinating investigator will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 15 days after the coordinating investigator has first knowledge of the serious adverse events.

SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse event. This is for a preliminary report with another 8 days for completion of the report.

8.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:
the event must be serious (see chapter 9.2.2); there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in: Summary of Product Characteristics (SPC) for an authorised medicinal product or Investigator's Brochure for an unauthorised medicinal product.

The coordinating investigator will report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.
The expedited reporting of SUSARs through the web portal *ToetsingOnline* is sufficient as notification to the competent authority. All participating centres receive SUSARSs once a month by mail.

The expedited reporting will occur not later than 15 days after the coordinating physician has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

In summary, patients report potential adverse effect/ event (AE) of the study drug to their own respiratory physician as well in their diary chart. The respiratory physician reports this adverse effect/event to the coordinating investigator within one week and in SAE (e.g. hospital admission) as soon as possible. The coordinating investigator will inform the METC as described before.

The list of randomisation will be stored at the department of Pulmonology of the Noordwest Ziekenhuisgroep, location Alkmaar. Breaking the code will only be performed by the coordination physician.

8.3 Annual safety report

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States.
This safety report consists of: a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study; a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

8.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

8.5 Safety Committee/ Independent expert

The safety committee consist of one member, called the independent expert who is independent of the set-up and execution of the trial. This independent expert will receive the definite protocol and all revisions. The independent expert will convene every three to six months and review the results, i.e. results split by experimental and control arms. The independent expert has the power to recommend termination of the study based on the evaluation of these results. There are typically three reasons an independent expert might recommend termination of the study: safety concerns, outstanding benefit, and futility. The primary mandate of this independent expert is to protect patient safety. If adverse events of a particularly serious type are more common in the experimental arm compared to the control arm, then the independent expert would have to strongly consider termination of the study. This evaluation has to be made in consideration of risk/benefit. In many cases, the experimental arm could cause serious adverse events, but the resulting improvement in survival could outweigh these adverse events.
The idependent expert should inform the findings or conclusions to the study investigators by mail or e-mail. If there is any dispute between the independent expert and study investigators, the independent expert should notify the METC Noord-Holland.

The independent expert is:
Casper de Graaff longarts, Heiloo
Email: cgraaff0@gmail.com

9. STATISTICAL ANALYSIS

9.1 Calculation of study numbers

See 4.4. sample size calculation

We used the Poisson regression model for the power analysis[39]:

Numeric Results when X1 is Binomial with Proportion = 0,5 And Phi (Over-Dispersion Parameter) = 1,0000

Power	Sample Size (N)	Mean Response Rate Ratio	Baseline Rate Exp(B0)	Exposure Time (MuT)	R-Squared X1 vs Other X's (R2)	Two-Sided Alpha	Beta
0,80000	36	0,5000	2,1000	1,0000	0,0000	0,05000	0,20000

The hypothesis is that prolonged treatment with tobramycin reduces the number of exacerbations per patient by 50%. This reduction seems clinical relevant and is based on the assumption that maintenance treatment with TIS OD as well as intermittent TIS BID is comparable to that of azithromycin treatment. This assumption is derived from the data of the BAT trial (placebo: mean 2,1 exacerbations (sd 1.6); azithromycin: mean 0,8 exacerbations (sd 1.1))[49]. The reduction in percentage is used for the determination of trial size.

We used a poisson regression model to determine group size[39]. For type I error and type II error 0.05 and 0.2 were used respectively. The hypothesis will be tested two sided. With a baseline exacerbation rate of 2.1 in the placebo group and an expected response rate ratio of 0.5 with an exposure time of 1 year a total of 18 evaluable patients are required to be on each treatment arm.

With a drop-out percentage of 30% we have to include totally 48 (24 patients per group) patients[10;22]. Due to unforeseen reasons we initially include two extra patients per group. But after the interim analysis three extra patients will be included in the study, because the drop-off percentage is higher as expected in advance. Reason for discontinuation of the study is the intensive treatment and cleaning schedule of the inhaled study medication. So with a total of 58 patients (29 per group) with bronchiectasis, and not the initially 52 patients (26 per group), we expect to achieve the intended effect size.

9.2 Randomisation method

Randomisation will be done by SPSS, statistics 20 with an allocation ratio of 1:1 between groups. Once a number is assigned to a patient, the investigator will open the treatment regimen assignment and the subject will receive treatment according to the assigned strategy. The numbers are anonymous dispensed in closed envelopes and stored at department of pulmonary diseases Medical Center Alkmaar. The main-investigator will be responsible for maintaining the storage and allocation of the envelopes.

9.3 Analysis populations

9.3.1 Clinical Intent-To-Treat analysis (ITT)

All randomized patients with non CF-bronchiectasis will be included in the final ITT-population.

9.3.2 Modified Intent-To-Treat analysis (mITT)

The patients who are randomised but dropped out from the study directly after the tolerance test due to a moderate-severe bronchial obstruction or a severe cough, are excluded from the mITT analysis. So the mITT population includes the patients who passed the tolerance test with TIS or placebo according to the randomisation.

9.3.3 Per protocol Treatment analysis (PTT)

All randomized patients who received and completed treatment according to study protocol will be included in the per protocol analysis. Patients will be considered as non-evaluable if they do not complete a total treatment for at least 9 months. Termination of the study or incomplete data collection is also defined as non-evaluable.

9.4 Methods of analysis

9.4.1 General statistical considerations

All data will be collected and analysed using SPSS statistics 20.
Statistical analysis will be performed on an intent-to-treat basis by the investigator and an independent statistician. All continuous variables will be tested for normal distribution with the Kolmogorov-Smirnov test for normal distribution. The Student-t test will be used for normally distributed variables, the Mann-Whitney U test for not normally distributed variables and the χ^2 test for dichotomous variables. The software package SPSS 20 for Windows (IBM-SPSS Inc., Chicago, Illinois, USA) is available for statistical analysis. A value of $p<0.05$ will be considered significant.

9.4.2 Comparison of baseline characteristics

Baseline comparison of the treatment groups with regard to demographic variables will be compared with general used tests.

9.4.3 Primary study parameter(s)

A poisson regression model was used to analyse the primary outcome measure, evaluating both events and exposure (person-time), employing a quasilikelihood factor (with overdispersion correction), and incorporating the following covariables: treatment assignment, age, sex, smoking history, and presence of *P aeruginosa* and azithromycin maintenance use at baseline.

9.4.4 Secondary study parameter(s)

Time to first exacerbation during the treatment period, as well as during the wash-out period, will be assessed using Cox proportional hazards regression and reported graphically using Kaplan-Meier estimates.

Statistical significance in change of FEV1 (percent of predicted) and FVC (percent of predicted) attributable to treatment will be calculated with a linear mixed-model analysis. The effect of time on outcome variables will be checked for linearity by means of plots and model Proportional hazards assumptions will be tested with log-minus-log plots. Time will be entered as an interval variable, with the number of intervals depending on the frequency of follow-up visits at which the outcome will be measured. Predefined confounders are entered stepwise as fixed effects. Predictors remain in the regression equation if the model fit increases significantly. Thereafter, random effects will be explored for intercept (patients) and slope (time and patients). If random effects do not change the model fit significantly, a fixed effect will be assumed. Change in quality of life was analyzed using linear mixed-model analysis as well. The minimal important difference (MID) in bronchiectasis was reported only for the Quality Of Life-Bronchiectasis questionnaire (QOL-B), with a minimal important difference (MID) for the Respiratory symptoms scale of 8 points represent clinical relevance[46]. The MID for the leicester cough questionnaire in chronic cough is 1.3 points in total and represent clinical relevance[47]. The Leicester cough questionnaire was initially developed for patients with chronic cough, but has been validated in patients with bronchiectasis. Consequently, the minimal important difference of 1.3 points will be used in this study and represent clinical relevance. Secondary to these questionnaires the LRTI-VAS questionnaire will be used. This questionnaire is a validated and reliable tool for symptom measurement in non-CF bronchiectasis[48].

9.4.5 Other study parameters

Baseline comparison of the treatment groups with regard to demographic variables (such as age, gender, number of co-morbidities, smoking, alcohol use, etc.) and time of TIS treatment. These parameters will be assessed by using the Student-t test for normally distributed variables, and the Mann-Whitney U test for not normally distributed variables.

9.4.6 Interim analysis

After inclusion and follow up of 50% of the randomized patients an interim analyses will be conducted. A poisson regression model is used for our power analysis; See chapter 9.1.

The interim analysis is used to calculate the predetermined effect size, and whether more patients should be included depending on this effect size. Depending on the frequency of exacerbations at baseline and the effect size, a power analyses will be done by using the poisson regression model.

10.ETHICAL CONSIDERATIONS

10.1 Regulation statement

This study will be conducted in compliance with Good Clinical Practice (GCP), including the International Conference on Harmonization (ICH) guidelines and the most recent version of the Declaration of Helsinki.
All amendments to the protocol and informed consent forms must be reviewed by the local Independent Ethics Committee for approval before being implemented. In the event of any deviation from the protocol, the investigator must document the nature of and rationale for the deviation.
Informed consent must take place prior to any study specific procedure or test. Written signed and dated informed consent will be obtained from each subject (or his/her legally acceptable representative) in accordance with GCP and with local regulatory and legal requirements. The completed informed consent will be retained by the investigator as part of the study records.

10.2 Recruitment and consent

Patients will be asked to participate in this study by their own physician or the investigator at the time of the hospital visit or are contacted by phone. All patients receive the patient information letter and informed consent form during this visit or this information will be provided by mail.
Within one week the patient will be contacted. Any questions will be answered. If the patient is willing to participate to the study, an appointment at the outpatient department will be made. During this visit informed consent will be signed by both the patient and sub-investigator.

10.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable.

10.4 Benefits and risks assessment, group relatedness

Low risk study according to the risk-classification as designed by the Dutch Foundation of University Medical Centres. The full risk classification (in Dutch) can be found in Appendix 4.

10.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7, subsection 9 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23th June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.

- € 650.000, -- (i.e. zes hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
- € 5.000.000, -- (i.e. five million Euro) for death or injury for all subjects who participate in the Research;

- € 7.500.000, -- (i.e. seven million five hundred thousand Euro) for the total damage incurred by the organisation for all damage disclosed by scientific research for the Sponsor as 'verrichter' in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

10.6 Incentives (if applicable)

Not applicable.

11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

11.1 Handling and storage of data and documents

All data will be collected by the researcher on the electronic Case Report Form (e-CRF). The data will be entered into a database, where subjects will be assigned a study number. Their personal information will not be entered into the database. A separate subject identification list, the Investigator Site File, will be kept by the investigator at the study site in case the study data needs to be linked to individual subjects.
All study data will be kept for 15 years. Blood samples and sputum samples will be stored for 3 years.

11.2 Monitoring and Quality Assurance

The conduct of the study and data entries will be monitored by an external monitor, J. Doodeman. He will select a sample of cases and check them for irregularities. If any are found, the monitor may choose to select a larger sample or review all available data. He will report the irregularities to the sponsor who is responsible for correcting any mistakes.
All adverse events will be analysed periodically by the statistician of the DSMB. If SAE's or SUSARs are more common in the experimental arm compared to the control arm he will inform the sponsor and other members of the DSMB which may then take actions as described in chapter 8.5. All serious adverse events will be reported to the accredited METC.

11.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor. All amendments will be notified to the METC that gave a favourable opinion.

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;

- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by all other amendments and will be notified to the METC that gave a favourable opinion.

11.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems and amendments.

11.5 End of study report

The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.
In case the study is ended prematurely, the investigator will notify the accredited METC within 15 days, including the reasons for the premature termination.
Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

11.6 Public disclosure and publication policy

The results will be published within a year after completing the study. The study is completed after the follow up of a year of the last person. The main article will be published in an international respiratory journal with a high impact factor. Due tot the CCMO-guidelines the Sponsor acknowledges the importance of public disclosure/publication of information collected or generated by the Institution or Principal Investigator, under the condition that public disclosure/publication takes place under the provisions of article 8 of the Clinical Trial Agreement, called the onderzoekscontract BATTLE.

12. STRUCTURED RISK ANALYSIS

12.1 Potential issues of concern

a. Level of knowledge about mechanism of action

The vicious cycle hypothesis of bronchiectasis argues that bacterial colonization of the normally sterile respiratory tract provokes and perpetuates airway inflammation. According to this hypothesis, if bacteria are the primary drivers of airway inflammation, bacterial clearance through the use of short- or long-term antibiotic therapy would be expected to reduce airway inflammation, allow airway healing, and modify the long-term course of the disease. There is strong evidence from CF bronchiectasis to support this view, with data suggesting that bacterial colonization is associated with airway inflammation and that antibiotic treatment during stability and at exacerbation can reduce markers of inflammation[40-43]. Extrapolation from CF to non-CF bronchiectasis is difficult because the pathophysiology is different and the failure of recombinant DNase treatment to provide benefit in non-CF bronchiectasis demonstrates that responses to treatment can be very different in CF compared with non-CF bronchiectasis[6]. Another point of uncertainty is the different pharmacokinetics in CF patients particularly for aminoglycosides and b-lactam-antibiotics when compared with normal individuals. The higher body clearance due to increased renal and non renal elimination demands that higher antibiotic doses are administered more frequently[44]. However, differences between CF-patients and non-CF individuals in this context do not seem to be as large as used to be thought and may have been exaggerated by the lack of properly matched controls for clinical studies[44].

However numerous studies in CF patients have shown that TIS has a positive effect on lung function, quality of life and in some on the number of exacerbations. There are limited studies evaluating the effect of bacterial clearance in non-CF bronchiectasis. From earlier studies we know that bacterial load (e.g. *P.aeruginosa*) can be reduced by TIS. Bacterial killing effects markers of airways and systemic inflammation inpatients with bronchiectasis and therefore decreases clinical symptoms such as cough, dyspnoea and sputum production. The reduction of these symptoms has a positive effect on the health related quality of life.

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

There is tremendous experience with TIS as chronic treatment in CF-patients. In general practice it is well tolerated. Only few studies have been performed in non-CF bronchiectasis patients (see section 6.2 and 6.3). Although not registered, numerous patient are already treated with TIS (TOBI® and Bramitob®). These patients are tolerating TIS well and nebulizing this drug seems very effective (personal experiences of Dutch pulmonologists).

c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?

Not applicable.

d. Selectivity of the mechanism to target tissue in animals and/or human beings
Not applicable.

e. Analysis of potential effect
see section 6.1, 6.2 and 6.3.

f. Pharmacokinetic considerations
see section 6.1 and 6.2.

g. Study population
non-CF bronchiectasis.

h. Interaction with other products
Combination with furosemide, ureum or mannitol should be avoided because of potential nephro- and/or ototoxicity. Especially, nephrotoxicity may occur in combination with IV prescribed aminoglycosides, amphotericin B, cephalosporins, polymyxins, ciclosporin, tacrolimus and platinum containing drugs. A combination with botulinetoxine or anticholinesterases (e.g., neostigmine, pyridostigmine) may induce a prolonged neuromuscular blockade.

i. Predictability of effect
Effect can possibly be measured by biomarkers (inflammation), lung function and bacterial load in sputum.

j. Can effects be managed?
Not applicable.

12.2 Synthesis

Because of the previous experience with TIS in CF patients, but also in non-CF patients there is low risk of toxicity. First dose of study drug administered under supervision of study staff may give information of the tolerance. A number of safety measurements are included: phone call after one week, other outpatient visits, serial laboratory testing, dairy card, and safety checks by the independent expert.

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Appendix 1. Lower Respiratory Tract Infection Visual Analogue Scale (LRTI-VAS) -Dutch edition-

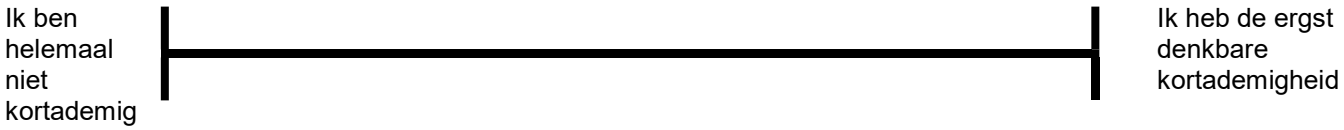
KLACHTEN SCHAAL

Randomisatie nr. | | | |

DAG: Naam:

Zet a.u.b. een kruisje op de volgende lijnen:

1. KORTADEMIGHEID



2. VERMOEIDHEID

3. HOEST

4. WAT VOOR SPUTUM GEEFT U OP?

5. PIJN

Geen pijn — Ik heb de ergst denkbare pijn

Appendix 2. Leicester Cough Questionnaire -Dutch edition-

Naam:
Geboortedatum
Bezoeknummer:
Datum:

HOEST VRAGENLIJST

Deze vragenlijst is ontworpen om de gevolgen van het hoesten op diverse aspecten van uw leven te meten. Lees iedere vraag aandachtig en OMCIRKEL het antwoord dat de **afgelopen twee weken** het meest op u van toepassing is (slechts één antwoord per vraag). Beantwoord a.u.b. alle vragen, en zo eerlijk mogelijk.

In de **afgelopen twee weken**…		altijd	meestal	heel vaak	regelmatig	af en toe	zelden	nooit
1.	had u door het hoesten last van pijn op de borstkas of in de maag?	1	2	3	4	5	6	7
2.	had u door het hoesten last van slijm ophoesten?	1	2	3	4	5	6	7
3.	bent u door het hoesten vermoeid geraakt?	1	2	3	4	5	6	7

In de **afgelopen twee weken**…		nooit	zelden	af en toe	regelmatig	heel vaak	meestal	altijd
4.	had u het idee het hoesten onder controle te hebben?	1	2	3	4	5	6	7

In de **afgelopen twee weken**…		altijd	meestal	heel vaak	regelmatig	af en toe	zelden	nooit
5.	hoe vaak schaamde u zich voor het hoesten?	1	2	3	4	5	6	7
6.	werd u ongerust door het hoesten?	1	2	3	4	5	6	7
7.	verstoorde het hoesten uw werk of andere dagelijkse bezigheden?	1	2	3	4	5	6	7
8.	bemerkte u dat het hoesten het plezier in het leven vergalde?	1	2	3	4	5	6	7
9.	moest u hoesten van verflucht of andere prikkelende luchtjes?	1	2	3	4	5	6	7

10.	hoe vaak werd uw nachtrust verstoord door het hoesten?	1	2	3	4	5	6	7
11.	hoe vaak hoestte u op een dag?	1	2	3	4	5	6	7
12.	voelde u zich gefrustreerd door het hoesten	1	2	3	4	5	6	7
13.	was u het hoesten zat?	1	2	3	4	5	6	7
In de **afgelopen twee weken**…		altijd	meestal	heel vaak	regelmatig	af en toe	zelden	nooit
14.	was u hees door het hoesten?	1	2	3	4	5	6	7
In de **afgelopen twee weken**…		nooit	zelden	af en toe	regelmatig	heel vaak	meestal	altijd
15.	zat u vol energie?	1	2	3	4	5	6	7
In de **afgelopen twee weken**…		altijd	meestal	heel vaak	regelmatig	af en toe	zelden	nooit
16.	was u bezorgd dat uw hoest door een ernstige ziekte veroorzaakt werd?	1	2	3	4	5	6	7
17.	was u bezorgd dat anderen dachten dat u wat ernstigs mankeerde, door uw hoesten?	1	2	3	4	5	6	7
18.	verstoorde uw hoest uw praten of een telefoongesprek?	1	2	3	4	5	6	7
19.	meende u dat het hoesten vervelend is voor uw partner, familie of vrienden?	1	2	3	4	5	6	7

Gebaseerd op de **Leicester Cough Questionnaire** © Birring

Appendix 3. Quality of Life Questionnaire Bronchiectasis (QOL-B) -Dutch edition-

QOL-B VRAGENLIJST KWALITEIT VAN LEVEN — BRONCHIËCTASIE

Het begrijpen van de impact van uw ziekte en behandelingen op uw dagelijks leven kan uw arts helpen uw gezondheid te controleren en uw behandelingen aan te passen. Om die reden hebben we een vragenlijst opgesteld om de kwaliteit van leven te meten, speciaal voor mensen met bronchiëctasie. Hartelijk dank dat u deze vragenlijst wilt invullen.

Aanwijzingen: De volgende vragen gaan over uw huidige gezondheidstoestand zoals u deze ervaart. Met deze informatie krijgen wij beter inzicht in hoe u zich in het dagelijks leven voelt.

Beantwoord alstublieft alle vragen. Er zijn **geen** goede of foute antwoorden! Als u niet zeker weet wat u moet antwoorden, kies dan het antwoord dat uw situatie het beste weergeeft.

Demografische gegevens

Vul de gegevens in of vink het vakje aan bij uw antwoord.

A. Wat is uw geboortedatum?

Datum ☐☐-☐☐-☐☐☐☐
Dag Maand Jaar

B. Wat is uw geslacht?

☐ Man ☐ Vrouw

C. Bent u de **afgelopen week** op vakantie geweest, of hebt u niet gestudeerd of niet gewerkt om redenen die **NIET** met uw gezondheid te maken hadden?

☐ Ja ☐ Nee

D. Wat uw huidige burgerlijke staat?

☐ Alleenstaand/nooit getrouwd
☐ Getrouwd
☐ Weduwe/weduwnaar
☐ Gescheiden
☐ Uit elkaar
☐ Hertrouwd
☐ Samenwonend

E. Welke van de volgende opties beschrijft het beste uw etnische achtergrond?

☐ Nederlands
☐ Turks
☐ Marokkaans
☐ Surinaams
☐ Antilliaans
☐ Aziatisch
☐ Anders (graag toelichten)_____
☐ Deze vraag beantwoord ik liever niet.

F. Wat is uw hoogst genoten opleiding?

☐ Enkele jaren (of minder) voortgezet onderwijs
☐ Diploma voortgezet onderwijs
☐ MBO
☐ Enkele jaren HBO
☐ Diploma HBO
☐ Diploma WO

G. Welke van de volgende opties beschrijft het beste uw huidige opleidings- of werksituatie?

☐ Ik volg buitenshuis een cursus/opleiding
☐ Ik volg thuis een cursus/opleiding
☐ Ik ben werkzoekend
☐ Ik werk voltijds of deeltijds (buitenshuis, of vanuit huis)
☐ Ik ben huisman/huisvrouw
☐ Ik volg geen opleiding en heb geen werk vanwege mijn gezondheid
☐ Ik werk niet om een andere reden/ik ben gepensioneerd

Ga verder naar de volgende bladzijde

QOL-B VRAGENLIJST KWALITEIT VAN LEVEN – BRONCHIËCTASIE

Deel I. Kwaliteit van leven

Vink het vakje aan dat uw antwoord aangeeft.

*In welke mate had u gedurende de afgelopen **week** moeite met:*	Veel moeite	Matige moeite	Beetje moeite	Geen moeite
1. Verrichten van inspannende activiteiten zoals tuinieren of fietsen	☐	☐	☐	☐
2. Net zo snel kunnen lopen als anderen (familie, vrienden, enz.)	☐	☐	☐	☐
3. Zware dingen dragen zoals boeken of boodschappentassen	☐	☐	☐	☐
4. Eén trap oplopen	☐	☐	☐	☐

*Geef aan hoe vaak u zich gedurende de afgelopen **week** zo voelde:*	Altijd	Vaak	Soms	Nooit
5. U voelde zich goed	☐	☐	☐	☐
6. U voelde zich moe	☐	☐	☐	☐
7. U was gespannen/u maakte zich zorgen	☐	☐	☐	☐
8. U voelde zich energiek	☐	☐	☐	☐
9. U voelde zich uitgeput	☐	☐	☐	☐
10. U voelde zich verdrietig	☐	☐	☐	☐
11. U voelde zich depressief	☐	☐	☐	☐

Wordt u op dit moment behandeld (zoals met orale of te inhaleren geneesmiddelen, een PEP- of Flutter®-apparaat, borstfysiotherapie of Vest) voor uw bronchiëctasie?

☐ Ja ☐ Nee (ga verder naar vraag **15** op de volgende bladzijde)

Omcirkel het cijfer dat uw antwoord aangeeft. U mag bij elke vraag maar één antwoord geven.

12. In welke mate maken de behandelingen van uw bronchiëctasie uw dagelijks leven moeilijker?
1. Helemaal niet
2. Een beetje
3. Matig
4. Veel

13. Hoeveel tijd besteedt u op dit moment elke dag aan uw behandelingen voor bronchiëctasie?
1. Veel tijd
2. Matige hoeveelheid tijd
3. Een beetje tijd
4. Bijna geen tijd

14. Hoe moeilijk vindt u het om uw behandelingen voor bronchiëctasie elke dag in te passen?
1. Helemaal niet moeilijk
2. Een beetje moeilijk
3. Matig moeilijk
4. Erg moeilijk

Ga verder naar de volgende bladzijde

QOL-B VRAGENLIJST KWALITEIT VAN LEVEN – BRONCHIËCTASIE

Omcirkel het cijfer dat uw antwoord aangeeft. U mag bij elke vraag maar één antwoord geven.

15. Hoe vindt u uw gezondheid op dit moment?
1. Uitstekend
2. Goed
3. Matig
4. Slecht

Selecteer het vakje dat uw antwoord aangeeft.

*Als u nadenkt over uw gezondheid gedurende de afgelopen **week**, geef aan in welke mate elke uitspraak voor u waar is.*	Helemaal waar	Grotendeels waar	Een beetje waar	Helemaal niet waar	
16. Ik moet inspannende activiteiten zoals wandelen of fietsen beperken.....	☐	☐	☐	☐	
17. Ik moet vaker thuisblijven dan ik zou willen	☐	☐	☐	☐	
18. Ik ben bang om in aanraking te komen met anderen die ziek zijn	☐	☐	☐	☐	Niet van toepassing
19. Het is moeilijk om intiem te zijn met een partner (zoenen, knuffelen, seksuele activiteit).....	☐	☐	☐	☐	☐
20. Ik leid een normaal leven.....	☐	☐	☐	☐	
21. Ik maak me zorgen dat mijn gezondheid achteruit zal gaan	☐	☐	☐	☐	
22. Ik denk dat anderen last hebben van mijn gehoest.....	☐	☐	☐	☐	
23. Ik voel me vaak eenzaam.....	☐	☐	☐	☐	
24. Ik voel me gezond.....	☐	☐	☐	☐	
25. Het is moeilijk om vooruit te plannen (vakantie, bijwonen van familiefeestjes, enz.)	☐	☐	☐	☐	
26. Ik voel me opgelaten als ik hoest	☐	☐	☐	☐	

Omcirkel het cijfer of vink het vakje aan dat uw antwoord aangeeft.

*Gedurende de afgelopen **week**:*

27. In welke mate had u moeite bij te blijven met uw werk, huishoudelijke taken of andere dagelijkse activiteiten?
1. U had geen moeite bij te blijven
2. U kon bijblijven maar het kostte moeite
3. U bent achtergeraakt
4. U bent helemaal niet in staat geweest deze activiteiten te verrichten

	Altijd	Vaak	Soms	Nooit
28. Hoe vaak belemmert uw bronchiëctasie u bij het bereiken van doelen op uw werk, in het huishouden of gezin of op het persoonlijke vlak?.....	☐	☐	☐	☐

Ga verder naar de volgende bladzijde

QOL-B VRAGENLIJST KWALITEIT VAN LEVEN – BRONCHIËCTASIE

Deel II. Luchtwegverschijnselen

Vink het vakje aan dat uw antwoord aangeeft.

*Geef aan hoe u zich gedurende de afgelopen **week** voelde:*	Veel	Matig	Een beetje	Helemaal niet
29. Had u het gevoel dat uw borst vol zat?	☐	☐	☐	☐
30. Hebt u overdag gehoest?	☐	☐	☐	☐
31. Hebt u slijm op moeten hoesten?	☐	☐	☐	☐

32. Was het slijm meestal:

☐ Helder ☐ Helder tot geel ☐ Geelgroen
☐ Bruin tot donkerbruin ☐ Groen met bloedsporen ☐ Weet ik niet

*Hoe vaak gedurende de afgelopen **week**:*	Altijd	Vaak	Soms	Nooit
33. Was u kortademig bij meer activiteit, zoals huishoudelijke taken of tuinieren?	☐	☐	☐	☐
34. Had u last van een piepende ademhaling?	☐	☐	☐	☐
35. Had u pijn op de borst?	☐	☐	☐	☐
36. Was u kortademig bij het praten?	☐	☐	☐	☐
37. Werd u 's nachts wakker door het hoesten?	☐	☐	☐	☐

Kijk alstublieft na of u alle vragen hebt beantwoord.

HARTELIJK DANK VOOR UW MEDEWERKING!

Appendix 4. Risico-classificatie investigator initiated onderzoek -Dutch edition-

Risico-classificatie investigator initiated onderzoek

Versienummer: 1 Versiedatum: 21-01-2016

Toegevoegd risico	
Wat is het toegevoegde risico van de onderzoekshandelingen voor de veiligheid van de proefpersoon?	Tobramycine verneveling is geregisteerd voor gebruik bij patienten met CF-bronchiectasieen. In deze studie zullen wij tobramycine gaan voorschrijven bij patienten met non-CF bronchiectasieen, waarvan de etiologie iets anders is. Echter het medicament is precies hetzelfde. Bijwerkingen kunnen zijn, lokale klachten van irritatie van de luchtwegen en hoesten. Echter deze klachten zijn passager. Ook kan tinitus voorkomen en worden nierfunctiestoornissen beschreven, wat beiden weer normaliseert na het staken van het medicament.

Frequentie/schade	
Hoe groot is de kans op schade?	☒ klein ☐ matig ☐ groot
	Toelichting: blijvende schade is nooit eerder beschreven.

Risico onderzoekshandeling	
Hoeveelheid kennis en ervaring met de interventie, het geneesmiddel, voedingsmiddel of medisch hulpmiddel bij mensen?	Tobramycine verneveling is geregisteerd bij patienten met CF-bronchiectasieen. Zodoende is er veel kennis en ervaring mee en zijn er uitgebreide studies mee gedaan die de effectiviteit van het middel laten zien. Met als bijwerking met name passagere lokale klachten als hoesten.
Bekende risico's:	hoesten, bronchusobstructie, droge mond. Zeer zelden huiduitslag, tinitus en nierfunctiestoornissen.
Kans op het optreden van onbekende risico's:	Die is nihil, aangezien het een geregisteerd geneesmiddel is wat al veelvuldig gebruikt wordt. De kans op onbekende risico's is daardoor nihil.
Ernst van de mogelijke nadelige effecten/mate van schade:	☒ lichte schade ☐ matige schade ☐ ernstige schade
	Toelichting: Zo goed als geen schade, aangezien alle bijwerkingen passager zijn en elke bijwerking weer normaliseert wanneer het middel gestaakt wordt.
Voorspelbaarheid van nadelig effect:	Die is voorspelbaar met een zeer lage kans op een nadeling effect.
Mogelijkheid om ongewenste effecten te beheersen:	Het staken van de inhalatiemedicatie waarvoor het ongewenste effect verdwijnt. Voorafgaand aan gebruik van de inhalatiemedicatie het gebruiken van salbutamol aerosol, wat de kans op bornchusobstructie verkleint.
Reversibiliteit van de mogelijke nadelige effecten:	volledig reversibel
Lichamelijke belasting (pijn, ongemak):	ongemak, wat volledig reversibel is en wat snel opgelost kan worden door het staken van de tobramycine

	verneveling en ter verlichting van de klachten het gebruik van salbutamol
Psychische belasting (angst, stress):	zeer nihil, bij goede uitleg van de eventuele bijwerkingen zoals eerder beschreven, weet een patient wat hij/zij te wachten staat

Kenmerken onderzoekspopulatie	
Kwetsbaarheid (ernstig zieken, kwetsbare ouderen, jonge kinderen):	Patienten boven de 18 jaar met bronchiectasieen en frequnete exacerbaties daarvan. Van jong volwassenen tot de oudere mensen. Patienten worden intensief gemonitord en frequent op de polikliniek gezien.

Maatschappelijke risico's	
Voor de proefpersoon (privacy, stigmatisering, uitsluiting van verzekering):	dubbelblind onderzoek, dus de privacy is gewaarborgd. Geen kans op uitsluitng van verzekering aangezien het een gangbare en geregisteerde antibiotische behandeling is. Daarnaast is het een poliklinisch onderzoek dus patienten hoeven niet opgenomen te worden.
Voor het onderzoek (maatschappelijk draagvlak, gevoeligheid van het onderzoek):	Groot maatschappelijk draagvlak specifiek voor deze patientengroep waar nog weinig evidence is naar de behandeling en dit voor de toekomst juist een weinig invasieve en elegante behandeling kan zijn, waardoor patienten veel minder in het ziekenhuis worden opgenomen.

Risico's samenhangend met onderzoeksopzet en –uitvoering (risico op protocol violations)	
Complexiteit van het protocol:	Patienten worden geincludeerd in tobramycine verneveling of placebo verneveling, waarbij instructies worden gegeven bij elk polibezoek, patienten worden vanaf dan 1 jaar vervolgd op de polikliniek waarbij gevraagd wordt naar sputumkweken en bloedonderzoek (wat ook bij de reguliere controles hoort), ook wordt 4x een longfunctieonderzoek gedaan, wat ook bij de reguliere zorg hoort.
Aantal te includeren proefpersonen:	78

Conclusie risico-classificatie	
Maak aan de hand van tabel 1[1] een keuze uit de opties:	☒ verwaarloosbaar risico ☐ matig risico ☐ hoog risico ☐ opwaarderen naar hoger risico[2]
Geef een toelichting op de gemaakte keuze.	Toelichting: Het is een geregisteerd medicijn die eerder al getest is bij patienten met bronchiectasieen bij cystic fibrose. Wij zullen dit medicijn geburiken bij patienten met non-CF bronchiectasieen. het riscio is eerder al laag ingeschat en de eventuele ongewenste effecten die kunnen optreden zijn passager en zullen verdwijnen na het staken van de medicatie. Patient zijn 18 jaar en ouder, dus het is niet alleen maar de kwetsbare oudere patient die meedoet aan deze studie. Ook jongere mensen met non-CF bronchiectasieen worden geincludeerd.