Quinsair® (levofloxacin hemihydrate)

POST AUTHORISATION SAFETY STUDY (PASS) INFORMATION

Title	A Post-marketing, Observational Safety Study of Quinsair (Levofloxacin Hemihydrate) in Patients with Cystic Fibrosis [CLI-LEVFLAA1-01]
Version identifier	5.0
Date	13 October 2022
EU PAS register number	EUPAS20990
Active substance	Levofloxacin hemihydrate
Medicinal product	Quinsair® 240 mg nebuliser solution
Product reference	EU/1/14/973/001
Procedure number	EMEA/H/C/002789
Marketing authorisation holder (MAH)	Chiesi Farmaceutici S.p.A.
Joint PASS	No
Research question and objectives	*Primary objective* To evaluate the long-term safety of Quinsair over a five-year period (2017 to 2021) compared to other inhaled approved antibiotic therapies in CF patients who are enrolled in the United Kingdom (UK) CF Registry. The Primary objective is extended to evaluate the safety profile of Quinsair over a three-year period (2019 to 2021) compared to other inhaled approved antibiotic therapies in CF patients who are enrolled in the German CF Registry. The safety of Quinsair and other inhaled approved antibiotic therapies in CF patients will be described by the following: • Adverse events of special interest (AESIs): haemoptysis, hepatotoxicity, and tendon rupture;

	• Discontinuation of Quinsair and other inhaled approved antibiotic therapies in CF due to adverse events (AEs); • Development of antimicrobial resistance of *Pseudomonas aeruginosa (P. aeruginosa)* isolated from Quinsair-treated patients, where these data are collected in clinical practice.
Country of study	UK Germany Other EU countries with CF registries may be included if warranted to achieve sample size and if data collection methods are considered appropriate to achieve the objectives of this protocol.
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Clinical Study Code No.: CLI-LEVFLAA1-01	Version No.: 5.0	Date: 13 October 2022
EUPAS Number: EUPAS20990		

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2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Explanation
AE	Adverse Event
AESI	Adverse Event of Special Interest
BID	Twice Daily
CF	Cystic Fibrosis
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
DLP	Data Lock Point
EC	Ethics Committee
ECFS	European Cystic Fibrosis Society
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FEV_1	Forced Expiratory Volume in 1 Second
FQ	Fluoroquinolone
FVC	Forced Vital Capacity
GVP	Good Pharmacovigilance Practice
HCP	Health Care Provider
HR	Hazard Ratio
IPW	Inverse Propensity Score Weighting
IRR	Incidence Rate Ratio
IV	Intravenous
IZKS	Interdisciplinary Center for Clinical Trials, University Medical Center Mainz
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MI	Mukoviszidose Institute gGmbH
MP-376	Investigational Name for the Product Quinsair
MSM	Marginal Structural Models

NNH	Number needed to harm
P. aeruginosa	*Pseudomonas aeruginosa*
PASS	Post Authorisation Safety Study
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT	Preferred Term
RMP	Risk Management Plan
RR	Relative Risk
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Event
UK	United Kingdom

3. RESPONSIBLE PARTIES

The Marketing Authorisation Holder (MAH), Chiesi Farmaceutici S.p.A. (hereafter referred to as Chiesi), is responsible for development of this protocol. The UK Cystic Fibrosis (CF) Registry and German CF Registry will be responsible for data collection and preparation of interim and final reports subject to review and approval of the MAH. In particular, the UK CF Registry and the Interdisciplinary Center for Clinical Trials, University Medical Center of Mainz will be in charge of data analysis for UK and Germany, respectively.

The MAH is responsible for any presentations and/or publications of the data and results of this study (see section 12 for publishing rights and responsibilities).

4. ABSTRACT

4.1. Title

A Post-marketing, Observational Safety Study of Quinsair® (Levofloxacin Hemihydrate) in Patients with Cystic Fibrosis.

4.2. Rationale and Background

Cystic fibrosis is an inherited, long-term debilitating and life-threatening disease affecting approximately 0.8 people in 10,000 in the EU. The accumulation of thick mucus in the lungs in CF patients allows bacteria to grow and colonize more easily, causing chronic infections. *Pseudomonas aeruginosa* (*P. aeruginosa)* is a frequent cause of chronic pulmonary infections in CF patients. As reported in the 2015 Annual Data Report of the UK CF Registry, of the almost 11,000 CF patients enrolled, 234 (6.2%) children aged less than 16 years and 2,625/5,742 (46.5%) patients aged 16 years and older experienced a chronic *P. aeruginosa* infection. The incidence of *P. aeruginosa* steadily increased with age, peaking among patients aged 32 to 35 years at 59%. The standard of care for treating CF patients with *P. aeruginosa* has been to use inhaled antibiotic therapies chronically in order to improve lung function and quality of life and reduce the occurrence of pulmonary exacerbations.

Quinsair® 240 mg nebuliser solution is intended for the management of chronic pulmonary infections due to *P. aeruginosa* in adult CF patients. Quinsair is a new formulation of levofloxacin (levofloxacin hemihydrate) for aerosol administration. Levofloxacin is an antibacterial fluoroquinolone (FQ) acting by inhibition of bacterial DNA gyrase and topoisomerase IV enzymes. In the EU, there are four inhaled antibiotics that have been approved by the European Medicines Agency (EMA) for the treatment of chronic infection in CF patients with *P. aeruginosa*, i.e. inhaled formulations of tobramycin, aztreonam lysine, colistimethate and levofloxacin. Quinsair was granted a Centralised marketing authorisation by the European Commission through a binding decision (EU/1/14/973) on 26 March 2015, based upon the positive benefit/risk assessment

provided by the EMA.

In clinical studies, Quinsair was well-tolerated (N=472) when administered at 240mg BID (twice daily) to patients with CF with chronic *P. aeruginosa* infection for up to six consecutive cycles (N=56 who received up to 6 cycles), each comprising 28 days on treatment and 28 days off treatment.

Quinsair is intended for use as long as the physician considers the patient is receiving clinical benefit. The Pharmacovigilance Risk Assessment Committee (PRAC) requested the MAH to obtain additional data on patients treated with Quinsair in long term use. The marketing authorisation was made conditional (category 1) on an evaluation of the long-term (five-year) safety of Quinsair use in clinical practice. Hepatotoxicity, haemoptysis and tendon rupture, the development of antimicrobial resistance of *P. aeruginosa* in Quinsair treated patients and the safety of off-label use, specifically musculoskeletal events in patients <18 years, are considered important potential risks of Quinsair and are to be evaluated in this study. Off-label use and full drug development pipeline underscore desire for more safe/effective options in CF treatment (Dave Nickols, Settle, USA). The off-label use of drugs in the treatment of a specific patient is often appropriate and may represent the standard of care. However, the off-label use needs to be tracked and risks should be assessed.

In addition, discontinuations of Quinsair treatment due to adverse events (AEs) are to be evaluated. Comparison data will be obtained from patients who are treated with other approved inhaled antibiotics and not receiving Quinsair.

The current non-interventional post-authorisation safety study (PASS) with a cohort comparative design using secondary data from the UK CF Registry was considered appropriate to determine the long-term 5-year safety of Quinsair (EPAR 2015).

In the first year (2017) of data collection in the UK, only 3 patients were treated with Quinsair. Considering these very low patient numbers and in light of the aim of including at least 400 patients treated by Quinsair in this PASS, Chiesi decided to involve a new Registry using secondary data from the German CF Registry. *(For more details regarding this section please refer to section 7.0)*

4.3. Research Question and Objectives

The overall objective of the study is to evaluate long-term, five-year, safety data of CF patients who are treated with Quinsair compared to other inhaled approved antibiotic therapies in CF.

4.3.1. Primary Objective

To evaluate the safety profile of Quinsair over a five-year period (2017 to 2021) compared to other inhaled approved antibiotic therapies in CF patients who are enrolled in the UK CF Registry.

The Primary objective is extended to evaluate the safety profile of Quinsair over a three-year period (2019 to 2021) compared to other inhaled approved antibiotic therapies in CF patients who are enrolled in the German CF Registry.

Specifically, the study will evaluate the incidence and occurrence over time of each adverse event

of special interest (AESI) concerning haemoptysis, hepatotoxicity, and tendon rupture, the discontinuation of treatment due to AEs and the emergence of anti-microbial resistance of *P. aeruginosa* isolated from Quinsair-treated patients, where these data are collected in clinical practice.

4.3.2. Secondary Objective

To evaluate the safety of Quinsair off-label use in patients <18 years of age, specifically, the incidence rate of musculoskeletal events (including arthritis, arthropathy, tendinitis, other tendinopathy, and tendon rupture).

4.4. Study Design

4.4.1. Overview

This is an observational comparative cohort study involving two different CF registries (UK and Germany) using secondary data collected from patients treated with Quinsair and a comparison cohort of patients treated with other inhaled approved antibiotic therapies enrolled in the UK CF Registry between 2017 and 2021 and between 2019 to 2021 in the German CF Registry.

The cohorts of interest in each registry to be analysed are:

1. Quinsair-treated CF patients (Quinsair cohort),
2. CF patients treated with other inhaled approved antibiotic therapies (non-Quinsair comparison cohort).

Table 2.1: Secondary Data Variables to be Collected in the UK CF Registry Database. for UK and Table 2.2: Secondary Data Variables to be collected in the German CF Registry Database. for Germany in Section 9.3 depict the variables that are to be collected for this PASS. Variables that are currently collected as part of the UK and German CF Registry annual data collection process (such as haemoptysis and hepatotoxicity), as well as variables that have been added for purposes of this protocol (such as tendinitis, other tendinopathy and tendon rupture) are specified.

4.4.2. Primary Endpoints

The primary endpoints are:

- The occurrence of each AESI: haemoptysis, hepatotoxicity, and tendon rupture;
- Discontinuation of Quinsair and other inhaled approved antibiotic therapies due to AEs;
- Patterns of antimicrobial resistance of P. aeruginosa isolated from Quinsair-treated patients (where data collection methods make this information available).

Details of the endpoints are described in Section 9.7.3 Analysis of Primary Endpoints.

4.4.3. Secondary Endpoint

The secondary endpoint is the occurrence of musculoskeletal events (including arthritis, arthropathy, tendinitis, other tendinopathy, tendon rupture) in patients < 18 years of age who are using Quinsair off-label.

Details of the endpoints are described in Section 9.7.7 Secondary Endpoints: musculoskeletal events.

4.4.4 Exploratory Endpoint

The exploratory endpoint is the occurrence of pulmonary exacerbation.

Details of the endpoints are described in Section 9.7.8 Exploratory Endpoint: pulmonary exacerbations.

4.5. Population and Setting

4.5.1. Population

Inclusion criteria:

- Adult and paediatric CF patients who are enrolled in and consented to data collection in the UK CF Registry or in German CF Registry;
- Adult and paediatric CF patients who are treated with Quinsair or other inhaled approved antibiotic therapies by their health care providers (HCPs) in clinical practice.

Exclusion criteria:

- None.

4.6. Variables

The following variables will be collected annually from HCPs by the UK CF Registry and German CF Registry:

4.6.1. Demographics, Disease Characteristics and Medical History

- Demographics (age, sex, clinical centre, race, CF genotype);
- Disease characteristics (date of CF diagnosis, severity [FEV_1/FVC], pulmonary exacerbations, history of respiratory infections);
- Prior treatment with inhaled approved antibiotics for *P. aeruginosa*, prior discontinuation of or intolerance to anti-pseudomonal antibiotics, haemoptysis, liver disease (variables historically collected by the Registry).

4.6.2. Exposure

- Quinsair and other inhaled approved antibiotic therapy exposure details: dosage regimen, start and stop dates, number of days of treatment, drug utilization pattern like: cyclical (28 days ON and 28 days OFF Quinsair), alternate (28 days ON Quinsair and 28 days ON other antibiotics), continuous (28 days ON Quinsair and 28 days ON Quinsair (OFF

LABEL)), duration of treatment period, reasons for discontinuation;

- Use of other antibiotic treatment, and other medications (for example steroids, bronchodilators, other respiratory medications, CF Transmembrane Conductance Regulator (CFTR) modulating treatments, and other concomitant medications).

4.6.3. Adverse Events (Complications)

- Haemoptysis, volume and number of episodes, hospitalization required
- Liver disease, liver failure (cirrhotic, non-cirrhotic), liver enzyme elevation, suspected drug induced etiology
- Tendon rupture, location, duration, unilateral/bilateral, treatment, outcome
- Discontinuation of treatment due to AEs (dysgeusia, haemoptysis, liver disease, tendon rupture)
- Musculoskeletal events in patients < 18 years of age, including arthritis, arthropathy, tendinitis, other tendinopathy, and tendon rupture

4.7. Data Sources

The data source for this study will be secondary data collected by the UK CF Registry and German CF Registry. The UK and German CF Registries contain data for patients with CF respectively in the UK and Germany and are adequate to provide a representative sample of patients, standard of care, and prescribing practices that are generalizable to the results of other Western European countries, based on comparison of demographic and disease characteristics data collected by the UK and German CF Registry and the European Cystic Fibrosis Society (ECFS) Patient Registry. For both national CF registries and the ECFS data, similar distributions are noted for age, gender, the number of adults (≥ 18 years), FEV_1% of predicted (in patients without lung transplant) and *P. aeruginosa* infections (See Section 9.9.4 Generalisability).

4.8. Study Size

A minimum of a total of 400 patients are expected to be treated with Quinsair and included in the UK and German CF Registries over the 5-year course of the study. Enrollment will be monitored annually and, if deemed necessary, the MAH will include other national CF registries to extend data collection to meet the objectives of this protocol. The MAH will provide an assessment of enrollment and the need to include additional registries, in the first and subsequent Annual Interim Analysis Reports.

Based on available information of event rates for unexposed patients from the 2015 UK CF Registry Annual Report, a sample size of 400 Quinsair cohort patients and 400 non-Quinsair comparison cohort patients is expected to provide at least 80% power to detect a relative risk (RR) of 1.5 for haemoptysis and 1.5 for hepatotoxicity between the Quinsair cohort and the non-Quinsair comparison cohort (see Section 9.5 for details on the assumed incidence rates for the two cohorts). Tendon rupture has not been collected to date by the UK CF Registry and will be added for the purpose of this PASS. If the incidence proves to be 0.4% or higher, a sample size of 400 is expected

to provide a probability of approximately 80% to detect at least one event.

The number of patients who are treated off-label with Quinsair is expected to be low (probably n < 100), including those under 18 years of age.

4.9. Data Analysis

Analyses will be conducted on demographic, disease-related and safety annual data collected by the UK CF Registry and by the German CF Registry. The analyses will be conducted separately for each registry, for the first year on data collected in the previous year. Then, for each consecutive year until the end of the study, a cumulative analysis will be performed including data from all previous years (see also section 9.7 and the Statistical Analysis Plans for full details of the analyses).

No formal hypothesis testing is planned. No adjustment for multiplicity will be made. Missing data will not be imputed unless stated otherwise.

For each registry analyses will be conducted in the following cohorts:

1. Quinsair-treated CF patients (Quinsair cohort);
2. CF patients treated with other inhaled approved antibiotic therapies (non-Quinsair comparison cohort).

Cohorts will be open and will enroll new Quinsair and non-Quinsair patients for each of the concerned years of the study. The Quinsair cohort used in the analyses will consist of all patients who have evidence of treatment with Quinsair, i.e. newly treated patients and patients with prior exposure to Quinsair. The comparison cohort (non-Quinsair) will consist of all patients with no evidence of Quinsair treatment at any time point and evidence of treatment with another inhaled approved antibiotics (e.g., inhaled dry powder antibiotics colistimethate or tobramycin, tobramycin solution for inhalation, aztreonam lysine) in the same year. At each successive year, new Quinsair and new non-Quinsair patients will be identified and followed until the end of the study. Patients who switch from the non-Quinsair comparison cohort to the Quinsair cohort will remain in the Quinsair cohort for the duration of the study even if they have no Quinsair use in a subsequent year.

Descriptive analyses will be conducted to describe demographic features of patients.

As this is an observational study the patients treated with Quinsair may differ systematically from non-Quinsair patients; an adjustment for confounders will be conducted. As general approach, unadjusted analyses will first be presented and then adjustment for confounders and effect modifiers will be conducted.

Several factors will be evaluated as potential effect modifiers or confounding factors: age, gender, previous medication such as oral or intravenous (IV) FQ, investigational agents, other medications (with known hepatic or musculoskeletal toxicity), pulmonary exacerbation history, and prior Quinsair usage including continuous or alternating therapy. As an indicator of disease status at time of initiation of therapy, a potential further confounder variable may be FEV_1. Potential confounding factors will be used in the calculation of propensity scores for use in propensity score related analytical methodology.

One of two methods of adjusting for confounders may be used depending on sample and data

availability: 1) matching of treatment according to propensity scores or 2) reweighting using inverse propensity score weighting (IPW) as part of marginal structural models (MSM).

Incidence rates of hepatotoxicity, haemoptysis, tendon rupture and discontinuation due to AEs will be compared between the Quinsair and the non-Quinsair comparison cohorts.

The following analyses will be performed for each AESI and for discontinuation due to AEs:

1. The number and percentage of patients experiencing each AESI and crude RRs with 95% confidence intervals (CIs). Where possible adjusted relative risks with 95%CI will be calculated using log-binomial regression, on the balanced sample.
2. The incidence rate per 1000 person-years of exposure and crude incidence rate ratios (IRRs) with 95% CIs will be calculated. Comparisons of incidence rates will be performed using adjusted IRR estimates derived by negative binomial regression, on the balanced sample.
3. Time-to-event analyses to examine the time until the first event. This will include the creation of Kaplan-Meier plots and the calculation of hazard ratios (HR) from Cox regression models, on the balanced sample.

In addition, only descriptive statistics will be conducted to describe the incidence of antimicrobial resistance of *P. aeruginosa* isolated from Quinsair-treated patients (one of the primary endpoints).

The secondary objective of the study is to evaluate the safety of Quinsair off-label use in patients < 18 years of age. Specifically, in view of the known safety pharmacology of FQ, the incidence and type of musculoskeletal events (categorized as arthritis, arthropathy, tendinitis, other tendinopathy, tendon rupture) will be collected for all enrolled patients in this age group at each annual visit and reported as descriptive statistics. Pulmonary exacerbations will be also summarized for explorative purposes.

In this PASS, any off-label use identified during data collection will be considered for additional subgroup analysis. In particular, the cases of continuous Quinsair use (28 day ON-28 day ON) as mono or in combination with other approved inhaled antibiotics. Based on sample availability, AESI will be summarized by cohort distinguishing subgroup of patients using Quinsair on label from patients using Quinsair continuously (off label) at least once.

Drug utilization patterns of Quinsair and other inhaled approved antibiotic therapies (dose, whether treatment is cyclical, alternate or continuous or another regimen) will be examined.

5. AMENDMENTS AND UPDATES

Changes to the protocol will be formally amended.

Version	Date	Change History
3.0	*20th January 2017*	*First version approved by PRAC*
4.0	*9th April 2019*	*Updated protocol version in order to include German registry*

5.0	*13th October 2022*	*The following changes have been implemented:* • *Updated author information and CRP* • *Updated information of MAH contact person* • *Updated Milestone "5-Year Final Report of Study Results" to September 2023*

6. MILESTONES

Based on approval and implementation of the final protocol for this PASS, the milestone for data collection and analyses are presented in Table 1 below.

The updated milestones below are based on data collection and reporting using data from the UK CF Registry and German CF Registry.

Each year, these Registries create a data set and an annual report. The process includes a data lock point (DLP), followed by a data entry and data cleaning period when sites are queried for data discrepancies. The final data made available to the MAH each year will comprise patient data from the previous calendar year. The MAH will review the draft report provided by the two registries.

Cumulative analyses will be performed at annual intervals for 5 consecutive years, with the Final Study Reports expected to be submitted as per below timelines. Cumulative interim analyses (Years 1-4) and a final analysis (Year 5) will be completed annually during the 5-year study period.

German Registry and UK Registry Annual Interim Analysis Update Reports will be created, reviewed and submitted separately.

Table1: Study Milestones

Study Milestone	Planned Date for UK Registry	Planned Date for German
Registration in EU PAS Register	20 September 2017	NA
Start of Data Collection [b]	January 2017	January 2019
End of Data Collection [b]	December 2021	December 2021
Year 1: Annual Interim Analysis Update Report	February 2019	NA
Year 2: Annual Interim Analysis Update Report	February 2020	NA
Year 3: Annual Interim Analysis Update Report	February 2021	February 2021
Year 4: Annual Interim Analysis Update Report	February 2022	February 2022
5-Year Final Report of Study Results	September 2023	September 2023

Study has been registered in the EU PAS Register following Pharmacovigilance Risk Assessment Committee approval of final protocol and before study initiation.

[b] Per EU Good Pharmacovigilance Practices VIII.A.1, the start and end of data collection for secondary use of data are available when the analytical datasets are available.

7. RATIONALE AND BACKGROUND

7.1. Background

Cystic fibrosis is an inherited, long-term debilitating and life-threatening disease affecting approximately 0.8 people in 10,000 in the European Union. The accumulation of thick mucus in the lungs in CF patients allows bacteria to grow and colonize more easily, causing chronic infections. *P. aeruginosa* is a frequent cause of chronic pulmonary infections in CF patients. The prevalence of *P. aeruginosa* infections increases with age. Forty-six percent of patients age 16 and older have chronic *P. aeruginosa* and by the age of 32 to 35 years approximately 59% of patients with CF are chronically infected with *P. aeruginosa*, per data from the UK Cystic Fibrosis Registry (UK CF Registry Annual Report 2015). Chronic pulmonary infections due to *P. aeruginosa* in patients with CF may be serious and life-threatening and are the major contributor to lung function decline and pulmonary exacerbations leading to hospitalizations, missed days from school and work, and significant morbidity and mortality. Existing antibiotic treatments are limited by emerging resistance and loss of response, allergic reactions and limited tolerability for some patients. The standard of care for treating CF patients with *P. aeruginosa* has been to use inhaled antibiotics therapies chronically in order to improve lung function and quality of life and reduce the occurrence of pulmonary exacerbations.

Quinsair, called MP-376 in clinical trials, is an antibiotic used for treating chronic lung infection caused by the bacteria *P. aeruginosa* in adults who have CF. Quinsair is a new formulation of levofloxacin for aerosol administration. Levofloxacin is an antibacterial FQ acting by inhibition of bacterial DNA gyrase and topoisomerase IV enzymes. In the EU, there are four inhaled antibiotics that have been approved by the EMA for the treatment of chronic pseudomonas infection in patients with CF and *P. aeruginosa*, i.e. inhaled formulations of tobramycin, aztreonam lysine, colistimethate and more recently, levofloxacin. Quinsair (levofloxacin hemihydrate) was approved by the EMA in March 2015. Quinsair has a different mechanism of action relative to other inhaled antibiotics and may confer additional benefit to CF patients who continue to suffer from declining lung function and pulmonary exacerbations. The systemic form of levofloxacin, currently available in oral tablets and IV solution has been marketed as Tavanic in EU since 1997 and is approved for the treatment of lower respiratory tract infections, acute bacterial sinusitis, acute pulmonary exacerbations of chronic bronchitis, urinary tract infections and prostatitis, and inhalational anthrax (Tavanic Summary of Product Characteristics, 2013). On 18 December 2014, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, and marketing authorisation was granted on 26 March 2015 for the medicinal product Quinsair 240 mg nebuliser solution intended for the management of chronic pulmonary infections due to *P. aeruginosa* in adult patients with CF. The systemic exposure (AUC) to levofloxacin in patients after inhalation of MP-376 240 mg BID is approximately 50% of the systemic exposure that is generally achievable following oral and IV administration of 500 mg levofloxacin once daily.

7.2. Rationale

In clinical studies, Quinsair was well-tolerated when administered at 240 mg BID to patients with CF with chronic *P. aeruginosa* infection for up to six consecutive cycles (N=472), each comprising 28 days on treatment and 28 days off treatment. The safety profile of MP-376 in the paediatric CF population (aged 12 to 17 years) was similar to that in the adult population. Ninety percent of AEs were mild or moderate in severity. The most common treatment emergent adverse events (TEAEs) during MP-376 treatment (reported by ≥20% patients) were dysgeusia (abnormal/bad taste), cough, sputum increased, respiratory tract congestion, increased viscosity of bronchial secretion, fatigue, weight decreased, and paranasal sinus hypersecretion. No life-threatening or fatal AEs were reported. Although FQs as a class have been associated with a number of serious and/or life- threatening adverse reactions, no cases of tendon rupture, serious or life-threatening hepatotoxicity, Torsade de Pointes, ventricular arrhythmias, or severe cutaneous or severe hypersensitivity AEs were reported with MP-376. One patient in the Quinsair group experienced non-serious convulsion. Two cases of peripheral neuropathy were reported, both mild and resolving within a few days. Two observations of QT prolongation, both of which occurred 1 to 4 weeks after the last dose of Quinsair, were not associated with symptoms or arrhythmias, and were considered unrelated to Quinsair use. Tendinitis was reported for two patients treated with MP-376 240 mg BID, both were considered treatment-related and led to discontinuation of treatment. Bronchospasm, which is a common adverse event reported with inhaled medicinal treatment, was observed in two subjects treated with MP-376. Haemoptysis, which is a fairly common complication in patients with CF, was reported in similar proportions of patients treated with MP-376 and placebo.

Marketing authorisation of Quinsair was based on clinical data from 409 CF patients exposed to MP-376 240 mg BID in 3 controlled trials: 2 placebo-controlled single cycle studies MPEX-204 and MPEX-207 (MP-376 n=257 vs placebo n=146) studies and 1 active controlled cycle study MPEX-209 (MP-376 n = 182 vs Tobramycin Inhaled Solution (TIS) n=90). In addition, in an extension study 56 patients (treated with MP-376 in core phase) received MP-376 240 mg BID for up to 6 cycles, and 32 patients (previously treated with TIS) were treated for 3 cycles. No additional safety signals were evident from the extension study. Quinsair is intended for use as long as the physician considers the patient is receiving clinical benefit. The PRAC requested the MAH obtain additional data on patients treated with Quinsair in long term use. The marketing authorisation was made conditional (category 1) on an evaluation of the long-term, (five-year) safety of Quinsair use in clinical practice.

The current non-interventional PASS using secondary data from the UK CF Registry with a cohort comparative design was considered appropriate to determine the long-term safety of Quinsair (EPAR 2015). During long-term use, hepatotoxicity, haemoptysis and tendon rupture as well as the development of antimicrobial resistance of *P. aeruginosa* in adult patients and the safety of off-label use, specifically musculoskeletal events, in patients <18 years are considered important potential risks of Quinsair and are to be evaluated in this study.

As CF is a rare disease, existing national CF registries with extensive observational data collected are an ideal source to obtain real-world safety in a post-marketing setting for Quinsair and other inhaled approved antibiotic therapies. In addition, national CF registries have the flexibility to collect additional safety data which complements the “standard” data already being collected.

The UK CF Registry contains information on almost 10,500 CF patients (UK CF Registry Annual Data Report 2016) representing more than 23% of the 44719 CF patients reported in the combined

ECFS Annual Data Report of 2016 (ECFS Patient Registry Annual Report 2016, the most recent report available). Per the UK CF Registry and the ECFS data, similar distributions are noted for age, sex, the number of adults (≥18 years), FEV_1% of predicted (in patients without lung transplant) and *P. aeruginosa* infections. Forty-eight per cent of the patients included in the ECFS Annual Report 2016 are younger than 18 years of age. Per the UK CF Registry Report, the median age of UK CF patients in 2016 is 20 years, and 60.6% of patients are age 16 years or older.

Per the 2016 Annual Data Report of the UK CF Registry, of the 9,695 patients with an annual review, 2585 experienced a chronic *P. aeruginosa* infection (246 patients < 16 years old) and 2480 patients (230 patients < 16 years old) used at least one of the following antibiotics: tobramycin inhalation powder, aztreonam lysine and colistimethate.

In Western Europe the standard of care for treating CF patients chronically infected with *P. aeruginosa* is chronic use of inhaled antibiotic therapies to improve lung function and quality of life and reduce the frequency of pulmonary exacerbations. There have been extensive global efforts to standardize CF care through collaboration between HCPs and the ECFS.

In 2017, from the patients enrolled in the UK CF Registry, only 3 were treated with Quinsair. Considering the low number of patients treated by Quinsair in the UK, the MAH decided to involve the German Registry in this PASS.

Per the 2017 German Cystic Fibrosis Annual Report, the median age of patients enrolled was 20 years, including 58,1% of adults (≥18 years). Of the 6,106 CF patients enrolled, 35,0% experienced a chronic *P. aeruginosa* infection (10,4% patients < 18 years and 54,6% patients ≥18 years).

88.2% of CF patients aged ≥ 18 years with *P. aeruginosa* chronic infection were treated by an inhaled antibiotic and 39.2% by Azithromycin. 90.8% of CF patients aged < 18 years with *P. aeruginosa* chronic infection were treated by an inhaled antibiotic and 19.2% by Azithromycin.

Data from the UK and German CF Registries should thus be adequate to provide a representative sample of patients, standard of care, and prescribing practices (including off-label use in patients less than 18 years of age) that is representative of other Western European countries.

8. RESEARCH QUESTION AND OBJECTIVES

The overall objective of the study is to evaluate long-term, five-year, safety data of CF patients who are treated with Quinsair compared to other inhaled approved antibiotic therapies.

8.1. Primary Objective

To evaluate the safety profile of Quinsair over a five-year period (2017 to 2021) compared to other inhaled approved antibiotic therapies in CF patients who are enrolled in the UK CF Registry.

The Primary objective is extended to evaluate the safety profile of Quinsair over a three-year period (2019 to 2021) compared to other inhaled approved antibiotic therapies in CF patients who are enrolled in the German CF Registry.

Specifically, the study will evaluate the incidence and occurrence over time of each AESI concerning

haemoptysis, hepatotoxicity, and tendon rupture, the discontinuation of treatment due to AEs and the emergence of antimicrobial resistance.

8.2. Secondary Objective

To evaluate the safety of Quinsair off-label use in patients <18 years of age, specifically the incidence rate of musculoskeletal events (including arthritis, arthropathy, tendinitis, other tendinopathy, and tendon rupture).

9. RESEARCH METHODS

9.1. Study Design

9.1.1. Overview

This is an observational comparative cohort study using secondary data collected from patients treated with Quinsair and a comparison cohort of patients treated with other inhaled approved antibiotic therapies enrolled in the UK and German CF Registries.

In the UK, data collection occurs at annual patient encounters using the UK CF Registry's annual reporting form. Health care professionals caring for patients with CF at participating centres complete questions for all enrolled patients in the reporting period (year). Some variables required to meet the protocol's objectives are collected per the Registry's current practice and additional variables will supplement the current data collection to fulfill the objectives of this study.

In Germany, patients' data are documented in the German CF online register tool MUKO.web by the participating CF-sites. 75% of patients are documented by the CF centres on encounter basis several times a year. The data of these patients are aggregated by the Interdisciplinary Center for Clinical Trials, University Medical Center Mainz (IZKS) data management to an annual data set for analysis of this study. The other 25% of patients are documented by the CF centres on an annual basis. Some variables required to meet the protocol's objectives are collected per the Registry's current practice and additional variables will supplement the current data collection to fulfill the objectives of this study.

The variables below are considered of interest and will be analyzed for each interim and final report. Table 2.1: Secondary Data Variables to be Collected in the UK CF Registry Database. for UK and Table 2.2: Secondary Data Variables to be collected in the German CF Registry Database. for Germany in Section 9.3 depict the specific variables that will be collected annually.

Demographics, Disease Characteristics and Medical History

- Demographics (age, sex, clinical centre, race, CF genotype);
- Disease characteristics (date of diagnosis, severity [FEV_1/FVC], prior year history of pulmonary exacerbations;
- Prior treatment with inhaled approved antibiotics for *P. aeruginosa*, prior discontinuation of or intolerance to anti-pseudomonal antibiotics, history of respiratory infections, liver disease and haemoptysis.

Exposure

- Quinsair and other inhaled approved antibiotic therapy exposure details: dosage regimen, start and stop dates, cyclical, alternate or continuous, reasons for discontinuation;
- Use of other antibiotic treatment (oral or inhaled), and other medications (for example steroids, bronchodilators, other respiratory medications, CFTR modulating treatments, and other concomitant medications).

Primary Endpoints

The primary endpoints are:

- The occurrence of each AESI: haemoptysis, hepatotoxicity, and tendon rupture;
- Discontinuation of Quinsair and other inhaled approved antibiotic therapies due to AEs;
- Patterns of antimicrobial resistance of *P.aeruginosa* isolated from Quinsair-treated patients (where these data are collected).

Details of endpoints are presented in section 9.7.3, Analysis.

Secondary Endpoint

- The occurrence of musculoskeletal events (including arthritis, arthropathy, tendinitis, other tendinopathy, tendon rupture) in patients <18 years of age who are using Quinsair off-label.

Details of endpoints are presented in section 9.7.4 Descriptive Analysis.

Exploratory endpoint

- The occurrence of pulmonary exacerbations

9.2. Setting

9.2.1. Study Patient Population

This PASS will be based on data collected:

- Over 5 years between 2017 and 2021 through the UK CF Registry's anonymised database, which includes data from enrolled UK CF patients through specialist CF care centres. Standard data collection forms are used by the UK CF Registry to capture data related to CF itself, patient demographics, medical care, and complications of the disease.
- Over 3 years between 2019 and 2021 through the Germany CF Registry's anonymised database, which includes data from enrolled Germany CF patients through specialized CF care centres. Standard data collection forms are used by the German CF Registry to capture data related to CF itself, patient demographics, medical care, and complications of the disease.

The cohorts to be included in the study are in each country:

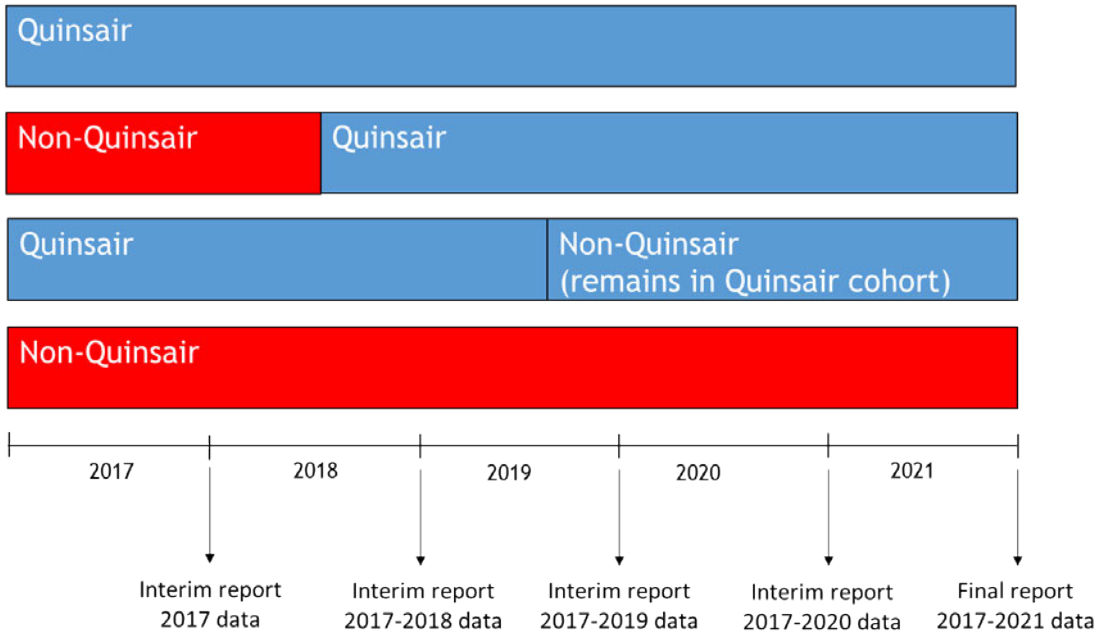
1. Quinsair-treated CF patients (Quinsair cohort); includes all patients enrolled with evidence of treatment with Quinsair at any time during the 5-year observation period.
2. CF patients treated with other inhaled approved antibiotic therapies (non-Quinsair comparison cohort); includes all patients without evidence of Quinsair treatment at any time point and with only evidence of treatment with another (or more than one other) inhaled antibiotic (inhaled dry powder antibiotics colistimethate or tobramycin, tobramycin solution for inhalation, aztreonam lysine) during the 5-year observation period of the study.

   The cohorts will be open and switching of patients may occur during the observation period. Details of how new users, continuing users, and patients who switch treatments during the study period are accounted for in section 9.7.1, Populations.

9.2.2. Cohort Schematic

Figure 1 below shows a schematic representation of the Quinsair cohort and the non-Quinsair comparison cohort over the five-year study period. For each year an Annual Interim Analysis Update Reports will be prepared including cumulative data for each consecutive year after 2017 and 2019 for UK and Germany respectively. The Final Report will include all cumulative data. The time points of drug switches in Figure 1 below were arbitrarily chosen for the purpose of the examples.

Figure 1: Study Data Collection and Reporting Schematic



In the schematic above, the first 3 bars represent patients who will be classified in the Quinsair cohort successively over their years on study; the first bar represents a patient who is treated only with Quinsair during the entire study period. The two middle bars represent patients switching treatment during the study. Patients switching from treatment with only non-Quinsair comparator inhaled antibiotics to Quinsair will be classified in the Quinsair cohort. Patients switching from Quinsair to a non-Quinsair inhaled antibiotic will remain categorized in the Quinsair cohort. The

bottom bar represents patients who are treated only with non-Quinsair comparator inhaled antibiotics during their entire time on study.

9.2.3. Inclusion and Exclusion Criteria

Inclusion criteria:

- Adult and paediatric CF patients who are enrolled in and consented to data collection in the UK CF Registry or in German CF Registry;
- Adult and paediatric CF patients who are treated with Quinsair or other inhaled approved antibiotic therapies by their HCPs in clinical practice.

Exclusion criteria:

- None.

9.3. Variables

In UK and Germany, data will be collected annually via the Registry's standard data collection form. Table 2.1 and 2.2 depict the data variables to be collected for this PASS. For each variable it is indicated whether the data are currently collected by the UK and German CF Registries respectively (eg. Standard Variable) or will be added to the standard data collection software prior to the start of the study to meet the objectives of this PASS (e.g. Additional Variables). Refer to Section 9.7.3 for details on confounding variables.

Table 2.1: Secondary Data Variables to be Collected in the UK CF Registry Database.

Variables	Standard Variables*	Additional Variables**
Demographics		
Age	X	
Sex	X	
Clinical centre	X	
Race	X	
CF genotype	X	
Disease Characteristics		
Date of diagnosis	X	
FEV_1/FVC including a best annual FEV_1 of all FEV_1 measurements	X	
Pulmonary exacerbation history	X	

History of respiratory infections (incl. hospitalisations)	X	
Medical History		
Prior treatment with inhaled approved antibiotics for *P. aeruginosa*	X	
Prior discontinuation of or intolerance of anti-pseudomonal antibiotics	X	
History of AESIs: liver disease, haemoptysis*** Liver disease: specify if enzyme elevation, cirrhosis, non-cirrhosis, other	X	
Exposure to Quinsair and other inhaled approved antibiotic therapies and concomitant medications		
Dosage regimen	X (inhaled antibiotics excl. Quinsair)	X (Quinsair)
Date started and stopped****	X (inhaled antibiotics excl. Quinsair used for 3 months or more)	X (inhaled antibiotics incl. Quinsair used for any length of time)
Cyclical *****–28 days ON and 28 days OFF Quinsair Alternate–28 days ON Quinsair and 28 days ON other antibiotics Continuous - 28 days ON Quinsair and 28 days ON Quinsair (OFF LABEL) "other" (specify)	X	-

Reasons for discontinuation	X (e.g. inhaled dry powder colistimethate and tobramycin, tobramycin inhalation solution, aztreonam lysine)	X (for Quinsair, add dysgeusia, haemoptysis, hepatotoxicity, other adverse event)
Use of other antibiotics, other medications (e.g., steroids, bronchodilators, other respiratory medications, CFTR modulating treatments, and other concomitant medications)******	X	X
Primary Endpoints		
Haemoptysis number of episodes	X	
Haemoptysis date	X	
Haemoptysis severity: • Massive (>240 ml blood loss) • Severe (>60 to ≤240 ml in24h) • Moderate (>5 to ≤60 ml in24h) • Scanty (≤5 ml in24h)	X	
• Hospitalization for haemoptysis		X
Liver disease/liver failure (cirrhotic, non-cirrhotic, hospitalization, start and stop dates, cause of death)	X (cause of death)	X (hospitalization)
Elevated liver enzymes (ALT, AST, GGT, alkaline phosphatase, bilirubin) including date drawn and elevation x ULN	X (1-3 x ULN, 3-5 x ULN, 5-10 x ULN, > 10 x ULN)	
Tendon rupture		X
Tendon rupture start date (relative to Quinsair treatment) and stop date		X
Tendon rupture location (Achilles, other, and whether unilateral or bilateral)		X

Tendon rupture treatment (medications, physical therapy, surgery, hospitalisation, etc.)		X
Tendon rupture outcome		X
Emergence of resistance to antibiotics (where data are collected in clinical practice)	X	
Secondary Endpoint		
Musculoskeletal events in CF patients <18 years old	X (arthritis, arthropathy)	X (tendinitis, other tendinopathy, tendon rupture)
Exploratory Endpoint		
Pulmonary exacerbation reported in the last 12 months	X	

*Standard variables are currently collected by the UK CF Registry in their standard data collection form.
**Additional variables will be added to the UK CF Registry data collection software before the start of the study.
*** Due to limitations of data collection, history of tendon rupture, tendinitis and other tendinopathy will not be available in the Registry prior to study start.
**** Dates of treatment for Quinsair and other inhaled antibiotic comparators to include start and stop of treatment; for monthly cyclical use, off-treatment days will not be recorded as stop dates but stop date is to be recorded as the date when treatment ceases.
***** Cyclical use as defined here is not a pre-specified option on the registry. It will be identified from "alternate" case regimen where only Quinsair is recorded.

****** Systemic FQ use will be reported if use is currently being collected by the UK CF Registry; not all instances of systemic FQ use are captured. Due to limitations of Registry historic data collection, history of prior FQ use will not be reported.

Table 2.2: Secondary Data Variables to be collected in the German CF Registry Database.

Variables	Standard Variables*	Additional Variables**
Demographics		
Age	X	
Sex	X	
Clinical centre	X	
Race	X	
CF genotype	X	

Disease Characteristics		
Date of diagnosis	X	
FEV1/FVC including a best annual FEV1 of all FEV1 measurements	X	
Pulmonary exacerbation history	X	
History of respiratory infections (incl. hospitalizations)	X	
Medical History		
Prior treatment with inhaled approved antibiotics for *P. aeruginosa*	X	
Prior discontinuation of or intolerance of anti-pseudomonal antibiotics	X	
History of AESIs: liver disease, haemoptysis*** Liver disease: specify if enzyme elevation, cirrhosis, non-cirrhosis	X cirrhosis, non-cirrhosis	
Exposure to Quinsair and other inhaled approved antibiotic therapies and concomitant medications		
Dosage regimen	X (inhaled antibiotics excl. Quinsair)	X (Quinsair)
Date started and stopped****	X (inhaled antibiotics excl. Quinsair used for 3 months or more)	X (inhaled antibiotics incl. Quinsair used for any length of time)
Cyclical *****–28 days ON and 28 days OFF Quinsair Alternate–28 days ON Quinsair and 28 days ON other antibiotics Continuous - 28 days ON Quinsair and 28 days ON Quinsair (OFF LABEL)	X	-

"other" (specify)		
Reasons for discontinuation	X (e.g. inhaled dry powder colistimethateand tobramycin, tobramycin inhalation solution, aztreonam lysine)	X (for Quinsair, add dysgeusia, haemoptysis, hepatotoxicity, other adverse event)
Use of other antibiotics, other medications (e.g., steroids, bronchodilators, other respiratory medications, CFTR modulating treatments, and other concomitant medications)******	X	
Primary Endpoints		
Haemoptysis number of episodes	X	
Haemoptysis date	X	
Haemoptysis severity: • Massive (>240 ml blood loss) • Severe (>60 to ≤240 ml in24h) • Moderate (>5 to ≤60 ml in24h) Scanty (≤5 ml in24h)	X	
• Hospitalization for haemoptysis		X
Liver disease/liver failure (cirrhotic, non- • cirrhotic, hospitalization, start and stop dates, cause of death)	X (cause of death)	X (hospitalization)
Elevated liver enzymes (ALT, AST, GGT, alkaline phosphatase, bilirubin) including date drawn and elevation x ULN	X (1-3 x ULN, 3-5 x ULN, 5-10 x ULN, > 10 x ULN)	

Tendon rupture		X
Tendon rupture start date (relative to Quinsair treatment) and stop date		X
Tendon rupture location (Achilles, other, and whether unilateral or bilateral)		X
Tendon rupture treatment (medications, physical therapy, surgery, hospitalization, etc.)		X
Tendon rupture outcome		X
Emergence of resistance to antibiotics (where data are collected in clinical practice)	X (MRSA, 3/4 MRGN)	
Secondary Endpoint		
Musculoskeletal events in CF patients <18 years old	X (arthritis, arthropathy)	X (tendinitis, other tendinopathy, tendon rupture)
Exploratory endpoint		
Pulmonary exacerbation reported in the last 12 months	X	

*Standard variables are currently collected by the German CF Registry in their standard data collection form.
**Additional variables will be added to the German CF Registry data collection software before the start of the study.
*** Due to limitations of data collection, history of tendon rupture, tendinitis and other tendinopathy will not be available in the Registry prior to study start.
**** Dates of treatment for Quinsair and other inhaled antibiotic comparators to include start and stop of treatment; for monthly cyclical use, off-treatment days will not be recorded as stop dates but stop date is to be recorded as the date when treatment ceases.
***** Cyclical use as defined here is not a pre-specified option on the registry. We will identify this from those with "alternate" regimen indicated but only Quinsair is recorded.
****** Systemic FQ use will be reported if use is currently being collected by the German CF Registry; not all instances of systemic FQ use are captured. Due to limitations of Registry historic data collection, history of prior FQ use will not be reported.

9.4. Data Sources

The data source for this study will be secondary data collected by the UK and German CF Registries. The UK CF Registry contains all patients with CF in the UK. In 2017, the German registry MUKO.web includes over 6,106 CF patients from 91 specialized CF sites across Germany, representing approximately over 80% of all CF patients in Germany. Involvement of German CF

Registry in this PASS on top of UK CF one should be adequate to provide a representative sample of patients, standard of care, and prescribing practices that are generalizable to the results to other Western European countries during study duration.

The UK CF Registry and the German CF Registry already collect data on complications such as haemoptysis and liver disease in CF patients, and they will add variables for reporting of drug exposure and the AESI tendon rupture, discontinuation of treatment due to AEs, and musculoskeletal events in patients under age 18. See Section 9.9.4 for additional details on the generalisability of data from the UK and German CF Registry to other European countries.

9.5. Study Size

A minimum of 400 patients is expected to be treated with Quinsair and included in this study over the 5-year course of the study. Enrollment will be monitored annually and if deemed necessary, the MAH will include other national CF registries to the extent their data collection can meet objectives of this protocol. The MAH will provide an assessment of enrollment and need to include additional registries in the first and subsequent Annual Interim Analysis Reports.

The prevalence of haemoptysis (12.6%), captured as blood loss of at least 5 mL or greater in24 hours, was reported for CF patients aged 16 years and older in 2015 UK CF Registry Annual Report.

In the CF clinical trials with MP-376, haemoptysis was captured and defined differently. Any blood in sputum, including streaking, was to be captured and the incidence of haemoptysis was reported as a single Preferred Term (PT) and as a pre-defined MedDRA grouping (including PTs bronchial haemorrhage and sputum discoloration). Further, patients with a history of active haemoptysis (> 30 mL) within 30 days prior to enrollment were excluded from trial participation. In a pooled analysis of all CF efficacy and safety studies (including the placebo-controlled MPEX- 204, MPEX-207 and the active-controlled MPEX-209 studies) the incidence rate of haemoptys is in the MP-376 treatment group was 23% (94/409) [95% CI 19 to 27.4] compared to 21% (31/146) [95% CI 14.9 to 28.8] in the placebo group (Quinsair EU RMP SV11.3). As a single PT, haemoptysis was reported in 14.9% of patients in the MP-376 group compared to 11.6% in the placebo group. Given that haemoptysis occurs frequently as a manifestation of the underlying CF disease and has been reported in similar proportions across clinical trials to that reported with the other inhaled antibiotic treatments, the risk for haemoptysis in Quinsair-treated patients is not expected to exceed the risk observed in patients treated with comparator agents. If, however, the RR of haemoptysis is greater in Quinsair treated patients, a sample of 400 Quinsair-treated patients and 400 non-Quinsair comparison cohort patients will have 85.9% power to detect a RR of 1.5 if the incidence is 18.9% in Quinsair-treated patients and 12.6% in non-Quinsair-treated patients.

Liver disease is a common co-morbidity in patients with CF. The prevalence of increased liver enzymes was reported for CF patients aged 16 years and older in the 2016 UK CF Registry Annual Report (14.8%). The incidence of hepatotoxicity reported as an AE in the MP-376 clinical trials was 3.2% (13/409) [95% CI 1.7 to 5.4] compared to 2.1% (3/146) [95% CI 0.4 to 5.9] in the placebo group (EU RMP Sec SVII.5.1 dated November 28, 2014). The presence of active liver disease was an exclusion criterion in the MP-376 clinical trials, but is not a contraindication for treatment with

Quinsair. The risk of liver disease is expected to be similar among Quinsair and non-Quinsair treated patients. If, however, the risk of liver disease is greater in Quinsair treated patients, a sample of 400 Quinsair-treated patients and 400 non-Quinsair comparison cohort patients will have at least 90% power to detect a RR of 1.5 based on a hepatotoxicity incidence of 22.2% in Quinsair-treated patients and 14.8% in non-Quinsair-treated patients.

The rate for discontinuation of treatment due to AEs for patients was not specified in the 2015 UK CF Registry Annual Report. Based on data from MP-376 clinical trials, the RR of discontinuation of treatment due to AEs is expected to be 0.98 (12.0% discontinuations in the MP-376 group and 12.3% discontinuations in the placebo group). The most frequent reasons for discontinuation reported in the MP-376 group included disease progression (5.1%) and dysgeusia (2%). The risk of discontinuation due to AEs is expected to be similar among Quinsair and non-Quinsair treated patients. If, however, the risk is greater in Quinsair treated patients, a sample of 400 Quinsair- treated patients and 400 non-Quinsair comparison cohort patients will have 84.3% power to detect a RR of 1.5 if discontinuation is as high as 18.0% in Quinsair-treated patients and 12.0% in non-Quinsair-treated patients.

The power to detect a RR difference of 1.5 for haemoptysis, hepatotoxicity and discontinuation due to AE, between patients treated with Quinsair and patients treated with other inhaled approved antibiotics (non-Quinsair comparison cohort) is presented in Table 3 below.

Table 3: Power to Detect a Difference in AESI Rates Between the Quinsair-treated Patients and Patients Treated with Other Inhaled Approved Antibiotics

AESI	RR	AESI Rate (non-Quinsair)	AESI Rate (Quinsair)	Power (N=300; Quinsair)	Power (N=400; Quinsair)	Power (N=500; Quinsair)
Haemoptysis	1.5	12.6%	18.9%	76.8%	85.9%	91.6%
Hepatotoxicity	1.5	14.8%	22.2%	83.1%	90.9%	95.2%
Discontinuation due to AE	1.5	12.0%	18.0%	74.9%	84.3%	90.3%

Note: calculated by one-sided Fisher exact test for comparing two proportions; alpha=0.10 and equal allocation between the cohorts.

Tendon rupture has been associated with systemic FQs based on post-marketing reports. Though the incidence has been described as rare, this cannot be estimated due to the post-marketing nature of the source. The incidence of tendinitis has been estimated at less than 1/1,000 with systemic levofloxacin (Tavanic SPC) whereas tendon rupture is expected to be less common than tendinitis. No cases of tendon rupture were reported in the MP-376 clinical trials and tendinitis was reported infrequently (0.7%). Kim *et al.* reported a population background incidence for tendon rupture of 6- 37/100,000 and a 3.8-fold increased RR of tendon rupture with FQ exposure. In the same article it is reported that tendinitis frequently precedes tendon rupture (Kim *et al.* 2010). Tendon rupture has not been collected to date by the UK CF Registry and will be added for the purpose of this PASS. If the incidence of tendon rupture proves to be 0.4% or higher, a sample size of 400 is expected to provide a probability of approximately 80% to detect at least one event.

Off- label use of Quinsair for purposes of this study includes patients < 18 years. The number of patients < 18 years treated off-label with Quinsair is expected to be low (probably n<100).

9.6. Data Management

9.6.1. UK Registry Data management

The UK CF Registry takes necessary steps to ensure data accuracy and completeness. Data from the UK CF Registry can only be accessed at the user site and not be moved between sites, the Registry Team, a 'trusted third party', which fully adheres to the Data Protection Act. This team regularly monitors centres and clinics through logged study monitoring visits. The Registry is operated by the CF Trust in a locked, pass-word protected office in accordance with the ethical requirements for approval of the Registry. The Registry Team as well as a Registry Helpdesk are available to respond to queries by e-mail or telephone.

A national team based at the CF Trust maintains the UK Registry Database and takes the necessary steps to ensure its accuracy and completeness by:

- Providing training and support, including on-site visits for clinics new to the CF Registry, user guides, training video, and contextual 'help' within the data entry system pertaining to individual variables;
- Automated validation and range-checks ensure data meet pre-defined quality criteria at point of entry;
- Manual data quality checks to pick up nuanced clinical data issues; both by the in-house UK CF Registry team and analytical team at Imperial College London with input from the Principal Investigator.

A national team maintains the UK CF Registry Database by:

- Maintaining the quality of data in the national database;
- Verification of all data returned from clinics. Only data that passes the stringent quality checks is merged into the national UK database. Data for a complete calendar year is merged in March of the following year;
- Once all the data is merged, the Registry team maintains the integrity of the data by ensuring the data is robust, complete and accurate;
- Assisting with data entry for participating centres;
- Software development and support.

Data security by the Cystic Fibrosis Trust is ensured by:

- Using a file storage system called BOX for downloads of pseudonymised and anonymised data from the UK CF Registry accessible by the Registry team only;
- BOX is HIPAA compliant and certified for EU and Swiss Safe Harbour frameworks. Files are encrypted at point of entry (TLS multi layered encryption at rest with 256-bit AES encryption keys stored at separate locations) with individual files password protected and user access controlled with full audit trails. The data centres use biometric entry authentication, CCTV and 24/7 armedguard;
- The core UK CF Registry Database runs off a dedicated ISO 27001, 27017 and 27018

certified Europe-based Microsoft Azure server. The software incorporates two factor authentication and password strength criteria. There is a full audit trail of login attempts and activity on the site. Independent penetration testing is carried out in line with major software updates to ensure no vulnerabilities are introduced;

- Identifiable information from the Registry is only accessed in a healthcare environment (e.g. when data are inputted at a CF centre) or within the dedicated UK CF Registry office at CF Trust. Any required physical documentation is kept in a locked cabinet in this room, which itself is unlocked when unoccupied. Keys are only held by authorized members of the UK CF Registry team;
- Standard Operating Procedures (SOPs) govern staff training and Registry processes such as site set up and data requests. All Registry staff undertake annual Good Clinical Practice training.

9.6.2. German Registry Data management

The German CF Registry is a database of CF patients in Germany maintained by the Mukoviszidose Institute GmbH (MI). The MI is the operator of the German CF registry and is a non-profit limited company for therapeutic research and development (MI) and is a wholly-owned subsidiary of the Mukoviszidose e.V. (German cystic fibrosis association). The registry aims to record, analyze and improve the CF patients care in Germany. In 2017, the registry included over 6,106 CF patients from 91 CF-sites across Germany, representing approximately over 80% of all CF patients in the country.

Patient data are documented in the German CF registry in the online register tool MUKO.web by the participating CF-sites. Data management is done by IZKS. IZKS is a 'trusted third party', which fully adheres to the Data Protection Act. Standard Operating Procedures (SOPs) govern IZKS staff training and processes such clinical monitoring and data analysis. All staff undertake regularly Good Clinical Practice training.

Data quality is the responsibility of the CF-sites and IZKS. This is regulated in contracts between CF-sites and IZKS and MI.

The IZKS maintains the German Registry Database and takes the necessary steps to ensure its accuracy and completeness by:

- Data can only be accessed by authorized users and the IZKS.
- IZKS is available to respond to queries by e-mail or telephone.
- IZKS provides training and support, user guides, training webinars.
- IZKS assists with data entry for participating centres

Standardized processes are established to check data quality:

- The IZKS regularly monitors centers and clinics by on-site visits.

- An automated validation and range-check is established to ensure that data meet the pre-defined quality criteria at point of entry.
- IZKS performs regular manual data quality checks to secure verification of date and integrity of data.
- Duplicates are regularly merged by the identification management
- Lost-to-follow up checks are carried out

Data security:

- The Registry is operated in a locked, pass-word protected area in accordance with the ethical requirements. Data security is ensured by password protection and user access control with full audit trails.
- Identifiable information from the Registry is only accessed in a healthcare environment (e.g. when data are inputted at a CF center) or within the IZKS.

9.7. Data Analysis

Registries will conduct analyses on demographic, disease-related and safety data annually. The analyses will be conducted for the first year on data collected in the previous year. Then, for each consecutive year until five years, a cumulative analysis will be performed including data from all previous years.

A detailed analysis plan is presented in a separate statistical analysis plan (SAP) for each registry. For the UK CF Registry, all analyses will be performed by biostatisticians at the UK Cystic Fibrosis Trust and for the German CF registry by a biostatistician at the IZKS.The final analyses will conform to the analysis specifications described in the SAP.

No formal hypothesis testing is planned. No adjustment for multiplicity will be made. Missing data will not be imputed unless stated otherwise.

Cumulative analyses will be performed at annual intervals during the 5-year study period, subject to the review and approval of the MAH. The Annual Interim Analysis Update Reports are intended to be submitted annually in conjunction with the Quinsair PSUR. A Final Study Report (all data through Year 5) is intended to be submitted in February 2023.

9.7.1. Population

The cohorts to be included in the study are:

1. Quinsair-treated CF patients (Quinsair cohort) includes all patients in the UK CF Registry or German CF Registry with evidence of treatment with Quinsair at any time during observation period. The Quinsair cohort for the analyses below will consist of all patients who have evidence of treatment with Quinsair at any time during observation period.

   The interim analysis at Year 1 will include all patients starting Quinsair at any point during

the first year of the observation period (2017 in UK and 2019 in Germany). For the cumulative interim analysis at Year 2, the patient sample of the Year 1 interim analysis (including Quinsair and non-Quinsair patients) will be expanded by new patients starting treatment with Quinsair and new comparison cohort patients with evidence of treatment with another inhaled approved antibiotic in the second year of the observation period. The same process will be followed for the interim analyses at Year 3 and 4, and for the final analysis.

Patients switching from the non-Quinsair comparison cohort (i.e. those treated with other inhaled approved antibiotics) to the Quinsair cohort will be classified in the Quinsair cohort. Patients switching from Quinsair to a non-Quinsair product will remain categorized in the Quinsair cohort.

The Quinsair cohort for each period (year) of analysis will include:

a. Patients who newly started treatment with Quinsair
b. Patients who are continuing with Quinsair treatment
c. Patients who were treated with Quinsair in a prior period and are no longer using Quinsair
a. Patients using Quinsair in rotation with other antibiotics

2. CF patients treated with other inhaled approved antibiotic therapies (non-Quinsair cohort). This cohort will include all patients without evidence of Quinsair treatment at any time point and only with evidence of treatment with another (or more than one other) inhaled approved antibiotic (e.g., inhaled dry powder antibiotics colistimethate or tobramycin, tobramycin solution for inhalation, aztreonam lysine) during the 5-year observation period of the study. The patient sample of the Year 1 interim analysis will be restricted to non- Quinsair treated patients. The same process will be followed for the interim analyses at Year 3 and 4, and forthefinal5-year analysis.

   This may further be restricted to specific inhaled antibiotics to construct drug-specific comparison cohorts.

   Adult cohorts will include all patients in the cohort reporting age 18 years or older at Day 1. Paediatric cohorts will include all patients in the cohort reporting age < 18 years at Day 1.

9.7.2. Descriptive Analysis

Continuous variables will be summarized using descriptive statistics such as number of observations (n), mean, standard deviation, medium, minimum and maximum. Categorical variables will be tabulated using frequency (n) and percent (%).

Descriptive analyses will be conducted to describe the demographic features of patients. In addition, only descriptive statistics will be conducted to describe the incidence of antimicrobial resistance of *P. aeruginosa* isolated from Quinsair-treated patients (one of the primary endpoints) and the incidence of primary and secondary endpoints for patients who are treated off-label with Quinsair including patients <18 years.

9.7.3. Analysis of Primary Endpoints

As this is an observational study the patients treated with Quinsair may differ systematically from non-Quinsair patients; therefore, an adjustment for confounders will be conducted. As general approach, unadjusted analyses will first be presented and then adjustment for confounders and effect modifiers will be conducted.

Several factors will be evaluated as potential effect modifiers or confounding factors: age, gender, previous medication such as oral or IV FQ (where this information is available), investigational agents, other medications with known hepatic or musculoskeletal toxicity, if reported), pulmonary exacerbation history, and prior Quinsair usage, including continuous or alternating therapy. As an indicator of disease status at time of initiation of therapy, a potential further confounder variable may be FEV_1. Potential confounding factors will be used in the calculation of propensity scores for use in propensity score related analytical methodology.

Two methods of adjusting for confounders may be used depending on sample and data availability:

1. matching of treatment according to propensity scores

   or

2. reweighting using inverse propensity score weighting (IPW) as part of marginal structural models (MSM).

For the first method, propensity scores are estimated from the data as the probability of treatment assignment given selected baseline confounders and using a logistic regression model.
For the second method, MSM will be applied to re-weight the two treatment cohorts to remove the influence of confounding factors using IPW.
The marginal approach will first reweight the patients so that both treatment cohorts have a similar confounder distribution and create a balanced sample to be used for the analysis.
This is the preferred method over patient matching on propensity scores because it does not exclude Quinsair treated patients if a suitable propensity score matched control patient cannot be found.

9.7.4. AESIs (i.e., haemoptysis, hepatotoxicity, tendon rupture) in adult CF patients

The AESIs (i.e., haemoptysis, hepatotoxicity, tendon rupture) in adult CF patients will be compared between the Quinsair and the non-Quinsair cohort as follows:

1. The number and percentages of patients experiencing the event of interest and corresponding number of events in the two cohorts will be calculated at each applicable time point (i.e. year of reporting). In addition, crude RRs (with corresponding 95% CIs) will be calculated by dividing the proportion of patients experiencing the event of interest in the Quinsair cohort by the proportion of patients experiencing that event in the non-Quinsair comparison cohort. Where possible adjusted relative risks with 95%CI will be calculated using log-binomial regression, on

the balanced sample.

2. Incidence rate for the event of interest will be calculated in the two cohorts by dividing the number of events reported during follow-up by the sum of person-years at risk in that cohort and summarized in each cohort with associated 95% CI. The sum of person-years at risk in the cohort is defined as the duration as the sum of total duration of the observation period for all patients in that cohort (i.e. from day of first intake to end of period, consent withdrawal or death, whichever comes first). Adjusted incidence rate ratios (IRRs) together with 95% CIs will be also be estimated by negative binomial regression models on the balanced sample.
3. Time-to-event analyses will be performed for each AESI (haemoptysis, hepatotoxicity, tendon rupture) to examine the time to the first event of interest.
   i Kaplan-Meier (KM) estimates and 95% CIs will be calculated based on estimated variance for log-log transformation of the estimate.
   ii Event free survival will be compared between the cohorts using the log rank test. KM time to event curves will be presented.
   iii Adjusted hazard ratios (HR) together with 95% CIs will be also be estimated by using the propensity scores as a covariate to the Cox regression models on the balanced sample.

9.7.5. Discontinuation due to (AEs)

For premature discontinuation of Quinsair treatment or other inhaled approved antibiotic therapies due to AEs, the reason for discontinuation and the timing of discontinuation relative to start of Quinsair treatment will be collected. Discontinuation due to AEs will be analyzed as described for AESI.

9.7.6. Patterns of antimicrobial resistance of *P. aeruginosa* isolated from Quinsair-treated patients

The number and percentage of patients presenting positive reports of *P. aeruginosa* resistance to fluoroquinolone (FQ)and multidrug-drug resistant (MDR) will be presented. Summaries will be based on the adult Quinsair cohort. In addition to the analyses based on the adult Quinsair cohort, subgroup analysis will be performed based on the Quinsair cohort treated as indicated or with other patterns of use. Only descriptive statistics will be done for this endpoint and the data are expected to be sparse.

9.7.7. Secondary Endpoints: musculoskeletal events

The secondary endpoints are the occurrence of musculoskeletal events (arthritis, arthropathy, tendinitis, other tendinopathy, and tendon rupture) in patients < 18 years of age to describe paediatric cohorts.

Number and percentage of patients reporting each musculoskeletal endpoint event will be summarized. Analyses will be performed as those described for the primary endpoints.
Analyses above will be performed at year 1, and in consecutive years up to year 5 for the paediatric

Quinsair and non-Quinsair cohorts.

9.7.8. Exploratory Endpoint: pulmonary exacerbations

The number and percentages of patients with pulmonary exacerbation and corresponding number of events in the two cohorts will be calculated at each applicable time point (i.e. year of reporting). Exacerbation rate will be calculated in the two cohorts by dividing the number of events reported during follow-up by the sum of person-years at risk in that cohort and summarized in each cohort with associated 95% CI. Analyses above will be performed at year 1, and in consecutive years up to year 5 for the Quinsair and non-Quinsair cohorts.

9.8. Data Quality

The hosting UK CF Registry performs regular quality testing with regard to encryption and safety of the data held in accordance with EU recommendations and in compliance with the applicable regulations including those concerning protection of personal data. All entries are checked for accuracy with discrepancies documented and verified with the sites. The UK CF Registry has data validation rules included in their data collection system that will report values out of the normal range directly to the sites and, in some instances, to the Registry Team. Throughout the year, monthly data verification is carried out by the Registry Team by monitoring unusual data entries (e.g., abnormal height and weight) where sites are queried for verification. In addition, monthly checks are performed to check for duplicate registration of patients; if found, records are merged without loss of data, thus maintaining a "clean" data set of patients. Following the annual data cut, extensive data cleaning is undertaken in conjunction with the biostatisticians at the UK Cystic Fibrosis Trust in London. Data completeness, which is assessed each year, is high: in 2016 95% of the records contained complete data (91% after exclusion of newly diagnosed patients).

In the German CF Registry, data quality is the responsibility of the CF-sites and IZKS. This is regulated in contracts between CF-sites and IZKS and MI. The IZKS maintains the German Registry Database and takes the necessary steps to ensure its accuracy and completeness Data cleaning and data management is done by IZKS. In the German CF registry, many of the entries (e.g. size, weight, FEV1) are automatically checked for correctness by plausibility checks. Data validation tools report values outside of the normal range to the site at data entry. Data integrity checks are done by IZKS regularly throughout the year and CF sites are contacted when needed. All changes to entries in the registry are recorded by audit trail. Following the annual data cut, extensive data cleaning is undertaken by IZKS and data queries are sent to the CF-sites by IZKS. Since 2018 on-site monitoring visits are established and around 5% of the data documented in the registry are considered in this quality assurance process per year.

9.9. Limitations of the Research Methods

9.9.1. Data Availability

Secondary data from registries is prone to missing data, which can introduce misclassification of exposure and outcomes.

The UK and German CF Registries have processes in place to minimise the amount of missing data as described in Section 9.6.1 and 9.6.2.

In addition, using secondary data, the power of the study is contingent on available data with regards to the number of patients that adhere to inclusion criteria with outcomes of interest. The power of the study is discussed in Section 9.5.

Due to the inherent limitations of secondary data collection, not all the desired data variables will be able to be collected by the Registries.

One limitation of data collection will be that prior or concurrent systemic (oral or IV) fluoroquinolone use is not routinely collected by the UK CF Registry. The Registry acknowledges that a substantial proportion of CF patients will be treated with FQs in a given treatment period, however, FQ use during the reporting period will be captured only if reported by the HCP.

Until recent agreement with the UK and German CF Registries to include additional variables, the Registries did not collect prior history of tendon rupture, tendinitis, or other tendinopathy, so the analysis of any events reported during the study period will be subject to this limitation.

Testing of sputum bacterial isolates is not routinely done for susceptibility to various antibiotics; thus, the collection of these data will be limited to when such data are analyzed in clinical practice. Typically, per current clinical practice, this would be done only at the time of an initial identification of a *Pseudomonas* isolate.

Further, not all concomitant medications or supplements taken by enrolled patients are reported in the annual data collection; thus, analysis of the relationship of any events reported during the study period to Quinsair or non-Quinsair antibiotics will be subject to this limitation.

9.9.2. Confounding Bias

The observational nature of the study could introduce bias related to a skewed distribution of independent risk factors for the events of interest among Quinsair patients relative to patients treated with other inhaled approved antibiotic treatments. This potential confounding by indication can result from physician decisions to prescribe a new therapy like Quinsair to patients with more severe CF, frequent pulmonary exacerbations or reduced pulmonary reserve. Propensity score techniques will be used to adjust for the influence of confounding factors in the comparisons between the Quinsair and non-Quinsair cohorts.

9.9.3. Selection Bias

Selection bias can result, if certain patients or certain types of data are excluded or not included into the study data source. The UK and the German CF Registries seek to include all CF patients. The UK health care system is a national system with special resources committed to the recognition and care of CF patients, so it is likely that all CF patients are brought to the attention of the CF Registry. In Germany 91 experienced CF centers are highly motivated to invite every patient to join the Register. In addition, although only a subset of all patient information is reported to the Registers, the Registers make substantial efforts to ensure that information is collected uniformly across all patients. It is possible, however, that physicians may pay more attention to patients using a new drug like Quinsair and provide more detailed information to the Registries relative to other patients

where they feel the observed patterns are likely to be expected within that patient. The extent of this potential reporting bias is not known but is expected to be small.

9.9.4. Generalisability

The CF population in the UK is representative of the CF population throughout Western Europe, based on comparison of demographic and disease characteristics data collected by the UK CF Registry and the ECFS Patient Registry. The 10,500 CF patients included in the UK CF Registry in 2016 represent more than 23% of the 44719 CF patients reported in the combined ECFS Annual Data Report of 2016 (ECFS Patient Registry Annual Report 2016 the most recent report available). Per the UK CF Registry and the ECFS data, similar distributions are noted for age, sex, the number of adults (≥18 years), FEV_1% of predicted (in patients without lung transplant) and *P. aeruginosa* infections. Forty-eight per cent of the patients included in the ECFS Annual Report 2016 are younger than18.0 years of age. Per the UK CF Registry Report, the median age of UK CF patients in 2016 is 20 years, and 60.6% of patients are age 16 years or older.

Furthermore, the standard of care for treating CF patients who are chronically infected with *P. aeruginosa* throughout Western European countries has been to use inhaled antibiotic therapies chronically in order to improve lung function and quality of life and reduce the frequency of pulmonary exacerbations. There have been extensive global efforts to standardize CF care through collaboration between HCPs and the ECFS.

Data from the UK Registry will thus be adequate to provide a representative sample of patients, standard of care, and prescribing practices (including off-label use in patients less than 18 years of age) that is generalisable to other European countries.

Adding the German CF Registry in this PASS will allow collecting data from another representative CF population in Western Europe. Data from the German CF Registry have been considered adequate to provide the needed information for this PASS.

9.10. Other Aspects

At any time, the MAH may terminate this study due to any of the following:

- Data are no longer available from participating registry(ies);
- Study objectives have been met or;
- Decision by a regulatory authority.

10. PROTECTION OF HUMAN SUBJECTS

The UK and the German CF Registries are conducted in accordance with the ethical principles founded in the Declaration of Helsinki and with applicable local laws and regulations, some of which sought to implement the relevant European law requirements governing medicinal products and protection of personal data including health data.

To safeguard the well-being and rights of participants in this PASS, the UK and the German CF

Registries will comply with all relevant laws of the EU that are directly applicable or of direct effect and all relevant laws and statutes of the country in which the Registry is located. These include, for the UK CF Registry, but are not limited to, the Human Rights Act 1998, the Data Protection Act 1998, Human Medicines Regulations (SI 2012/1916) replacing certain parts of the Medicines Act 1968, the Medicines for Human Use (Clinical Trial) Regulations 2004 (although it does not apply to non- interventional studies), and with all relevant guidance relating to medicines and clinical trials, the World Medical Association Declaration of Helsinki entitled "Ethical Principles for Medical Research Involving Human Subjects" (1996 version), and the NHS Research Governance Framework for Health and Social Care (version 2, April 2005).

10.1. Ethics Committee (EC)

Informed consent is obtained by the UK CF Registry and the German CF Registry as part of the registry's patient enrolment procedures.

For the UK CF Registry and German CF Registry, patients and their parent or legal guardian are informed that participation is voluntary and that they may withdraw from the Registry at any time without prejudice to their current and future care. After answering all their questions and voluntary agreement to participation, each patient or legal representative is asked to sign and date the ICF and assent form (as applicable). Only after signing the ICF, any Registry-related activities are allowed to be performed. A copy of the completed ICF and assent form (if applicable) is provided to the patient or the legal representative.

10.2. Access to Records

Patient information is obtained and maintained by the UK and the German CF Registries. The MAH has no access to patient level identified or identifiable information.

10.3. Patient Confidentiality

To maintain patient confidentiality, all analyses will be presented by the UK CF Registry to the MAH using de-identified data ensuring patient confidentiality. All information in the UK CF Registry is held confidentially. The UK CF Registry is registered under the Data Protection Act (1998) and has Research EC approval. Patient identifier data is recorded only once for site data entry. An anonymous number is generated so that patients cannot be identified when the information from each clinic is pooled. Neither identified or identifiable data are released.

All information in the German CF Registry is collected in accordance with the national legal requirements (DSVGO: Datenschutz-grundverordnung) and treated confidentially. The registry procedure has been positively reviewed by the responsible data protection authorities. The registry is maintained in accordance with applicable laws and ethical guidelines. In the German CF Registry, identifying data of the patients are recorded and a unique pseudonym is generated from these data. This ensures that only one data record per patient will be analysed even if a patient is treated in several outpatient CF-sites.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ ADVERSE REACTIONS

Individual cases of AEs and adverse reactions will not be reported for this study because it is an observational cohort study designed to collect long-term safety information using secondary data. This is in line with EU Good Pharmacovigilance Practices (GVP) VI.C.1.2.1.2, non-interventional post-authorisation studies based on secondary use of data, which specifies that for non-interventional study designs based on secondary use of data, AE reporting of individual cases is not required. Annual Interim Analysis Update Reports and the Final Study Report will be prepared and submitted per Section 6. Individual case reports will be received by the MAH in the course of routine post-marketing pharmacovigilance. Individual case safety reports will be created as applicable to prevent duplicate reports in the global safety database.
Pharmacovigilance will review the individual cases on an ongoing basis and the aggregated data present in the annual reports for signal detection and the EMA and Competent Authorities will be notified promptly in the event of any information that affects the safety profile of Quinsair.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Annual Interim Analysis Update Reports of cumulative data and the Final Study Report of the Registry will be submitted to EMA per the milestones (see Section 6). The Interim and Final Reports will be prepared by the UK CF Registry and the German CF Registry for their respective countries contribution, subject to the review and approval of the MAH. In addition, the MAH may publish interim results from the Study in the form of abstracts and manuscripts.

The MAH is responsible for any presentations and/or publications of the data and results of this study. None of the parties involved in the management/conduct/analysis of this study may publish any study-related data without the written permission of the MAH or designated authority.
Publications and presentations proposed by the UK CF Registry or the German CF Registry, potential other selected national CF registries or local CF centres will be sent to the MAH for review and comment pursuant to the terms of the PASS services agreement between the Registry and MAH.

13. REFERENCES

1. Bradley JS, Kauffman RE, Balis DA, Duffy CM, Gerbino PG, Maldonado SD, Noel GJ. Assessment of musculoskeletal toxicity 5 years after therapy with levofloxacin. Paediatrics. 2014;134:e146-53.
2. EPAR, SmPC and RMP summary documents for Quinsair: see http://www.ema.europa.eu/ema/Quinsair.
3. ECFSPR Annual Report 2014, Zolin A, McKone EF, van Rens J et al., 2016.
4. EMA/873138/2011 Rev 1, 08 September 2014 - GVP Module VI: Management and reporting of adverse drug reactions to medicinal products.
5. Kim GK. The risk of fluoroquinolone-induced tendinopathy and tendon rupture: what does the clinician need to know? J Clin Aesthet Dermatol. 2010;3:49-54.
6. Quinsair® (levofloxacin hemihydrate) 2016 Summary of Product Characteristics.
7. Tavanic® (levofloxacin hemihydrate) Summary of Product Characteristics. Sanofi 2013.
8. UK Cystic Fibrosis Registry 2016 Annual Data Report - see www.cysticfibrosis.org.uk/registryreports.
9. German CF Register, Annual report 2017, release date October 31st 2017. See
10. https://www.muko.info/fileadmin/user_upload/angebote/qualitaetsmanagement/register/berichtsband_2017.pdf

14. ANNEX

Annex Number	Document Reference Number	Date	Title
1	N/A	2019	ENCePPChecklist for Study Protocols
2	Signature page		

ANNEX 1: ENCEPP CHECKLIST FOR STUDY PROTOCOLS (REVISION 3, AMENDED)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

ENCePP

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A'(Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies).TheChecklistisasupportingdocumentanddoesnotreplacetheformatoftheprotocolfor PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: A Post-marketing, Observational Safety Study of Quinsair (levofloxacin hemihydrate) in Patients with Cystic Fibrosis

Study reference number:
Quinsair PASS protocol 4.0 dated 9th/April/2019

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Study progress report(s)	☒	☐	☐	6
1.1.4 Interim progress report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS register	☒	☐	☐	6

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.6 Final report of study results.	X	☐	☐	6

Comments:

Section 2: Research question	Yes	No	N/A	Section Number
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	7.1, 7.2
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	8
2.1.2 The objective(s) of the study?	☒	☐	☐	8.1, 8.2
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	9.1
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	9.7

Comments:

Section 3: Study design	Yes	No	N/A	Section Number
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	9.7.2, 9.7.3
3.4 Does the protocol specify measure(s)of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	9.7.4
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.1 Is the source population described?	☒	☐	☐	9.7.1
4.2 Is the planned study population defined in terms of:				
Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2.1 Study time period?	☒	☐	☐	9.2.1
4.2.2 Age and sex?	☒	☐	☐	9.2.1
4.2.3 Country of origin?	☒	☐	☐	9.2.1

	4.2.4 Disease/indication? 4.2.5 Duration of follow-up?				9.2.1 9.2.1
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.2

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorizing exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.1, 9.3, 9.7
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.8
5.3	Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	9.1, 9.7.4
5.4	Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.1
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3, Table 2.1 and table 2.2
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	9.9.1
6.4	Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	9.7.3
7.1.1. Does the protocol address confounding by indication if applicable?	☒	☐	☐	9.7.3
7.2 Does the protocol address:				
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.9.2
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.9.3
7.3 Does the protocol address the validity of the study covariates?	☒	☐	☐	9.7.3

Comments:

Section 8: Effect modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.7.3

Comments:

Section 9: Data sources	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s)used in the study for the				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.3
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3
9.1.3 Covariates?	☒	☐	☐	9.3
9.2 Does the protocol describe the information available from the data source(s)on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	

9.3.3 Covariates?	☐	☐	☒	
Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9
10.2 Are descriptive analyses included?	☒	☐	☐	9.7.2
10.3 Are stratified analyses included?	☐	☐	☒	
10.4 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	9.7.3, 9.7.4
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.6
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.4
11.2 Are methods of quality assurance described?	☒	☐	☐	9.6
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.10

Comments:

Section 13: Ethical issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10, 10.1
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	10, 10.1
13.3 Have data protection requirements been described?	☒	☐	☐	10, 10.2, 10.3

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Protocol Main Author:

[redacted] MD
Clinical Program Leader
Chiesi Farmaceutici S.p.A.

Date:

A Post-marketing, Observational Safety Study of Quinsair (Levofloxacin Hemihydrate) in Patients with Cystic Fibrosis [CLI-LEVFLAA1-01]

Product: Quinsair® 240 mg nebuliser solution

Approval of the Post-Authorisation Safety Study Protocol by the Sponsor's Representative:

Clinical Program Leader _____ Date:_____
([redacted], MD)

EU Qualified Person for Pharmacovigilance _____ Date:_____
([redacted], MD)

Chiesi Farmaceutici S.p.A.
Via Palermo 26/A
43122 Parma – Italy

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Approval of the Post-Authorisation Safety Study Protocol by the UK CF Registry Representative:

UK CF Registry Lead Investigator _____ Date:_____

(Dr Nicholas Simmonds, M.D.
Royal Brompton Hospital and Imperial College,
London, England)

A Post-marketing, Observational Safety Study of Quinsair (Levofloxacin Hemihydrate) in Patients with Cystic Fibrosis [CLI-LEVFLAA1-01]

Product: Quinsair® 240 mg nebuliser solution

Approval of the Post-Authorisation Safety Study Protocol by the German CF Registry Representative:

German CF Registry Lead Investigator _____ Date:_____

(Dr. Lutz Nährlich, M.D.
Justus-Liebig-University Giessen
Giessen, Germany)