Study Title:

Observational Safety Study of Bronchitol (inhaled mannitol) in Patients with Cystic Fibrosis from the UK CF Registry

Contents

1. ABBREVIATIONS:

CF	Cystic fibrosis
EMA	European Medicines Agency
PASS	Post-authorisation safety study

2. RESPONSIBLE PARTIES:

Principal Investigator:	Dr Diana Bilton Consultant Respiratory Physician Royal Brompton Hospital London SW3 6NP UNITED KINGDOM
Study Statistician:	Dr Stephanie MacNeill National Heart and Lung institute Imperial College London SW3 6LR UNITED KINGDOM
Study Sponsor:	UK Cystic Fibrosis Trust Bromley BR1 1BY UNITED KINGDOM
Marketing Authorisation Holder:	Pharmaxis Ltd Frenchs Forest NSW 2086 AUSTRALIA

3. STUDY SYNOPSIS

Study Title	Prospective Case-Control Safety Study of Bronchitol (inhaled mannitol) in Patients with Cystic Fibrosis from the UK CF Registry
Protocol Version and Date	Version 1.0 - 18th June 2012
Principal Investigator	Dr Diana Bilton Royal Brompton Hospital London UK
Study Design	Observational cohort study
Rationale/Background	This post-authorisation safety study (PASS) is being conducted pursuant to an obligation imposed by the EMA as a condition of the granting of a marketing authorisation for Bronchitol (mannitol) to confirm the safety profile of Bronchitol, identify, characterise and/or quantify any emergent safety issues , and measure the effectiveness of agreed risk management strategies
Study Participants	Exposed: Adult (≥ 18years) patients in the CF registry database who are prescribed Bronchitol Unexposed: Non- treated patients matched for key characteristics with exposed patients)
Planned Sample Size	All Bronchitol-treated patients with evaluable data in the UK CF Registry during the 5-year study period
Planned Study Period	June 2012 – July 2017
Primary Objective(s)	To assess the rates of identified and potential risks of Bronchitol through a comparison of treated vs. non-treated patients
Secondary Objective(s)	❖ To compare the rates of identified and potential risks against background rates in the general CF population. ❖ To assess the rate of identified and potential risks in the population below 18 years of age ❖ To compare the effect on lung function in treated vs. non-treated patients ❖ To compare the effect on CF exacerbations in treated vs. non-treated patients
Data Sources	Data will be obtained from the UK CF Trust Registry
Data Analysis	At each analysis time logistic regression models will estimate propensity scores for treated and untreated patients. Bronchitol-treated patients will be compared with untreated patients matched on key characteristics. Descriptive statistics will be used to describe the treated and untreated patient groups. Negative binomial models will be used to compare the number of adverse events between treated and untreated patients. Cox's proportional hazards models will be used to compare time to the first adverse event. Random effects linear models will be used to study changes in FEV_1 over time. Modelling will be performed with and without

	adjustment for potential confounders. For comparisons with the full population similar models will be used adjusting for propensity scores.
Milestones	Interim analysis will be performed 6 monthly for 3 years and then annually for 2 years, the final study report is expected in Q1 2018.

4. RATIONALE AND BACKGROUND

Bronchitol™, a spray dried mannitol, was recently granted Marketing Authorisation by the European Medicines Agency (EMA)for the treatment of CF in adults aged 18 years and above as an add on therapy to best standard of care. Safety data for Bronchitol from two large phase III studies with Bronchitol, is available for up 18 months, however long term safety data has not be collected for exposure beyond 18 months.

In an orphan disease, the exposure to a new product may take considerable time to establish a large post marketing safety experience. Pursuant to an obligation imposed by the EMA as a condition to the granting of the marketing authorisation, Pharmaxis are undertaking a post-authorisation safety study (PASS) to; confirm the safety profile of Bronchitol, identify, characterise and/or quantify any emergent safety issues, and measure the effectiveness of agreed risk management strategies.

Disease/outcome registries are important resources when seeking to collect data on drug exposure and/or other factors associated with a clinical condition. Exposure registries address populations exposed to medicinal products of interest to determine if a medicinal product has a special impact on this group of patients. Some exposure registries address exposures to medicinal products in specific populations. Patients may be followed over time and included in a cohort study to collect data on adverse events using standardised questionnaires. Simple cohort studies may measure incidence, but, without a comparison group, cannot evaluate any association between exposures and outcomes. Nonetheless, they may be useful for signal amplification particularly for rare outcomes. This type of registry may be very valuable when examining the safety of an orphan drug indicated for a specific condition. Notwithstanding some inherent limitations in registry studies, they do provide an appropriate base for surveillance studies.

The European CF community is close knit and meets and communicates regularly in order to develop a consensus on best practice. As such, management of CF in most EU countries is broadly uniform, with shared long term goals. This situation means that it is possible to undertake a registry study in a member state of the EU and extrapolate the results more broadly to the EU CF community. If significant differences in prescribing patterns are subsequently identified, the matching of patients by concomitant medication use should, in time, allow examination of specific sub-groups based on particular prescribing patterns that may be more favoured in a region.

The Cystic Fibrosis Trust in the UK currently has a well established and comprehensive patient registry. The UK CF Trust Registry represents one of the largest and most mature databases available in Europe and is broadly viewed as representative for the wider EU. Over 90 CF treatment centres in the UK contribute data to the registry and information is collected on more than 7,000 patients with CF annually.

The purpose of this study is to assess the rates of identified and potential risks of Bronchitol in CF through a comparison of Bronchitol-treated vs. non-treated patients in a matched cohort study from the CF registry over 5 year period. Safety analysis will be conducted and reported on a 6 monthly basis for the initial three year period and then annually for two years.

5. RESEARCH QUESTIONS AND OBJECTIVES

Primary Objective:

To assess the rates of identified and potential risk of Bronchitol in CF through a comparison of Bronchitol treated vs. non-treated patients in a cohort matched for key characteristics from the CF registry over a 1 to 5 year period. Safety analysis would be conducted on a 6 monthly basis for three years and then annually for two further years..

Secondary Objectives:

- To compare the rates of identified and potential risks against background rates in the general CF population.
- To assess the rate of identified and potential risks in the population below 18 years of age who may receive Bronchitol "off-label".
- To compare the effect on lung function measured by FEV1 (mL, % change and % predicted change) in Bronchitol treated vs. non-treated patients with CFin a matched cohort from the CF registry as part of an overall benefit/risk assessment.
- To compare the effect on CF exacerbations (using IV antibiotic use as a surrogate) in Bronchitol treated vs. non-treated patients in a matched cohort from the CF registry as part of an overall benefit/risk assessment.

6. RESEARCH METHODS

Study Population and Main Criteria for Inclusion:

Adult (≥ 18 years) patients in the CF registry database who are prescribed Bronchitol. The unexposed group are untreated patients. These will be matched with treated patients on key characteristics .

At the time of the study starting, Bronchitol is only indicated for adult CF patients. Nevertheless, it may emerge that there are a significant number of paediatric and adolescent (6-17 years) patients who are prescribed Bronchitol "off-label". Furthermore, in time, an indication in children is also planned. If sufficient patient numbers make it feasible, a matched cohort of non-treated patients will be identified based on similar age, disease severity and concomitant medications (rhDNase, inhaled antibiotics, chronic antibiotics, presence of chronic Pseudomonas).

Duration of Study Treatment:

As this is an observational study, no intervention will be attempted and no attempt will be made to influence treatment decisions. The goal is to retrospectively determine whether the risk factors of interest differ between treated and untreated patients.

7. STUDY DESIGN

This is an observational cohort study which aims to collect anonymised data on all subjects taking Bronchitol who contribute annual data to the UK CF Registry and matched, untreated subjects. Data from individual subjects is currently entered into the Registry database annually. Data on

treated and untreated patients will be analysed on a regular basis (at six-month intervals for the initial three years and then annually).

8. SETTING

The UK CF Trust Registry represents one of the largest and most mature databases available in Europe and is broadly viewed as representative for the wider EU. Over 90 CF treatment centres in the UK contribute data to the registry and information is collected on more than 7,000 patients with CF annually. Data for analyses for this study will be wholly derived from patients with cystic fibrosis who have evaluable data available within the UK CF Registry.

9. STUDY SIZE

This is an observational cohort study with safety as the primary endpoint. Therefore, it is desirable to include as many patients as possible to observe the safety endpoint. As the CF Registry will be used as the source data, all patients aged 18 years and older who are recorded to be taking Bronchitol and who have evaluable data available for analysis in the CF Registry will be included in the study. Bronchitol patients will be matched with untreated patients; all matched data from the Registry will be included in the analysis.

The incidences of haemoptysis and bronchospasm were reported to be similar between patients who received Bronchitol versus untreated patients in the controlled clinical trials. With the limitation of the data source, it is not practical to design a superiority study with adequate power to test a small incidence difference. Therefore the main purpose of the study is to estimate the incidence of identified AEs and their confidence intervals based on all available data from the Registry.

10. DATA ANALYSIS

This is a safety observational study, and therefore the focus is the safety endpoints (AEs of special interest).

At each analysis time a propensity score analysis will be performed. Here we will use logistic regression to estimate the probability of being treated with Bronchitol. This will generate a propensity score for each patient which will be used in subsequent analyses.

- Full Analysis Population

  All patients (treated and untreated) from CF Registry will be included in the analyses. For this population, we will include:

  - Simple descriptive analyses (frequency and percentage) for AEs

- Negative Binomial regression for the count of events for each AE with adjustment for propensity scores.
- Cox regression for time to first event for each AE (Hazard Ratio), with adjustment for propensity scores.

❖ Matched Analysis Population

Analysis for the treated and matched untreated population will include:

- Descriptive analysis of the distribution of risk factors between the two groups of patients
- Simple descriptive analyses of AEs
- Negative Binomial regression for the count of events for each AE with and without any adjustment for potential confounders
- Negative Binomial regression assessing the interaction test between treatment and each important risk factor. Each risk factor will be tested one by one

❖ Subgroup analyses

- Simple descriptive analyses and negative binomial regression (without any adjustment) for each AE for each subgroup. Subgroups will be defined a priori. Forest plots will be used to plot the Rate Ratios for all subgroups.

Cox regression will be used to study the time to first event for each AE. As for the negative binomial regression models these will be done both with and without adjustment for potential confounders.

Random effects linear models will be used to study changes in FEV_1 over time. As with other regression models these will be performed with and without adjustment for potential confounders.

11. PROTECTION OF HUMAN SUBJECTS:

In order to safeguard the well-being and rights of participants in this post-authorisation safety study, the CF Trust will comply with all relevant laws of the European Union that are directly applicable or of direct effect and all relevant laws and statutes of the UK country in which the CF Trust Patient Registry is located. These include, but are not limited to, the Human Rights Act 1998, the Data Protection Act 1998, the Medicines Act 1968, the Medicines for Human Use (Clinical Trial) Regulations 2004, and with all relevant guidance relating to medicines and clinical trials from time to time in force including, but not limited to, the ICH GCP, the World Medical Association Declaration of Helsinki entitled 'Ethical Principles for Medical Research Involving Human Subjects' (1996 version), the NHS Research Governance Framework for Health and Social Care (version 2, April 2005).

12. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Adverse events will not be reported on an expedited basis for this study as it is an observational cohort study designed to collect long-term safety information using secondary data. All safety information will be assessed and submitted in interim analysis reports and will be submitted according to the schedule agreed as part of the post-authorisation commitment for this study. A full review of the safety information collected for the full study period will be presented in the final study report.

13. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Interim analysis will be performed 6 monthly for 3 years and then annually for 2 years, the final study report is expected in Q4 2017. Interim and final safety reports from this study will be submitted to appropriate regulatory agencies.

Policies regarding the publication and presentation of study data are defined in the Service Agreement between Pharmaxis Ltd and Cystic Fibrosis Services Limited.

14. QUALITY ASSURANCE

The UK CF Registry has regular quality testing by the hosting company with respect to the encryption and safety of the data held. The application is held in Amsterdam in accordance with EU recommendations. There are elaborate encryption protocols in the production of user access including a unique person specific username and unique password. The password has to be changed every 30 days. The data can only be seen by the user site and data cannot be moved between sites without the Registry team being involved. The registry is in the process of receiving the SLSP (Short Leap Shared Protection) Certificate and has the Secure Site Pro SSL Certificate required for large databases.

Within the Registry there are inbuilt verification tools which will "flag up" any abnormal values which are out with normal ranges directly to the sites and in some instances to the Registry Team. Throughout the year regular (monthly) data verification is carried out by the Registry Team running programmes looking at unusual data entries eg: abnormal Height, Weight etc. Any queries are then reported back to the sites for verification. Any duplicate registration of patients is also checked on a monthly basis and if found records merged with no loss of data. Thus maintaining a "clean" data set of patients.

Before any data cut is requested from the Hosting Company extensive data cleaning is undertaken in conjunction with the Bio-Statisticians at Imperial College London.

The Registry is run from the Cystic Fibrosis Trust in a password protected, locked office in accordance with the Ethical requirements for approval of the Registry. The Registry Team are "trusted third parties" and conform to the Data Protection Act in full.

Centres and Clinics will be monitored on a regular basis by the Registry Team. Study monitoring visits will be scheduled with the sites on a regular basis to ensure data is recorded in the patient notes as well as on the registry and in accordance with usual practice. All entries will be checked to ensure entries are correct. If there are any discrepancies then these will be documented and then verified with the sites. The logs for these visits will be kept up to date. Random sets of patients' notes will be checked at the visits so ensuring no bias.

In addition the regular monthly data verification will be continued by the Registry Team. There is a Registry Helpdesk which answers queries within 24 hours and all sites will be encouraged to use this for any queries. In addition the Registry Team will be contactable via email and telephone.

15. FINANCING AND INSURANCE

A financial agreement will be made between Pharmaxis Ltd and the UK CF Trust prior to commencement of the study.

The study is covered under the CF Trust liability insurance policy. The certificate of insurance and essential information about the policy can be provided upon request from the CF Trust.

16. GENERALISABILITY, LIMITATIONS AND POSSIBLE BIAS

The clinical use of a newly licensed product may often be predominantly limited to a more severe patient population in the first 6-12 months. The initial subjects studied may therefore not be representative of the whole CF population; however the matching cohort strategy will limit this potential bias. Additionally, the analytical models being employed include propensity scores thus controlling for the probability of being prescribed Bronchitol.

In addition, the majority of CF centres in the UK contribute data, so the CF Registry is able to be generalised to the UK CF population. As the UK CF Registry is one of the largest and most mature databases available in Europe, it can be viewed broadly as representative for the wider EU. If however, significant differences in prescribing patterns are identified, the matching of patients should, in time, allow examination of specific sub-groups based on particular prescribing patterns that may be more favoured in a region.

A limitation of having an adult's only label is that the data analysis will only be for the adult population. As it is not possible to predict any off-label usage in children and adolescents and also usage is likely to be very small, this data will only be provided in summary format.

A limitation in using routinely collected registry data in epidemiological research is that for some outcomes, such as the acquisition of new microbial infections and increased use of oral steroids, we do not have a precise date on which the outcome occurred. As such, the date of the event will be estimated based on when the annual review encounter took place. In the first annual review after

the index date, it is therefore possible that either of these two outcomes are mis-identified as being post-index date when the event may have occurred prior.

All analysis and reporting will be done independently by Imperial College for the Cystic Fibrosis Trust and in liaison with the Lead Investigator. Pharmaxis will receive the analyses at the different time points and include them as required in reports to the international regulatory bodies.

17. MILESTONES

Start of data collection	01/07 /2012
End of data collection	30/06/ 2017
Data collection periods for interim reports	01/07 /2012 – 31/12/ 2012 01/01/ 2013 – 30/06/ 2013 01/07/ 2013 – 31/12/ 2013 01/01/ 2014 – 30/06/ 2014 01/07/ 2014 – 31/12/ 2014 01/01/ 2015 – 30/06/ 2015 01/07/ 2015 – 30/06/ 2016 01/07/ 2016 – 30/06/ 2017
Data collection period for final study report	01/07/ 2012 – 30/06/ 2017