2 Synopsis

Name of Sponsor/Company: Profile Pharma Ltd, Chichester, West Sussex PO20 2FT, United Kingdom	*(For National Authority Use only)*
Name of Finished Product: Promixin	
Name of Active Ingredient: Colistimethate sodium	
Title of Study: A double-blind, vehicle-controlled, multi-centre, clinical study to investigate the efficacy and safety of up to 6 months of therapy with inhaled Promixin in the treatment of patients with non-cystic fibrosis bronchiectasis infected with *Pseudomonas aeruginosa* susceptible to Promixin	
Coordinating and Chief Investigators: Diana Bilton MD, Royal Brompton Hospital, London, UK and Charles Haworth MD, Papworth Hospital, Cambridge, UK.	
Study Centres: 35 centres in 3 countries (Russia, Ukraine and the United Kingdom) randomised patients; 2 additional centres screened, but did not randomise, any patients.	
Publication (reference): None	
Studied Period (years) **First Patient In:** 18-Mar-2009 **Last Patient Out**: 02-Feb-2012	**Development phase:** 3

Objectives:

The primary objective of the study was to demonstrate that inhaled Promixin, administered twice a day for up to 6 months, at a concentration of 1 million international units (MIU)/mL via a nebulising system, the I-neb Adaptive Aerosol Delivery System (referred to as the I-neb) with a 0.3 mL metering chamber, increases the time to a pulmonary exacerbation compared to vehicle, in patients with non-cystic fibrosis (CF) bronchiectasis infected with *P. aeruginosa* susceptible to Promixin. The secondary objectives were to assess: 1) the safety of Promixin when administered for 6 months to patients with non-CF bronchiectasis infected with *P. aeruginosa* susceptible to Promixin compared to vehicle; 2) the effect of Promixin on the weight of sputum produced in 24 hours compared to vehicle; 3) the impact of Promixin on symptoms by means of the St. George's Respiratory Questionnaire (SGRQ) compared to vehicle; 4) the effect of inhaled Promixin on the flora of sputum and to quantify the effect on the *P. aeruginosa* density as determined by the colony forming unit (CFU) count and their susceptibility to antibiotics compared to vehicle; 5) patients' compliance with the I-neb system and to explore if there was a correlation between compliance and outcome; 6) the incidence of bronchospasm as detected by a reduced forced expiratory volume in 1 second (FEV_1) following inhalation of the Promixin compared to vehicle; and 7) the severity of exacerbation (requires intravenous antibiotics = severe / requires oral antibiotics = moderate).

The study was completed according to Protocol version 5.0, dated 18 July 2011.

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Methodology: This was a multicentre, randomised, double-blind, parallel-group, vehicle-controlled study in patients with non-CF bronchiectasis and a history of exacerbations due to *P. aeruginosa* requiring antibiotic therapy (oral or intravenous). It was conducted at 35 centres in 3 countries. Patients were randomised (1:1) to Promixin (1 MIU/mL) or vehicle (0.45% saline), and self-administered their randomised treatment via an I-neb twice a day, in the morning and evening, for up to 6 months. Patients had a planned maximum of 5 scheduled clinic visits, 2 on-treatment telephone contacts and one post-treatment telephone contact 28 to 35 days after the end of treatment.

Visit 1 (Screening) took place within 21 days of completing a course of anti-pseudomonal antibiotic therapy for a pulmonary exacerbation. At this visit, all eligible patients provided a sputum sample and were discharged to home and asked to collect sputum over the 24 hours prior to their next visit. Patients returned to the clinic 7-10 days later for Visit 2 (Baseline/Randomisation visit/Day 0), when the sample taken at Visit 1 had to be positive for *P. aeruginosa* for the patient to continue in the study. If pathogens other than *P. aeruginosa* were identified in the sputum samples, patients could be recalled for appropriate antibiotic therapy and were then not eligible for the study at that time, but could be re-screened up to 21 days after completing the antibiotic therapy for their next exacerbation. Patients with positive sputum results for *P. aeruginosa*, and who continued to fulfil all the inclusion/exclusion criteria, were randomly allocated investigational medicinal product (IMP: Promixin or vehicle). Eligible patients had their 24-hour sputum sample collected for weighing and a separate fresh sample collected and sent for culture and susceptibility.

At Visit 2, the first dose of IMP was administered in the hospital under medical supervision. Patients had their FEV_1 monitored pre-dose, and 15 and 30 minutes post-dose to investigate if there was evidence of symptomatic bronchospasm ($\geq$15% reduction in FEV_1 at any measurement). Patients experiencing a $\geq$15% fall in FEV_1 were withdrawn from the study. For eligible patients, treatment (Promixin or vehicle) continued for 6 months or until the patient experienced an exacerbation.

After leaving the clinic at the end of Visit 2, patients were then seen and assessed at 4, 12, and 26 weeks (Visits 3, 4 and 5, respectively) post the first dose or at the time of an exacerbation. A telephone check was made at 2 and 18 weeks post-first dose. At Visits 2, 4 and 5, patients completed the SGRQ. At all clinic visits, patients reported AEs, had their FEV_1 assessed and recorded, and a sputum sample collected (24-hour samples also at Visit 3). Samples were assessed for quantitative culture and susceptibility of *P. aeruginosa* to Promixin. The 24-hour sputum collection was weighed and a fresh sample sent for culture and susceptibility. Patients also reported AEs at the telephone contacts.

Patients experiencing an exacerbation were instructed to contact the clinic to arrange a visit to the clinic on the next working day after the development of symptoms suggestive of an exacerbation. At the clinic visit the investigator decided if it was an exacerbation that met the protocol defined criteria and on the appropriate course of action. Oral or intravenous antibiotics were started as appropriate. If patients were admitted to hospital for intravenous antibiotics, they were to be visited by the research staff for an assessment within 72 hours of

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admission. Assessments were the same at these "visits" as at routine visits.

Patients' involvement in the study was completed at the time of the safety follow-up phone call that was conducted 4 weeks after a) the resolution of a proven exacerbation or b) the last dose of IMP. Resolution of a proven exacerbation was defined as the date of completion of a course of antibiotic therapy.

The maximum expected duration of participation in this study for an individual patient, including Screening and the 1-month follow-up period, was to be 8 months.

Number of Patients planned/analysed:
144 planned and 144 analysed

Diagnosis and Main Criteria for Inclusion: Male and female patients, aged 18 years and over, diagnosed with non-CF bronchiectasis by computed tomography, who had had *P. aeruginosa* grown from their sputum at least twice in the 12 months preceding the screening visit, and were within 21 days of completing a course of anti pseudomonal antibiotics for the successful treatment of an exacerbation. Patients with a history of CF, hypogammaglobulinaemia, inflammatory bowel disease, primary ciliary dyskinesia, myasthenia gravis or myloproliferative disease, previous course of therapy with inhaled colistimethate sodium and confirmed recent, active allergic bronchopulmonary aspergillosis, were ineligible, as were those requiring treatment with steroids excepting a stable dose of 15 mg/day or less.

Test Product, Dose, Mode of Administration, and Batch Numbers:
Promixin was supplied as a sterile powder in a glass vial. Each vial contained 1 MIU which weighed about 80 mg. Patients self-administered the prescribed IMP twice daily via an I-neb Adaptive Aerosol Delivery nebuliser system (referred to as I-neb). Patients nebulised 0.3 mL of a 1 mL Promixin solution (1 MIU/mL) made up in 0.45% saline. The I-neb had a 1 mL fill volume and was fitted with a 0.3 mL metering chamber.

CT Pack Batch Number E06237-01: Promixin Active vials Batch 2122263

All CT Pack Batch Numbers E06237-02 and 03: Promixin Active vials Batch 2322644.

Duration of Treatment: 6 months

Reference Therapy, Dose, Mode of Administration, and Batch Numbers: Patients nebulised 0.3 mL vehicle (0.45% saline) via the I-neb. The vials provided for the vehicle were identical in external appearance to those containing the IMP.

CT Pack Batch Number E06237-01: placebo vials Batch 2152201

All CT Pack Batch Numbers E06237-02 and 03: placebo vials Batch: 2322601

Concurrent medication: Starting with the first dose of IMP, all patients received their usual inhaled beta-agonist prior to receiving the IMP. Patients not usually receiving a beta-agonist were required to take a beta-agonist prior to receiving IMP to reduce any bronchoconstriction that might have occurred.

Criteria for Evaluation:

Efficacy: The primary endpoint was the time (in days) from Baseline/Visit 2 (first dose) to

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the first exacerbation after the start of treatment. The secondary efficacy endpoints were: weight of sputum expectorated in the 24 hours prior to Visits 2 and 3; total score for the SGRQ; number of CFUs of *P. aeruginosa* derived from the sputum cultures; severity of exacerbation; and time to exacerbation for subgroups of patients based on compliance data collected by the "logging system" in the I-neb.

Safety: The safety endpoints were: adverse events (AEs), serious AEs (SAEs), and suspected unexpected serious adverse reactions (SUSARs); number of patients experiencing bronchoconstriction (a fall in FEV_1 of $\geq$15%) in the 30 minutes post-first dose; number of patients withdrawing due to AEs related to IMP; incidence of strains of *P. aeruginosa* resistant to Promixin developing during treatment, as defined by disc testing; changes in concomitant medications; haematology and biochemistry; physical examination.

Pharmacokinetics: Not applicable

Statistical Methods:

Primary efficacy endpoint: The null hypothesis to be tested was: H_0: the time to an exacerbation for the Promixin treatment arm = the time to an exacerbation for the vehicle arm, and the alternative hypothesis: H_a: the time to an exacerbation for the Promixin treatment arm $\neq$ the time to an exacerbation for the vehicle arm. The time to the first exacerbation was calculated as the time (in days) from Visit 2 (Baseline/first dose) to the first exacerbation after the start of treatment. If at the last known follow-up a patient had not had an exacerbation then the time was taken to be the time to the date of the last dose in the I-neb download, and the time was taken to be censored at that time. A Kaplan-Meier survival curve of the time to an exacerbation was plotted for each treatment group, for each of the cohorts analysed. The median time to an exacerbation, and the time for 25% and 50% of patients to have an exacerbation was estimated for each treatment group using survival analysis techniques. The log rank test was used to compare treatments. The analysis was stratified by centre. Centres did not need to be grouped for this analysis. The log-rank test was used to examine the homogeneity of the centres with respect to the treatment effects.

Secondary efficacy endpoints were analysed as follows.

Weight of Sputum: weight of sputum expectorated in the 24 hours prior to Visits 2 and 3 was summarised by treatment and visit. Statistical analysis was performed using an analysis of covariance with the baseline weight as the covariate, and with treatment and centre included in the statistical model. Compliance with the normal distribution was determined by examination of plots of residuals.

The SGRQ: total score for the SGRQ was summarised and analysed as described for weight of sputum. The total and component scores were listed by treatment.

Number of CFUs of *P. aeruginosa* and Other Organisms: the number of CFUs of predefined organisms (including *P. aeruginosa*) derived from the sputum cultures were summarised in separate summary tables, by treatment group and visit. Changes from baseline were also calculated. Statistical analysis followed the methodology described above for weight of sputum, and was performed for all follow-up visits.

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Severity of Exacerbation: severity of each exacerbation (moderate or severe) was summarised by treatment group but not subjected to formal statistical analysis.
Time to Exacerbation Based on Compliance Data: time to exacerbation was summarised for subgroups of patients based on percentage compliance. Patients were divided into 4 subgroups based on quartiles with respect to percentage compliance. Results for each subgroup were summarised by treatment group, but not subjected to formal statistical analysis.

Safety:

AEs were summarised by body system and by Medical Dictionary for Regulatory Activities (MedDRA) preferred term; only treatment-emergent adverse events (TEAEs) were summarised. Summaries were also produced showing AEs by severity, seriousness and relationship to treatment. The following was summarised by treatment, and analysed for treatment differences using the χ^2 test: the numbers of patients withdrawn from the study due to AEs, reporting AEs, and withdrawing due to AEs related to IMP. The following were summarised by treatment, and tested for treatment differences using the Wilcoxon Rank Sum or χ^2 test as appropriate: the numbers of AEs, SAEs and SUSARs.
Number of patients experiencing bronchoconstriction (a $\geq$15% reduction in FEV_1 in the 30 minutes post-first dose) was summarised by treatment, and treatment differences were tested using the χ^2 test.
FEV_1 was summarised by treatment at Weeks 4, 8 and end of study. Changes were calculated, and statistical analysis was performed for end of study only, and followed the methodology described above for weight of sputum.
Extent of exposure was summarised by treatment as the total number of study treatments the patient received during the study.
Reasons for discontinuation of patients from study as assessed by the investigator were summarised by treatment. The total number of withdrawals for the study was tested for treatment differences using the χ^2 test.
Incidence of strains of *P. aeruginosa* resistant to Promixin developing during treatment were derived from the sputum cultures. All sputum culture data were listed.
Concomitant medications, haematology, biochemistry data, and changes occurring in the physical examination from baseline were listed, but not summarised.
No interim analyses were performed.

Summary of Results:

Efficacy Results (planned analysis):

Time to first exacerbation (primary endpoint): During the study, in the ITT population, 78 patients (54.2%) experienced an exacerbation: 36 patients in the Promixin group and 42 patients in the Vehicle group. The median time (25% quartile) to the first exacerbation was 165 days (42 days) in the Promixin group and 111 days (52 days) in the Vehicle group. The treatment difference was not statistically significant (p=0.11).

Weight of sputum: there was only a minor change from Baseline in weight of sputum collected over 24 hours prior to Visit 5; the treatment difference was not statistically

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significant (p=0.56).

SGRQ: The estimated mean treatment differences in change in SGRQ total score from Baseline to Week 12 and Week 26 were -1.09 (95% confidence intervals [CIs]: -5.18 to 2.99) and -10.51 (95% CIs: -17.87 to -3.14), respectively. This treatment difference reached statistical significance at Week 26 (p=0.006).

Number of CFUs of P. aeruginosa: The changes from Baseline in CFUs of *P. aeruginosa* for the full ITT population favoured the active treatment group, but the treatment differences did not reach statistical significance at any visit.

Severity of exacerbations: In both groups, the majority of exacerbations were considered moderate and were treated with oral antibiotics.

Efficacy Results (*post hoc* analysis)

Because of evidence suggesting good compliance affected efficacy outcomes, *post hoc* analyses were carried out on several efficacy endpoints for the subgroup of patients with compliance ≥80%. The results showed that patients who received Promixin and were ≥80% compliant with the medication regimen had a statistically significantly longer (p=0.028) time to first exacerbation (168 days) compared to those patients who received vehicle and were ≥80% compliant with the medication regimen (103 days).

The changes from Baseline in CFUs by log base 10 of *P. aeruginosa* were considered to be of more relevance than the absolute CFU count changes and were also analysed. The decrease in bacterial load of at least 10 fold was statistically significant at Week 4 (p=0.001) and Week 12 (p=0.008).

Analyses relating to the SGRQ and CFU counts were also analysed for the patients that were ≥80% compliant. These analyses showed similar results to the analyses of the ITT population.

Safety Results:

A summary of AEs during the study is presented in the following table:

Number of patients reporting TEAEs	**Promixin (N=73)**	**Vehicle (N=71)**
Any TEAEs, n (%)	47 (64.4)	38 (53.5)
Deaths, n (%)	1 (1.4)	2 (2.8)
Total number of TEAEs reported	143	108
SAEs	9 (6.3)	6 (5.6)
AEs leading to withdrawal	10 (7.0)	9 (8.3)
Severe AEs	10 (7.0)	4 (3.7)
Related AEs	35 (24.5)	20 (18.5)
Related AEs leading to withdrawal	8 (5.6)	6 (5.6)

A total of 251 AEs were reported for 85 patients (59.0%): 143 AEs in 47 patients (64.4%) in

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the Promixin group and 108 AEs in 38 patients (53.5%) in the Vehicle group (p=0.25). The most common AEs were predominated by events in the Respiratory, thoracic and mediastinal disorders, Infections and infestations, Gastrointestinal disorders, and Investigations System Organ Classes.

Thirty-five events (24.5%) in 18 patients in the Promixin group and 20 events (18.5%) in 9 patients in the Vehicle group were considered to be possibly, probably or definitely related to IMP. With the exception of preferred term wheezing (3 events/3 patients) and headache (4 events/3 patients) in the Promixin group all preferred terms that were considered to be at least possibly related to IMP were single occurrences in 1 or 2 patients.

No SUSARs were reported. There were 3 deaths, all considered unlikely to be related to IMP. One death (preferred term: cardiopulmonary failure) occurred in a Promixin patient and 2 deaths occurred in Vehicle patients (preferred terms: bronchiectasis and respiratory failure [1 patient] and acute coronary syndrome [1 patient]). The incidence of all SAEs (fatal and nonfatal) was similar in the Promixin and Vehicle groups: 9 (6.3%) events and 6 (5.6%) events, respectively. The incidence of AEs leading to discontinuation was similar in the Promixin and Vehicle groups: 7 patients in the Promixin group and 6 patients in the Vehicle group withdrew due to AEs. Of these AEs, 8 events (5.6%) and 6 events (5.6%) for Promixin and Vehicle respectively, were considered related to IMP; this difference was not statistically significant (p=0.75).

In both groups the majority of AEs were mild in intensity; the incidence of severe events was higher in the Promixin compared with the Vehicle group: 10 (7.0%) events versus 4 (3.7%) events, respectively.

The incidence of bronchoconstriction (a fall in FEV_1 of $\geq$15% reduction in the first 30 minutes post the first dose) was low: 1 patient in the Vehicle group experienced bronchoconstriction. Another patient in the Vehicle group experienced difficulty with the spirometry, but the clinical team could not detect any signs of bronchoconstriction.

There were no laboratory safety concerns or clinically important changes in physical examinations.

Conclusions:

The study did not achieve the primary objective statistically, but all the data demonstrates a clinically relevant improvement in patients taking Promixin compared to placebo. Compliance with the medication regimen does correlate with the efficacy of therapy.

Post hoc analyses of the data did show that for patients, who were at least 80% compliant with the medication regimen:

> The time to the next exacerbation could be clinically and statistically significantly increased by the use of Promixin 1 million IU delivered through the I-neb nebuliser system twice a day.

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Patients experienced a positive effect on the patients overall health, daily life, and perceived well-being as assessed by the SGRQ.

The use of Promixin has a positive effect on the bacterial load but no effect on the mass of sputum produced.

The use of Promixin was not associated with the development of resistance to colistimethate sodium by P. aeruginosa and no overgrowth of other bacteria occurred.

The safety profile of Promixin in patients with non-CF bronchiectasis is similar to the safety profile established for patients with CF bronchiectasis.

Date of Report: 30-Jan-13