Amsterdam, 30 October 2019
EMA/595944/2019
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Linhaliq

International non-proprietary name: ciprofloxacin hydrochloride

Procedure no. EMEA/H/C/4394

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

6mwt	Six Minute Walk Test
ACI	Andersen Cascade Impactor
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse events of special interest
ANCOVA	Analysis of covariance
API	Active Pharmaceutical Ingredient
AUC	Area under concentration-time curve
BAL	Bronco-alveolar lavage
BIC	Biofilm Inhibitory Concentration
BR	Benefit-risk
BTS	British Thoracic Society
CE	Conformité Européenne
CF	Cystic fibrosis
CFU	Colony forming units
CFI	Ciprofloxacin for Inhalation (slow release liposomal ciprofloxacin)
CFU	Colony-forming unit(s)
Cftr	Cystic fibrosis transmembrane conductance regulator
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CLI	Control Liposomes for Inhalation
CLSI	Clinical and Laboratory Standards Institute
CRO	Contract Research Organisation
CSR	Clinical Study Report
DILI	Drug Induced Liver Injury
DLCO	Diffusing capacity of the lungs for carbon monoxide
D/L	Drug to lipid ratio
DNEL	Derived no effect level
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ERS	European Respiratory Society
EU	European Union
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FA	Full Analysis
FCI	Free Ciprofloxacin for Inhalation
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
FPD	Fine particle dose
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP	Good Laboratory Practice
GVP	Good Pharmacovigilance Practice
Hb	Hemoglobin
HR	Hazard ratio
HRCT	High resolution computed tomography
HSPC	Hydrogenated soy phosphatidylcholine
I	Intermediate
ICH	International Conference on Harmonisation
IN	Intranasal
ISR	Incurred sample reanalysis
ITT	Intention to Treat

IWRS	Interactive Web Response System
IV	Intravenous
KM	Kaplan-Meier
LLT	Lower Level Term
LOCF	Last observation carried forward
LoOI	List of Outstanding Issues
LoQ	List of questions
MAA	Marketing Authorisation Application
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
MIC	Minimum inhibitory concentration
MIC_{50}	Minimum inhibitory concentration to inhibit the growth of 50% of organisms
MIC_{90}	Minimum inhibitory concentration to inhibit the growth of 90% of organisms
MLV	Multiple-lamellar vesicle
MRMM	Mixed model repeated measures
NA	Not available
NCFBE	Non-cystic fibrosis bronchiectasis
OC	Other concern
OLE	Open label extension
PASS	Post-Authorisation Safety Study
PEBAC	Pulmonary Exacerbation Blinded Adjudication Committee
PE	Pulmonary exacerbation
PD	Pharmacodynamic
PK	Pharmacokinetic
PIP	Paediatric Investigation Plan
PLI	Placebo Liposomes for Inhalation
PP	Per protocol
PPK	Population pharmacokinetics
PRAC	Pharmacovigilance risk assessment committee
PSMF	Pharmacovigilance System Master File
PT	Preferred term
QoL	Quality of Life
QoL-B	Quality of Life Questionnaire-Bronchiectasis
R	Resistant
RMP	Risk Management Plan
ROS	Reactive oxygen species
RR	Risk ratio
S	Susceptible
SA	Scientific Advice
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SI	Saline for Inhalation
SmPC	Summary of product characteristics
SOC	System organ class
SUV	Small uni-lamellar vesicles
TAMC	Total aerobic microbial count
TEAE	Treatment Emergent Adverse Event
TYMC	Total yeast/mould count
UNS	Unspecified
US	United States
Vc/F	Central volume of distribution
Vp/F	Peripheral volume of distribution
v/v	Volume/volume ratio
WFI	Waters for injection

1. Recommendation

Based on the CHMP review of the data on quality, safety, efficacy and risk management plan, the CHMP considers that the application for Linhaliq indicated for the prevention and reduction of frequent pulmonary exacerbations in non-cystic fibrosis bronchiectasis adult patients who have chronic lung infection with *Pseudomonas aeruginosa* (*P. aeruginosa*), is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the List of Outstanding Issues (see section 6).

In addition, satisfactory answers must be given to the "other concerns" as detailed in the List of Outstanding Issues.

The major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies:

- Two Major Objections remains on Quality, relating to the control of the final product Linhaliq.
- One Major Objection on Clinical Efficacy, considering that clinical efficacy has not been established.

Questions to be posed to additional experts

None.

Inspection issues

GMP inspection(s)

A pre-approval inspection of one manufacturing facility was conducted in 2018 by FDA and closed with an acceptable outcome.

A pre-approval inspection of another manufacturing facility was planned for October/November 2018 by FDA to confirm GMP compliance, for which the facility classification decisional letter by FDA was pending at the time of this report.

GCP inspection(s)

None.

New active Substance status

The active substance ciprofloxacin hydrochloride is already authorised and marketed in the European Union.

2. Executive summary

2.1. Problem statement

2.1.1. Disease or condition

The proposed indication is: prevention and reduction of frequent pulmonary exacerbations in non-cystic fibrosis bronchiectasis adult patients who have chronic lung infection with *Pseudomonas aeruginosa*.

2.1.2. Epidemiology

The prevalence of NCFBE has been estimated at 53 to 566 cases per 100 000 inhabitants.

European registry data shows that approximately 50% of European NCFBE patients have two or more pulmonary exacerbations (PE) per year and one third require hospitalisation at least once per year. Pulmonary exacerbations (PEs) are more frequent in this group of patients and the annual frequency of PEs predicts future mortality, hospital admissions, exacerbations, and quality of life in NCFBE patients. As a major contributor to patient morbidity and healthcare costs, PEs are a key target for therapy (Polverino *et al.*, 2017).

2.1.3. Aetiology and pathogenesis

Chronic airways infection, particularly with *P. aeruginosa*, is associated with an increased frequency of PEs. *P. aeruginosa* colonisation in NCFBE is associated with increased hospitalisation, reduced FEV_1, poorer quality of life, serious morbidity and reduced life expectancy (Finch *et al.*, 2015; Loebinger *et al.*, 2009; Wilson *et al.*, 1997; Goeminne *et al.*, 2014).

In a meta-analysis of 21 observational cohort studies in a total of 3683 patients with NCFBE, *P. aeruginosa* colonisation was associated with highly significant and consistent increases in all markers of disease severity, including mortality (odds ratio [OR] 2.95, 95% confidence interval [CI] 1.98-4.40; p<0.0001), hospital admissions (OR 6.57, 95% CI 3.19-13.51; p<0.0001) and exacerbations (mean difference 0.97 per year, 95% CI 0.64-1.30; p<0.0001). Furthermore, patients with *P. aeruginosa* had worse quality of life (St George's Respiratory Questionnaire [SGRQ]; mean difference 18.2 points, 95% CI 14.7-21.8; p<0.0001). (Finch *et al.*, 2015).

2.1.4. Clinical presentation, diagnosis

High-resolution computed tomography (HRCT) is the diagnostic test of choice for NCFBE, using criteria that include the following: (1) the internal diameter of the bronchus is larger than that of its accompanying vessel; or (2) the bronchus fails to taper in the periphery of the chest. Although airway wall thickening is often present, this radiographic finding is not diagnostic of bronchiectasis, as it is seen in other airway diseases such as asthma and COPD.

2.1.5. Prognosis

The meta-analysis conducted by Finch *et al.* (2015) concluded that *P. aeruginosa* is associated with an approximately 3-fold increased risk of death and an increase in hospital admissions and exacerbations in adults with NCFBE.

2.1.6. Management

The European Respiratory Society (ERS) guidelines on the management of NCFBE in adults (Polverino *et al.*, 2017) recommend long-term inhaled antibiotic treatment (≥3 months) in NCFBE and chronic *P. aeruginosa* infection in adults experiencing three or more pulmonary exacerbations per year. The guidelines are conditional recommendations for off-label use based only on a moderate level of evidence, as there are currently no authorised medicinal products for the treatment of NCFBE patients with chronic lung infection with *P. aeruginosa*.

Several randomised trials of nebulised antibacterial agents (including tobramycin, gentamicin, colistimethate, aztremonam) have been conducted in patients with NCFBE. Despite a significant reduction in *P. aeruginosa* bacterial density, most have shown poor tolerability due to bronchospasm even in the context of protective bronchodilators. In a recent hospital-based review of 146 patients using nebulised antibacterial agents for recurrent pulmonary exacerbations (PEs) of NCFBE between 2010 and 2016, 41% discontinued long-term treatment due to bronchospasm at a median treatment time of 7 weeks; 100% of patients with a test dose FEV1 decline > 15% who had co-administration of bronchodilators stopped the nebulised antibacterial drug treatment during the study due to bronchospasm despite the attempts to mitigate irritation with protective bronchodilators (Njafuh, 2017).

There is an unmet need for more effective interventions to reduce the frequency and severity of PEs in NCFBE patients with chronic *P. aeruginosa* infection, given the significant morbidity and mortality associated with these events.

2.2. About the product

Linhaliq is a new formulation of an old drug, combining liposomal encapsulated aqueous ciprofloxacin hydrochloride (ciprofloxacin for inhalation, CFI) and free aqueous ciprofloxacin hydrochloride (free ciprofloxacin for inhalation, FCI) in a fixed ratio, for administration using a commercially available nebuliser and compressor.

The active ingredient in Linhaliq is ciprofloxacin hydrochloride, a well-established, broad-spectrum, anti-pseudomonal fluoroquinolone antibiotic that is commercially available in more than 100 countries.

2.3. The development programme/compliance with CHMP guidance/scientific advice

CHMP Scientific Advice (SA) on clinical aspects of the development programme was first sought in 2011 (EMA/CHMP/SAWP/727418/2011) and follow-up advice on clinical and quality aspects was sought in 2016 (EMA/CHMP/SAWP/404122/2016 and 404123/2016).

The main issues discussed were the appropriateness of the non-clinical and clinical development programmes including choice of primary and secondary endpoints. The follow-up advice concerned an alteration of the analysis strategy for the primary endpoint of the phase III studies (see section 3.3.5. Clinical efficacy). The clinical programme was conducted in keeping with the received advice.

2.4. General comments on compliance with GMP, GLP, GCP

There are no concerns regarding compliance with GMP.

There are no concerns regarding compliance with GLP.

Potential concerns regarding compliance with GCP, were raised by the post-unblinding review and re-adjudication of study data, which is further discussed in Sections 3.3.6. and 3.3.7.

2.5. Type of application and other comments on the submitted dossier

- Legal basis – This application concerns a centralised procedure and has been filed as a mixed application in accordance with article 8(3) (NCE) of Directive 2001/83/EC and Regulation 726/2004.
- Accelerated procedure – Not applicable
- Conditional approval – Not applicable
- Exceptional circumstances – Not applicable
- Biosimilar application – Not applicable
- 1 year data exclusivity – Not applicable
- Significance of paediatric studies – On 13 February 2017, the applicant received a decision (P/0023/2017) from the Agency agreeing to a Paediatric Investigation Plan (PIP) (EMEA-001563-PIP02-15), comprising three deferred clinical studies of Linhaliq for treatment of cystic fibrosis related bronchiectasis associated with *P. aeruginosa* infection, and a waiver for the paediatric population from birth to less than 4 years of age, on the grounds that clinical studies are not feasible.

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

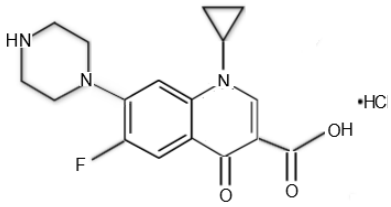
The finished product is presented as a nebuliser solution containing in total 189 mg of ciprofloxacin as active substance in two separate vials; one with 135 mg ciprofloxacin as a liposomal formulation and one with 54 mg as a free ciprofloxacin solution.

Other ingredients are: hydrogenated soy phosphatidylcholine (HSPC), cholesterol, histidine, sodium chloride, ammonium sulphate, sulphuric acid, sodium acetate (for pH adjustment), sodium hydroxide (for pH adjustment), glacial acetic acid (for pH adjustment) and water for injections.

The product is available in two separate Type I clear glass vials with siliconised rubber stopper and blue or red flip-off, tear-off aluminium seal. Each vial contains 3 mL solution.

3.1.2. Active Substance

The drug substance is ciprofloxacin hydrochloride, $C_{17}H_{18}FN_3O_3 \bullet HCl$, Mw=367.8 (anhydrous), with the structural formula:



Ciprofloxacin hydrochloride has a monograph in Ph. Eur.

A QP-declaration according to the EMA template and based on on-site audit is provided from the manufacturer responsible for batch release in the EU.

Ciprofloxacin is sparingly soluble in water and the solubility is pH dependent with higher solubility at low pH. Sufficient solubility of the drug substance is achieved at pH about 3.5 or lower.

The specification for ciprofloxacin hydrochloride is presented. Ciprofloxacin is controlled according to the Ph. Eur. monograph with additional tests for residual solvents, endotoxins and bioburden. The absence of a test for particle size is sufficiently justified. There is one question regarding the specification limit for bacterial endotoxins that needs to be clarified.

3.1.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Linhaliq consists of two vials; one liposomal formulation (ciprofloxacin for inhalation, CFI, 135 mg in 3 mL, 45 mg/mL) and one buffer solution (free ciprofloxacin for inhalation, FCI, 54 mg in 3 mL, 18 mg/mL). The finished product is prepared by the patient at time of use by pouring the contents of the two vials into the nebuliser. It is recommended that Linhaliq be used as soon as possible after preparation, not to exceed 3 hours.

The development goal was for a long-term stable formulation of ciprofloxacin achieving targeted delivery to the lung and sustained high concentrations with once a day dosing regimen.

Ciprofloxacin for inhalation (CFI)

CFI is an aqueous liposomal dispersion in which ciprofloxacin is added as a solid to an existing dispersion of small uni-lamellar vesicles (SUVs) composed of hydrogenated soy phosphatidylcholine HSPC)/cholesterol membranes.

The liposomes are characterised by cryo-TEM, ^{31}P-NMR, Differential Scanning Calorimetry (DSC) and dynamic light scattering. Additional, the zeta potential is evaluated.

Free ciprofloxacin for inhalation (FCI)

The objectives for FCI were to achieve a fully solubilised solution of ciprofloxacin at as high concentration as possible, at a pH and buffer capacity that when the FCI solution is mixed with the liposomal ciprofloxacin formulation it produces a dispersion that is stable and appropriately buffered for oral inhalation.

The liposomal ciprofloxacin formulation (CFI) requires refrigerated storage for stability and since the two vials would be packaged and stored together, a chemically and physically stable FCI formulation when stored at 2-8°C was developed.

Linhaliq – nebuliser dispersion

The clinical evaluation of 6 mL Linhaliq in the Phase 3 clinical trials ARD-3150-1201 and ARD-3150-1202 was performed The PARI LC® Sprint nebuliser with blue insert powered by the PARI Vios compressor was selected for use in North and Latin America and Asia. Outside North and Latin America and Asia, the PARI LC® Sprint nebuliser with blue insert was used with the PARI TurboBOY S or SX compressors.

The pharmaceutical development is, in general, conducted according to the quality guideline on inhalation products (EMEA/CHMP/QWP/49313/2005 Corr) but the requirements are not fully met and some characteristics needs to be further addressed. Additional information on physical characteristics, extractables and leachables, drug delivery rate and total drug delivered, shaking requirements and compatibility is requested.
An aerosol characterisation study was performed to characterise the aerosol particle size distribution using both Andersen Cascade Impactor (ACI) and laser diffraction (HELOS). The results showed that there is no meaningful difference in the aerosol performance or particle size distribution across the studied formulations when measured by either ACI or laser diffraction. The final mixture of CFI and FCI is administered by a CE marked nebuliser system (PARI LC Sprint nebuliser with PARI TurboBOY SX compressor).

Manufacture of the product and process controls

Cholesterol, ammonium sulphate, sodium chloride, sodium acetate, L-histidine, sodium hydroxide, sulphuric acid, glacial acetic acid and water for injection (WFI) are tested to compendial standards. Hydrogenated soy phosphatidylcholine (HSPC) is tested according to an in-house specification. Cholesterol is sourced from sheep wool referring to a valid TSE CEP.

Ciprofloxacin for inhalation (CFI)

The manufacturing process consists of lipid dissolution, lipid multiple-lamellar vesicle (MLV) formation, extrusion to small uni-lamellar liposomes (SUVs), diafiltration, ciprofloxacin loading, diafiltration, pre-filtration, sterile filtration, aseptic filling into vials and packaging. The process is described in sufficient detail.

Process validation has been performed. The results indicate that a liposomal formulation with the desired quality can be manufactured.

Free ciprofloxacin for inhalation (FCI)

The manufacturing process consists of dissolution of ciprofloxacin in acetate buffer, sterile filtration, filling into vials, terminal thermal sterilisation and packaging. The process is described in sufficient detail.

Process validation has been performed and the results indicate that a ciprofloxacin buffer solution with the desired quality can be manufactured.

Process validation of the sterilisation process has been successfully completed on three production scale batches of FCI.

Product specification, analytical procedures, batch analysis

The release and shelf-life specification for the finished product is presented. There are no specifications on Linhaliq since it is only formed at the time of use. The quality is controlled through release testing for its two components (CFI and FCI).

Ciprofloxacin for inhalation (CFI)

The liposomal formulation (CFI) is controlled according to an in-house specification. All limits, except for elemental impurities, are acceptable. The proposed limits for degradation products are sufficiently justified. The methods are sufficiently described and validated.

Aerodynamic particle size distribution (APSD) is a critical parameter and a test using cascade impaction will be included as part of the release and stability specification. An updated specification including specification limits justified by data should be provided. The method used should be fully validated and validation results should be provided. Reduced testing is not acceptable at the time of approval. This is raised as major objection.
Zeta potential will also be included as part of the release and stability specification. Justified limits should be provided.

No risk assessment with respect to the potential presence of elemental impurities in the drug product in accordance with ICH Q3D is performed. A control strategy to test each batch is applied and Class 1 and 3 elements are included in the release specification. The proposed acceptance limits is calculated according to ICH Q3D Option 2a. The maximum daily dose is converted to daily lung dose by correcting by the mean FPD. According to the guideline this may be applicable when local effect is expected. For an inhalation product, other fractions than the FPD may be absorbed and therefore the acceptance limit should be calculated assuming worst case scenario by using the maximum daily dose without correction. The acceptance limits for elemental impurities should be recalculated. Batch analyses results comply with the specifications.

Free ciprofloxacin for inhalation (FCI)

The free ciprofloxacin solution (FCI) is controlled according to an in-house specification. The test parameters and all limits, except for elemental impurities, are acceptable. The methods are sufficiently described and validated.

Batch analyses results are provided. All results comply with the specifications. Elemental impurities (ICH Q3D) testing was performed post release testing for the registration batches.

Linhaliq – nebuliser dispersion

No release testing is performed on the drug product after preparation for use. Liposomal formulations are dispersions and homogenous distribution of the active substance throughout the dispersion needs to be addressed. The aerodynamic particle/droplet size distribution is a critical parameter for dispersions and should be controlled. Tests covered by release specifications for any of the individual components (CFI and/or FCI) do not need to be repeated provided that it is demonstrated that they are not affected by the mixing process. The nebulisation process might disrupt the liposomes or modify the liposome size and shape and thereby impact the release rate. Therefore, it needs to be further demonstrated that the aerodynamic particle/droplet size distribution (APSD) of Linhaliq dispersion can be correlated by the APSD of the CFI component and that the addition of FCI does not alter the aerodynamic size distribution performance. It should be demonstrated by data that the proposed specification limit for APSD for the CFI component is sufficient to ensure consistent quality of the final product to be administered to the patient (i.e. Linhaliq). This is raised as major objection.

Stability of the product

Ciprofloxacin for inhalation (CFI)

Based on the provided stability data the proposed shelf-life of 2 years with the storage condition "Store in a refrigerator (2–8°C)" is accepted. Data are also provided demonstrating that storage up to 28 days at room temperature (25°C) is acceptable.

Free ciprofloxacin for inhalation (FCI)

Based on the provided stability data the free ciprofloxacin for inhalation (FCI) is stable up to 3 years when stored in a refrigerator (2–8°C). Since FCI and ciprofloxacin for inhalation (CFI) is co-packed in the same carton the accepted shelf-life of the combination pack is 2 years with the storage condition "Store in a refrigerator (2–8°C)".

3.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Two major objections remains on the control of the CFI component and the final product Linhaliq dispersion. In addition, some other concerns need to be resolved prior to an approval.

3.2. Non clinical aspects

3.2.1. Pharmacology

Primary pharmacodynamics

Ciprofloxacin is a broad-spectrum fluoroquinolone antibiotic. The bactericidal action of ciprofloxacin results from inhibition of the enzymes topoisomerase II (DNA gyrase) and topoisomerase IV, which are required for bacterial DNA replication, transcription, repair, and recombination. The applicant has conducted in vitro and in vivo studies to address the primary pharmacodynamics of Linhaliq. However, since the data generated from these studies are an intricate part of the clinical efficacy data they are presented and assessed in conjunction with the clinical data (see section 3.3. Clinical aspects).

Secondary pharmacodynamics

Secondary pharmacodynamics studies have been conducted to evaluate the efficacy of Linhaliq against infections by other bacteria than *P. aeruginosa*. These studies have not been assessed since the proposed indication in the current application is infection with *P. aeruginosa*.

No data on off target receptor binding has been presented. This is considered acceptable since the pharmacology of ciprofloxacin is well known.

Safety pharmacology

No standard safety pharmacology or cardiovascular safety study was performed. The applicant describes a 3-month repeat dose toxicity study in rat and a 9-month repeat dose toxicity study in dog in which the CNS and cardiovascular safety profile are discussed in more detail. No standard evaluation on CNS function was performed, only clinical observations twice daily.

The assessment of cardiovascular safety parameters was included in the 9-month dog study (8800-1445). In the first round of this procedure the data from the ECG tracings was not to be found. The individual ECG tracings, numerical data, and interpretations have been presented by the applicant.

Respiratory function was assessed as respiratory rate, minute volume and tidal volume, measured pre, during and post administration. The effects of ciprofloxacin in different formulations on respiratory function were assessed in 3 repeat dose toxicity studies in rat, and 1 in dog. The studies in rat showed that free ciprofloxacin and the Linhaliq-prototype (which includes free ciprofloxacin) was associated

with significant decrease in respiratory rate in both male and female rats. After two weeks of daily administrations with free ciprofloxacin, the respiratory rate decreased with 26 and 37 % in male and female rats during treatment. The respiratory rate in animals administered Linhaliq decreased with 40% in male rats and 48% in female rats. The liposomal formulations (CFI) were associated with decreases in tidal volume and minute volume (-43-55%), mainly in female rats. The effects of empty liposomes on the respiratory function were investigated in one rat study. The liposomes alone were also associated with decreased respiratory function (decrease in respiratory rate -28% during the first week of treatment). Inhalation of empty liposomes or the CFI formulation in dogs was not associated with any effects on respiratory function. See further discussion on species difference in the toxicology section.

Pharmacodynamic drug interaction

No data on pharmacodynamic drug interactions has been presented. Since ciprofloxacin is a known active substance and the systemic exposure will be lower than when administered i.v. or orally, this is considered acceptable.

3.2.2. Pharmacokinetics

Nonclinical PK studies with Linhaliq administered via the pulmonary route have been conducted in mouse, rat, dog, and rabbit. In addition, systemic pharmacokinetic literature data exist for ciprofloxacin administered via oral and IV routes, including analysis of its absorption, metabolism, distribution, and excretion.

The liposomal formulation of ciprofloxacin, CFI, was designed with the goal to retain a high concentration of ciprofloxacin in the lungs over 24 hours. The initial pharmacokinetic studies were designed to confirm high concentration of ciprofloxacin at the intended site of action.

Methods of analysis

A series of analytical and bioanalytical methods were developed and validated in order to support the Linhaliq nonclinical program. For non-GLP-compliant PK and absorption and metabolism studies, concentrations of ciprofloxacin or ciprofloxacin-related radioactivity in plasma or tissues were analyzed using multiple methods including liquid scintillation counting, liquid chromatography/tandem mass spectrometry (LC-MS/MS), and UV detections with high performance liquid chromatography (UV/HPLC) bioanalytical methods. Validated GLP-compliant bioanalytical methods were also developed for the quantification of ciprofloxacin to support the pivotal repeated-dose toxicology studies performed in rats (3 months) and dogs (39 weeks).

Absorption

Following intra nasal administration in mice, the half-life of clearance from the lung was <15 min for the free ciprofloxacin and 9.4 hours for the liposomal formulation. The pharmacokinetics of free ciprofloxacin administered intravenously was investigated in rats and dogs. The t1/2 in rats was approximately 2 hours and 3 hours in dogs. The liposomal ciprofloxacin formulation for inhalation (CFI) was investigated in rabbit. CFI was administered by inhalation daily for 5 days where after ciprofloxacin was measured in lung tissue, fluid and cells from the lavage fluid. The Cmax in the lung tissue was 72 µg/g and in plasma 0.14 µg/mL. Exposure at day 5, expressed as AUC0-24 was 0.87 µgxh/mL in plasma and 794 µgxh/g in lung tissue. The t1/2 in the lung tissue was 10.2 h and in the lung fluid 8.3 h.

Distribution

No specific distribution studies have been conducted with Linhaliq or CFI. The lack of specific distribution studies is acceptable considering the data publically available on ciprofloxacin administered orally and IV. Ciprofloxacin has a low protein binding (20-30%) and has a steady state distribution volume of 2-3 L/kg body weight.

Metabolism

In humans, after oral or IV administration of ciprofloxacin, four metabolites are detected; desethylene ciprofloxacin (M1), sulfociprofloxacin (M2), oxociprofloxacin (M3), and formylciprofloxacin (M4); these are excreted in urine and to a lesser extent in faeces. All the metabolites have antimicrobial activity, but are less active than unchanged ciprofloxacin. All four metabolites were detected in rat and dog after inhalation of Linhaliq or CFI. In rats, sulfociprofloxacin was the main metabolite with AUCs <1% of the parent in males and 4.8-5.6 % of the parent in females. Desethylene ciprofloxacin was the main metabolite in dogs with AUCx 4.7-5.8% of the parent.

Excretion

No specific excretion studies have been conducted with Linhaliq or CFI. It is expected that the excretion of ciprofloxacin absorbed from the lung and potentially swallowed following inhalation of Linhaliq, would be similar to ciprofloxacin that reaches the systemic circulation when given orally or by IV but at much lower concentrations. In humans, after both IV and oral administration, ciprofloxacin is excreted unchanged both renally and, to a lesser extent, faecally. Ciprofloxacin undergoes both glomerular filtration and tubular secretion.

Pharmacokinetic drug interactions

No pharmacokinetic drug interaction studies have been performed with Linhaliq or CFI. The pharmacokinetic interactions are expected to be similar to those of ciprofloxacin given orally or IV.

3.2.3. Toxicology

Linhaliq is a mixture of equal volumes of ciprofloxacin for inhalation (CFI) and free ciprofloxacin for inhalation (FCI), that are combined in a nebulised to produce a mixture of 35 mg/mL ciprofloxacin.

The toxicology studies supporting the MAA have been performed both with the ciprofloxacin liposome formation (CFI) itself and as the mixture formulations of CFI and FCI (Linhaliq or as other prototype mixtures of CFI and FCI). Linhaliq itself has been evaluated in a set of non-clinical studies including a single-dose study in dogs, repeat-dose toxicity studies for up to 3 months in rats and up to 9 months in dogs; and in a 2-year carcinogenicity study in rats. CFI has been evaluated in single-dose studies in rats and dogs, repeat-dose toxicity studies for up to 3 months in rats and up to 1 month in dogs. Additionally, in vitro and in vivo genotoxicity tests have been performed.

Ciprofloxacin has been in clinical use for long time in humans (as I.V and oral routes) and accordingly a mixed MAA is presented by the Applicant. Thus, no studies on developmental and reproductive toxicity studies have been done with Linhaliq which is considered acceptable.

Based on metabolic pattern, the species selected for toxicology testing (rat and dog) are considered relevant for human safety assessment, as all main human metabolites have been identified in these animal species.

The initial toxicology studies with Linhaliq were conducted only in rats since this species was considered to be more susceptible; however, following treatment, the rats developed lung fibrosis. In

view of this situation, the CHMP recommended (EMEA/H/SA/2140/1/2011/SME/III) conducting a longer-term toxicity study in an appropriate non-rodent species. Accordingly, the Applicant conducted a 9-month inhalation toxicology study of Linhaliq in dogs as a second species. The CHMP agreed in the follow-up Scientific Advice ((EMEA/H/SA/2140/1/FU/1/2016/SME/III) with the choice of species, duration, and route of exposure. Furthermore, although CHMP had not requested it in the former Scientific Advice (22 September 2011), the applicant also completed a 2-year inhalational carcinogenicity study of Linhaliq in rats (8800-1454) as required by the US FDA.

All in vivo studies were performed via inhalation which is the intended clinical administration route and were done using a PARI LC® plus nebuliser. In two of the acute studies (8800-1373 and 880-1374) and one of the repeat dose study (8800-1378) another nebulisers were tandemly used. But it was found that the aerosol output from the other nebulisers were not consistent, making it problematic to achieve constant aerosol concentrations leading to overdosing in the repeat toxicity study and death of some animals. Concordantly the other nebulisers were not used in the following repeat dose studies of Linhaliq.

Single-dose inhalation toxicity

The acute toxicity of inhalation of CFI and FCI/CFI were studied in rats and dogs. The acute toxicity appears to be low and no lethality occurred in the animals. Clinical signs include decrease in food consumption in both species and lung foci in rats. The lung foci observation in rats was dose dependent, but whereas it was due an increase dose of ciprofloxacin and/or the liposomes could not be evaluated. Consequently, the local effect and tolerance of ciprofloxacin and liposomes respectively, were monitored throughout the repeat toxicity studies.

Repeat-dose inhalation toxicity in rats

Several studies were conducted in rats. One of them only investigates the liposome ciprofloxacin (CFI) formula and not the combined mixture and free ciprofloxacin and CFI (8800-1375), whereas in 8800-1377 and 8800-1378 no liposome controls were included. These studies still give some information about the toxicity of ciprofloxacin, even though it cannot be discerned which adverse effects are due to ciprofloxacin or the liposomes.

Overall, the target organs of toxicity in rats were nasal turbinates, larynx and lung. The most noteworthy findings in these studies were the decrease in pulmonary function and macrophage accumulation and larynx squamous hyperplasia-metaplasia. These effects were dose-related, but if they are due to direct effects of ciprofloxacin or from the liposomes could not be determined. However, the results indicate that at least some of these findings may be induced by the empty liposomes (macrophage accumulation). The most relevant repeat-dose toxicity study conducted in rats where FCI/CFI mixtures were administered together with a liposome control was a 3-month study (8800-1423). In this 3-month repeat-dose toxicity study the FCI/CFI mixture of Linhaliq was the same as the to-be marketed product, and the study design included a control group of empty liposomes. Four exposure-related deaths occurred in the Linhaliq high dose group. These animals had fungal mats in the nares leading to restricted airflow. The fungal mats are likely a result of the ciprofloxacin treatment, disrupting the normal micro-flora.

As in the shorter repeat-dose toxicity studies, macrophage aggregates the lungs findings in included observations of macrophage aggregates. Moreover, after the longer treatment period of 3 months, fibrosis in the lung was observed as in contrast to the 14 and 28 days studies. The Applicant has argued that the lung fibrosis found in all CFI dose groups and in mid and high Linhaliq dose groups is consistent with particle overload due to a high liposome pulmonary dose in these groups and not a

reflection of the inherent toxicity of ciprofloxacin itself. This is supported by the high incidence of fibrosis also in liposome control group, probably due to particle overload. Particle overload has been described as an artefact of rats as inhalation model. It occurs when the lung burden exceeds the capacity of the macrophage to clear the particles and inflammatory reactions begin to appear (Morrow, 1992 and Oberdörster, 1995). The inflammatory reactions can lead to fibrosis even with low-toxicity particles and is likely not reflective of inherent toxicity of particles. However, it is the entire product that should be evaluated and it is important to understand and discuss the underlying causes. In view of the product induced rat fibrosis, the CHMP Scientific Advice 22 Sep 2011 recommended a longer-term toxicity study in non-rodents. Subsequently the Applicant conducted a study in dogs. Concordantly, lung liposome-induced fibrosis was not found in dogs treated for 9 months as investigated by the Applicant (see below). It is known that particle overload is a problem in rats (as well as other rodents). The lower reliance on macrophage clearance in dogs and humans compared to rats supports that they are less likely to develop alveolar inflammation and lung fibrosis resulting from macrophage-mediated response to particle overload. However, since liposome capsulated ciprofloxacin is a new formulation for inhalation the clinical outcome regarding fibrosis development and other pulmonary ADRs after long-term treatment cannot be ruled out.

An interesting finding from the 3-month rat study was the lower frequency of macrophage accumulation and fibrosis observed in the high Linhaliq group as compared to high CFI group even though the target pulmonary lipid dose was the same or lower. This may indicate that free ciprofloxacin exerts some protective effects as suggested earlier in the 14-days repeat-dose toxicity studies. This may be due to an immunomodulatory effect of FCI, as discussed more in 3.2.5

In the 3-month rat study, the NOAEL was set at the Linhaliq low dose (7.0/7.8 mg/kg/day, M/F) due to the lung fibrosis at mid/high dose. Systemic exposures at NOAEL were 1.7-1.8 (AUC) and 1.9-2.3 (Cmax) above the human exposure as determined in NCFBE patients.

Larynx squamous cell hyperplasia-metaplasia of minimal to moderate severity was observed throughout the studies in both CFI and FCI/CFI exposed groups, as well as in rats exposed to liposome vehicle only. The metaplasia was not fully reversible following 28 days recovery periods and longer recovery periods (>6 weeks) are likely needed for full reversibility. It is agreed with the Applicant´s conclusion that the larynx squamous cell hyperplasia-metaplasia is likely an adaptive non-specific response to inhalation exposure of particles and should not be considered as adverse in the rat repeat-dose toxicity studies. Laryngeal metaplasia is seen in approximately 10 % of all inhalation studies performed in rodents. Rats are more susceptible to develop squamous laryngeal metaplasia than humans due to anatomic differences, and metaplasia is a direct response to repeated local irritation that typically does not progress and is generally not considered relevant to human safety (Osimitz et al 2007). No progression into neoplasia was seen in the 2-year carcinogenicity study. However, in the 2-year study, a dose-related increased incidence of larynx squamous cell metaplasia was observed with incidences in the high Linhaliq groups being 2 to 3-fold above mid dose animals and air/liposome controls, which warrant further discussion (see 3.2.5)

Repeat-dose inhalation toxicity in dogs

Two repeat toxicity studies were done using Beagle dogs. The first study was a 28-day study whereas a 9-months study was done in view of CHMP scientific advice on 22 September 2011 to study longer-term toxicity in a non-rodent species. In dogs, the target organs of toxicity were larynx and lung.

In the 28-day dog study only CFI was administered and no mixtures of FCI/CFI. Noteworthy the accumulation of macrophage was also observed in some dogs in all CFI groups as well as in the empty liposome control indicating a liposome-induced effect. In the 9-month dog study, test-article related

findings were seen in lung (infiltration, neutrophilic, septal and accumulation of macrophages). According to the Applicant this could be due to increased circulating numbers of NEUT (which may indicate inflammation), a finding that was not dose-related. A clinical observation was prolapse of the third eyelid (cherry eye) in many animals in all groups and sexes, the specific frequency not provided in the report. This is considered a common condition in Beagle dog and does not raise a safety concern.

In agreement with the rat studies macrophage accumulation and lung fibrosis were found, but the fibrosis (minimal or mild in severity) was considered incidental and not induced by liposomes since it was also found in the Air Sham controls. At terminal necropsy, the observed incidences of fibrosis were 3/8 dogs (Air Sham controls, minimal or mild), 1/8 dogs (Liposome control, mild), 1/8 dogs (Linhaliq Low, minimal), 2/8 dogs (Linhaliq Mid, minimal) and 1/8 dogs (Linhaliq High, mild). After a recovery period, fibrosis (all of mild severity) were found in 1/6 dogs (Linhaliq Low), 1/6 dogs (Linhaliq High) and 1/6 dogs (Linhaliq alternating cycles), whereas no fibrosis was seen in the Air Sham controls.

Larynx hyperplasia was not observed in dogs, but larynx mononuclear cell infiltrates (minimal to mild) were observed in 3/8 dogs in each of the empty liposome control group and Linhaliq high dose group, respectively.

Additional findings include decreased globulin, total protein, increased albumin, decreased monocytes, decreased LDH, decreased white blood cells. Many of these findings were not dose dependent and most of them were normalized after 28 days recovery.

Toxicokinetics and exposure margins

Dose-dependent relationships with exposure were generally observed across the studies, with some accumulation at higher doses. Kinetic differences between dogs and rats were noted. In dogs, the inhalation of FCI/CFI mix resulted in higher serum concentrations as compared to when only CFI was inhaled. This difference may be due to species differences in drug clearance from the lung; the rats using alveolar macrophages phagocytosis as main clearance whereas in dogs (and humans) other clearance pathways are predominant.

Margins for local effects were calculated based either on mg/kg/day or on mg/g lung weight basis. At study NOAELs, the margins based on body weight comparisons are 8.8, 7 and 3 in the 3-month rat study, the 9-month dog study and the rat carcinogenicity study, respectively. When based on calculations on lung weight, the margins are 29, 12 and 10 in the 3-month rat study, the 9-month dog study and the rat carcinogenicity study, respectively. The systemic ciprofloxacin AUC exposure margins where around 2 times the clinical exposure. The safety profile of ciprofloxacin is well established following clinical use for a long time, with 10-fold higher systemic exposures after oral and IV treatment and hence the systemic exposure is from this product is not considered a clinical concern.

The liposome concentrations used in the animal studies were higher than the liposome dose in humans, being 10-30 and 4-5 times higher in the rat and dog studies, respectively. At study NOAELs, the estimated lipid lung dose per body weight are 9.5 mg/kg/day in the rat 3-month study, 6.8 mg/kg/day in the dog 9-month study, and 2.9 mg/kg/day in the 2-year rat carcinogenicity study to be compared with 5.1 mg/kg/day in patients.

Genotoxicity

No genotoxicity studies of the combination (CFI and FCI mixture) have been performed. However, CFI and FCI, were tested in a series of *in vitro* an *in vivo* genotoxicity studies.

CFI as a suspension was not clastogenic in a mammalian chromosome aberration assay in CHO cells. Repeated inhalation doses of CFI at up to 28/29 mg/kg/day (M/F) for 28 days did not induce micronucelus formation in bone marrow or peripheral blood in rats. No *in vitro* bacterial assay was conducted due to the antibiotic properties of ciprofloxacin.

The liposome components (i.e., HSPC and cholesterol) have not been evaluated to their specific dose limits. However, since cholesterol is a natural substance present in the human body including the lung and is a component of many food products, while HSPC has composition very similar to the naturally occurring phospholipids and is an approved food and drug ingredient (GRAS designated), this is considered acceptable.

Carcinogenicity

The 2-year carcinogenicity study in rats with Linhaliq, using lung doses of 0.24 to 2.4 mg/kg/day did not reveal any significant outcomes related to either survival or tumour incidence.

No lung fibrosis was observed when the lipid pulmonary doses of 2.9 mg/kg/day and ciprofloxacin pulmonary doses of 2.4 mg/kg/day were administered (as in contrast to 9-62 mg/kg/day liposome dose and 35 mg/kg/day ciprofloxacin used in the 3 month repeat toxicity study). The results further indicate that the fibrosis observed in the 3-month rat study is due to particle overload.

However, some findings in the 2-year carcinogenicity study are noteworthy. Larynx metaplasia (minimal or mild) was observed at a higher incidence at the Linhaliq high dose (32/50 males and 24/50 females) versus in the other study groups. The incidences in the air sham and empty liposome control groups were 5/56 males and 9/54 females, and 1/56 males and 5/56 females, respectively.

Reproductive and developmental toxicity

No reproductive and developmental toxicity studies have been conducted with Linhaliq. A literature overview was provided discussing the reproductive and developmental toxicity of ciprofloxacin following oral administration. The provided information is based on an FDA review of Proquin (21-744, 2005), SmPCs for CIPRO (Bayer) and on published literature. The published data is of mechanistic character in mice and rats and no standard reproductive toxicity studies are described.

In the FDA review, it is reported that ciprofloxacin did not impaired male or female fertility in rats at oral doses up to 600 mg/kg. Embryo-foetal development studies were conducted in rats and rabbits. In rats, maternal toxicity (reductions in body weight and body weight gain) was observed at 600 mg/kg. No embryo-foetal toxicity was not observed, but an elevated incidence of rudimentary rib in foetuses from pregnant dams from the 600 mg/kg dose level. The NOAEL was 300 mg/kg. In rabbits, ciprofloxacin caused abortions in 8 of 22 pregnant females at 30 mg/kg. Foetal effects included a lower foetal weight, elevated incidence of unossified hyoid bodies, talus and 5th and 6th sternebra, and reduced number of ossified cauda vertebra. The NOAEL for embryo-foetal development was 10 mg/kg. In a pre-and post-natal study, maternal toxicity was observed at >300 mg/kg, but no adverse effects were noted in any of the reproductive parameters or in the F1 generation. The NOAEL for reproductive and developmental effects was 600 mg/kg.

In the CIPRO SmPCs, it is stated that no evidence of impaired fertility was noted in rats at 100 mg/kg. Embryo-foetal development studies were performed in rats and mice using oral doses up to 100 mg/kg revealed no evidence of harm to the foetus. In rabbits, oral ciprofloxacin dose levels of 30 and

100 mg/kg caused gastrointestinal toxicity resulting in maternal weight loss and an increased incidence of abortion, but no teratogenicity was observed at either dose level.

In addition, the Applicant refers to published data reporting that ciprofloxacin can have adverse consequences testicular function and sperm.

Following systemic exposure of ciprofloxacin to juvenile animals, effects on immature cartilage has been observed.

Taken together, although Linhaliq is associated with 10-fold lower ciprofloxacin systemic exposure, the SmPC 4.6 text includes the same recommendations as ciprofloxacin for oral and I.V administration.

Immunotoxicity

The potential immunotoxicity of Linhaliq has been evaluated by standard assessments including bone marrow cytology in the 3-month rat (8800-1423) and 9-month dog (8800-1446) studies.

In the 3-month rat study, the high-dose Linhaliq males had a low incidence (14%) of lymphoid hyperplasia of minimal severity in both the bronchial and mediastinal lymph nodes that was fully reversible following the recovery period. No treatment-related changes in the lymph nodes were observed in the 9-month dog study. There were no other microscopic changes in tissues of the immune system in rats or dog.

Bone marrow cytology revealed no Linhaliq-related effects in rats. Myeloid to erythroid ratio and lymphocyte percentages in high dose groups were similar to both saline and empty liposome controls. In dogs, changes in the bone marrow cytology associated with Linhaliq included minimal decreases in the mean M:E ratio in high dose females and sporadic, minimal to mild decreases in the M:E ratio in individual animals in all Linhaliq groups. These changes were primarily associated with minimal increases in the number of erythroid lineage cells and did not correlate with changes in indicators of circulating erythrocyte mass. Clinical pathology revealed some mild Linhaliq-related changes in hematology parameters in rats and dogs with most of them being reversible.

Taken together, there are no significant concerns regarding immunotoxicity of Linhaliq or the empty liposomes.

Impurities

The specifications for ciprofloxacin impurities and respective degradants are considered justified.

The specification of the residual solvent, used in the manufacture of the liposomal component of Linhaliq, is considered acceptable. According to ECHA, this solvent is regarded as non-genotoxic and no classification is warranted for carcinogenicity and reproductive toxicity. The maximum level is about 22-fold lower than the ECHA-derived no effect level (DNEL) for long-term inhalation exposure for the general population.

Furthermore, the identified leachables from the closed container system (i.e. the rubber stopper) in the CFI component are not considered to pose a safety concern.

Safety and biocompatibility profiles of the liposome components of Linhaliq

The Applicant has adequately discussed the safety and biocompatibility profiles of the liposome components of Linhaliq. The results of the Empty Liposome control group in the 9-month dog study indicated that there were no adverse findings as a result of treatment with the liposome component of Linhaliq. It is noted that there were lipid-related changes in the larynx (mononuclear cell infiltrate) in Empty Liposome control group animals, however after the recovery period, there was reversal of the

laryngeal findings in males, while a single female at the recovery time point had mononuclear cell infiltrates in the larynx.

RMP safety specification

The applicant did not identify any non-clinical safety findings to be considered as potential or identified risks in the RMP. This is agreed.

3.2.4. Ecotoxicity/environmental risk assessment

The Applicant has submitted an ERA using the $PEC_{SURFACEWATER}$ calculation provided in the EMEA/CHMP/SWP/4447/00 guideline. The calculated $PEC_{SURFACEWATER}$ value is 0.06 µg/mL which is above the action limit for triggering a Phase II environmental fate and effect analysis. Therefore, a Phase II environmental risk assessment for the active substance ciprofloxacin in compliance with the guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 Corr 2) is required.

3.2.5. Discussion on non-clinical aspects

The current application presents a new formulation for inhalation with a known active substance ciprofloxacin. In the available approved products, ciprofloxacin is administered orally and intravenously and the safety profile of systemic exposure is thus well supported by the clinical experience. Consequently, the lack of several studies is acceptable and is also in line with the "Guideline on the non-clinical documentation for mixed marketing authorisation applications" (CPMP/SWP/799/95). From the non-clinical perspective, the main aspect will be the effects of inhalation of ciprofloxacin in combination with the liposomal formulation.

Pharmacology

The pharmacology of ciprofloxacin is well known and for this specific product discussed in section 3.3. Clinical aspects.

The lack of specific safety pharmacology studies regarding CNS and cardiovascular safety is acceptable. The safety profile of ciprofloxacin is mainly supported by the clinical experience. The clinical experience in the safety pharmacology context is not discussed in detail the non-clinical part of the MAA. However, in the suggested SmPC in section 4.4 "Special warnings and precautions for use" the use of ciprofloxacin is associated with CNS effects, e.g. to trigger seizures and induce depressions and psychosis. Furthermore, patients with known risk factors for prolongation of the QT interval should be precautions with ciprofloxacin. No indications of such effects were observed in the nonclinical studies submitted in the current application.

Since the current application presents a new formulation that will be inhaled, the effect of ciprofloxacin on respiratory function is of special interest. Respiratory rate, tidal volume, and minute volume were included as respiratory endpoints in repeat dose toxicity studies in rat and dog. The studies in rat showed that free ciprofloxacin and the Linhaliq-prototype (which includes free ciprofloxacin) was associated with significant decrease in respiratory rate in both male and female rats. The liposomal formulations (CFI) were associated with decreases in tidal volume and minute volume, mainly in female rats. Administration of empty liposomes was also associated with decreased respiratory function. Inhalation of empty liposomes or the CFI formulation in dogs was not associated with any effects on respiratory function. Since the studies showed that respiratory effects could be induced by Linhaliq, extensive monitoring was included in the clinical studies. The results of the analysis of

respiratory functions in the clinical studies does not provide any further support to sort out the contribution of the free ciprofloxacin and the liposomal fraction.

Pharmacokinetics

The pharmacokinetic profile of ciprofloxacin was assessed in mouse, rat, rabbit, and dog. The half-life of clearance from the lung was significantly prolonged when ciprofloxacin was administered in the liposomal formulation.

The applicant claims that the release of ciprofloxacin from the liposomes takes place in the lung prior to absorption. In the first round of the procedure, the Applicant was asked to further discuss this since no data confirming this theory has been presented. No new data was presented by the applicant and it is not clear how ciprofloxacin is released from the liposomes or how the liposomal fraction is cleared. The consequences for efficacy and safety in humans can thus not be established. It is however likely that the liposomal fraction in humans is cleared similarly as the lipids in the lung, whereas in the rat, uptake of the liposomes in macrophages and T2 cells contribute. The "particle overload" observed in rats is considered a rat-specific phenomenon and not relevant to humans, see further discussion in the toxicology section.

Toxicology

Overall, the presented toxicology package is considered adequate, and the studies have been conducted in accordance with GLP, relevant guidelines and recommendations given by CHMP.

The repeat-dose toxicity studies via inhalation revealed findings in the respiratory tract include nasal turbinates (fungal mats), larynx (hyperplasia) and lungs (macrophage accumulation and fibrosis). The observation of fungal mats in the nasal turbinates is likely explained by the antibacterial activity of the high dose of free ciprofloxacin component of the Linhaliq formulation disturbing the normal microflora of the nasal cavity and made it susceptible to the fungal infection. This is unlikely to be clinically applicable since the patients will inhale Linhaliq via the mouth.

In the rat larynx, a dose-related cell hyperplasia of minimal-mild severity was observed. However, the incidence and severity was within the range commonly seen in rat inhalation studies and can be explained by the anatomic constitution of rats. Also, no larynx hyperplasia findings were observed in dogs further indicating that this constitutes a rat-specific phenomenon and is not likely to be a concern in the clinical situation. However, in the 2-year carcinogenicity study, the incidence of larynx hyperplasia was higher in the rats exposed to the highest dose of Linhaliq than expected as an inherited rat species background and in comparison to the animals exposed to lower Linhaliq doses and control vehicles (see further discussion below).

The finding of macrophage aggregation was interpreted to be an adaptive response in the presence of liposome load in the lungs. In the 3 months repeat toxicity study the macrophage aggregations were associated with inflammatory induced fibrosis. The fibrosis appeared to be related to the liposome concentrations rather than ciprofloxacin itself. This is most likely due to particle overload, a well-known phenomenon in rat inhalation studies.

Overall, the respiratory tract findings are considered likely to represent non-specific responses to extended inhalation of particles in animals, and the risk for local respiratory adverse effects in humans appears low. However, in the literature, there are a number of publications addressing potential mechanisms behind fluoroquinolone including ciprofloxacin toxicity, including formation of reactive oxygen species (ROS) and downstream effects on e.g. mitochondria and extracellular matrix. There appears not to be any respiratory toxicity associated with ROS in conjunction with the use of ciprofloxacin after oral and I.V. administration. However, there are no studies available investigating

potential ciprofloxacin-induced local toxicity, therefore ciprofloxacin influence on oxidative stress-induced toxicity in the lung cannot be ruled out.

An interesting finding in the 3-month rat study was the lower frequency of macrophage accumulation and fibrosis observed in the high Linhaliq group as compared to high CFI group even though the target pulmonary lipid dose was the same or lower. This indicate that the free ciprofloxacin exert protective effects as also suggested in the 28-days rat studies. This may be due to immunomodulatory effects of FCI. In CFI treated rats an increase in IL-1B was observed, but in Linhaliq group no IL-1B increase was seen, indicating an IL-1B inhibitory effect of FCI. According to the Applicant the FCI in Linhaliq leads to a higher local concentration than when given as CFI which is in agreement with the fact that the immunomodulatory effects of ciprofloxacin is dose-dependent. However, no data has been provided showing that local concentration of ciprofloxacin is higher after inhalation of FCI, and this assumption was based on a faster T_{max}. Therefore, it is only a hypothesis that free ciprofloxacin exerts an immunomodulatory effect in the lung.

Regarding genotoxicity, the Applicant has stated that a bacterial gene mutation assay was not conducted on CFI due to the antimicrobial activity of ciprofloxacin. In accordance with ICH S2(R1), where compounds are toxic to bacteria (e.g. antibiotics), a bacterial reverse mutation test should still be carried out because mutagenicity can occur at lower, less toxic concentrations. However, the mutagenic potential of free ciprofloxacin (concentration not stated) has been assessed for the marketed product Ciproxin and was found to be negative. On the basis of the *in vitro* and *in vivo* findings to date relating to both CFI and ciprofloxacin, it is agreed that the lack of a bacterial reverse mutation assay on CFI could be accepted. The Applicant has presented and discussed literature data relating to genotoxicity studies of ciprofloxacin, showing that ciprofloxacin was genotoxic in some *in vitro* studies, whereas all *in vivo* studies were negative. Conclusively, the weight of evidence supports that ciprofloxacin and Linhaliq is not genotoxic.

In the 2-year carcinogenicity study in rats, no treatment-induced tumors were found and the genotoxicity studies show no genotoxicity and clastogenenic effects of ciprofloxacin. Some noteworthy findings were identified in the carcinogenicity study that the Applicant was asked to further clarify upon. The incidence of larynx hyperplasia was higher in the rats exposed to the highest dose of Linhaliq than expected as an inherited rat species background and in comparison to the animals exposed to lower Linhaliq doses and control vehicles. The Applicant argues that the larynx non-neoplastic lesions are rodent-specific and do not necessary pose a concern for humans, despite that it is related to the inhalation of the test compound/product. Overall this position is largely agreed. It is well accepted that the larynx of rodents is far more sensitive than that of non-rodents to aerosol damage. The reason for the susceptibility of the rodent larynx to aerosol formulations is based on several interrelated factors, but the most important of these are believed to be anatomical, airflow related, and histological. Thus, larynx metaplasia is generally considered to be an adaptive response to inhaled xenobiotics in rats. But in some rare cases larynx metaplasia may be due to a direct toxic insult, particularly when the findings are dose-related. Considering that the incidence of larynx hyperplasia was dose-related with the highest incidence in the high CFI dose group, the results indicate that ciprofloxacin exposure itself may contribute to the metaplasia. Nevertheless, inhalation exposure of non-genotoxic compounds causing larynx squamous metaplasia in rats have never been associated with tumor formations in humans according to available literature. Accordingly, Linhaliq is unlikely to present a carcinogenic risk in humans.

No reproductive toxicity studies have been submitted, instead a literature overview has been presented. However, the overview is contradictory regarding fertility, and the applicant is asked to

provide a consistent overview regarding data on male and female fertility and a sentence in SmPC 4.6 that reflect these data (**LoOI**).

Regarding the ERA, the applicant has submitted an ERA using the $PEC_{SURFACEWATER}$ calculation provided in the EMEA/CHMP/SWP/4447/00 guideline. The calculated $PEC_{SURFACEWATER}$ value is 0.06 µg/mL which is above the action limit for triggering a Phase II environmental fate and effect analysis. Therefore, a Phase II environmental risk assessment for the active substance ciprofloxacin in compliance with the guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 Corr 2) is required. The required studies can be submitted as post-marketing measure by Q2 2020. A respective letter of agreement should be provided, including an anticipated time schedule (**LoOI**).

3.2.6. Conclusion on non-clinical aspects

From a non-clinical perspective, two 'other concerns' need to be resolved prior to an approval, see LoOI.

3.3. Clinical aspects

- ***Tabular overview of clinical studies***

Study Number and Phase	Study Design	No. of Subjects in Key Efficacy Populations	Dose, Duration	Key Efficacy Parameters Evaluated
ARD-3150-1202 (ORBIT-4) (Phase 3)	Multinational, multicentre, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of Linhaliq compared with placebo in the management of chronic *P. aeruginosa* lung infections in subjects with NCFBE with a history of PEs	FA population: 304 (206 Linhaliq, 98 placebo) PP population: 252 (176 Linhaliq, 76 placebo)	Linhaliq (6 mL, 189 mg) or placebo (3 mL CLI + 3 mL normal saline) was administered by inhalation once daily during six 56-day treatment cycles. Each treatment cycle consisted of 28 days of study drug treatment (On-Treatment Period) followed by 28 days of no study drug treatment (Off-Treatment Period). Study drug was delivered using a commercially available PARI LC® Sprint nebulizer with a PARI Vios® compressor system (North America, Latin America, and Asia) or PARI TurboBOY® S or SX (Europe, Israel, Australia, and New Zealand). A 28-day Open-Label Extension with Linhaliq was included to extend the safety database.	Primary: time to first PE by Week 48 Secondary: number of, severity of PEs; QoL-B Microbiological: efficacy, MIC, sensitivity testing Other PE endpoints Changes in spirometry Other QoL and Productivity
ARD-3150-1201 (ORBIT-3) (Phase 3)	Multinational, multicentre, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of Linhaliq compared with placebo in the management of chronic *P. aeruginosa* lung infections in subjects with NCFBE with a history of PEs	FA population: 278 (183 Linhaliq, 95 placebo) PP population: 223 (145 Linhaliq, 78 placebo)	Same as ARD-3150-1202. Study drug was delivered using a commercially available PARI LC® Sprint nebulizer with a PARI Vios® compressor system (North America and Asia) or PARI TurboBOY® S or SX (Europe, Israel, and Australia).	Same as ARD-3150-1202.
ARD-3150-0902 (ORBIT-2) (Phase 2b)	International, multicentre, randomized, double-blind, placebo-controlled study designed to evaluate the safety and efficacy of Linhaliq in subjects with NCFBE	FA population: 42 (20 Linhaliq, 22 placebo) PP population: 38 (19 Linhaliq, 19 placebo)	Linhaliq (6 mL, 189 mg) or placebo (3 mL CFI + 3 mL normal saline) by inhalation once daily during three 28-day On-Treatment Periods (Months 1, 3, and 5) followed by three 28-day Off-Treatment Periods (Months 2, 4, and 6). Study drug was delivered via a PARI LC® sprint nebulizer with a PARI TurboBOY® S compressor (Australia and New Zealand).	Primary: change in sputum *P. aeruginosa* load (log CFU/gram) from baseline to Day 28 Secondary: microbiological efficacy; time to, number of, severity of, and time to resolve PEs; changes in spirometry [a]; QoL, 6mwt, SGRQ

6mwt = 6 minute walk test; ANCOVA = analysis of covariance; CFI = Ciprofloxacin for Inhalation; CFU = colony-forming units; CLI = Control Liposomes for Inhalation; DLCO = diffusing capacity of the lung for carbon monoxide; F = female; FA = Full Analysis population; M = male; NCFBE = non-cystic fibrosis bronchiectasis; PE = pulmonary exacerbation; PK = pharmacokinetic; PP = Per-Protocol population; QoL = quality of life; QoL-B = Quality of Life Questionnaire-Bronchiectasis; SGRQ = St. George's Respiratory Questionnaire.

[a] Pulmonary function tests (spirometry) were assessed as an efficacy measure in ARD-3150-0902.

3.3.1. Pharmacokinetics

Pharmacokinetic data of orally inhaled ciprofloxacin has been derived from five clinical studies. The final Linhaliq formulation was investigated in ARD-3150-1202 and ARD-3150-1201: global Phase 3 studies that evaluated the safety and efficacy of once daily Linhaliq (6 mL) in NCFBE patients with chronic *P. aeruginosa* lung infections. These studies were of identical design, except for the inclusion of a pharmacokinetics (PK) substudy in the Open-Label Extension of ARD-3150-1201.

In addition, a prototype formulation of Linhaliq combining 45 mg/mL CFI with 21.6 mg/mL FCI was used in Study ARD-3100-0801, a Phase 1 study in healthy volunteers and NCFBE patients. Pharmacokinetic data was also obtained from earlier studies using liposomal ciprofloxacin (CFI) alone: Study ARD-3100-0701 and ARD-3100-0702.

The pharmacokinetic studies aim at characterising the pharmacokinetics in plasma and sputum of orally inhaled ciprofloxacin and are mainly descriptive. The aim is to achieve high ciprofloxacin concentrations in the lung (sputum) and a low systemic exposure.

Methods

Analytical methods

The quantitation of ciprofloxacin in human plasma and sputum samples collected from subjects in the Phase 3 clinical studies, ARD-3150-1201 and ARD-3150-1202, was achieved using the LC/MS/MS assay method

Pharmacokinetic data analysis

Pharmacokinetic data was analysed using non-compartmental methods, as well as in a population pharmacokinetic analysis.

The population pharmacokinetics (PPK) models were developed based on data from the two Phase 3 studies ARD-3150-1201 and 3150-1202 (sparse sampling) including the PK-substudy of ARD-3150-1201 (rich sampling, n=16). Separate models for sputum and plasma were developed (plasma 341 subjects and sputum 323 subjects). Due to the presence of unexpected plasma ciprofloxacin concentrations at day 57, these data were excluded from the estimation of PK parameter values. Results indicated that for approximately 1/3 of subjects with measurable day 57 plasma concentrations (n=34; 11% in the analysis dataset), the observed concentration was likely due to prolonged exposure after the day 28 inhaled dose. The applicant postulated that the remaining 2/3 of observed concentrations at day 57 may reflect administration of non-study ciprofloxacin between days 28 and 57. Initial structural models were built using the intensively sampled data from the PK-substudy. Exploratory modelling found that models estimated using the full dataset did not converge successfully or parameter estimates were not plausible. As such the best models developed with the PK substudy data were considered the "final model". For plasma the final model was a 2-compartment distribution model with first-order input and first-order clearance. For sputum the final model was a 1-compartment distribution model with zero-order input and first-order clearance. No demographic covariate model building was undertaken for the current analysis.

Absorption

ARD-3100-0801

This randomised, cross-over study compared single doses of CFI and a prototype Linhaliq formulation (equal volumes of 45 mg/mL CFI and 21.6 mg/mL FCI) in healthy volunteers and in NCFBE patients.

The three treatment arms administered to healthy adults (n=8 with data) with a 5-day washout were:

A: CFI (1.5 mL: 67.5 mg) plus saline (1.5 mL) delivered using the PARI LC Sprint jet nebulizer and the AKITA dosimetric system;

B: Linhaliq-prototype (99.9 mg) comprised of CFI (1.5 mL; 67.5 mg) plus FCI (1.5 mL; 32.4 mg) delivered using the PARI LC Sprint jet nebulizer and the AKITA dosimetric system;

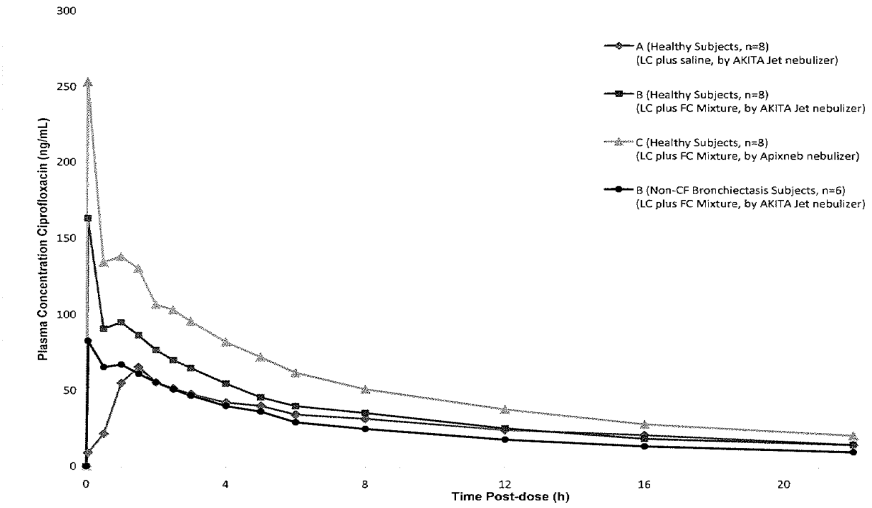
C: Linhaliq-prototype (66.6 mg) comprised of CFI (1 mL; 45 mg) plus FCI (1 mL; 21.6 mg) delivered using the Apixneb mesh nebulizer and the AKITA dosimetric system.

Treatment B was also given to a 4th treatment arm consisting of 6 NCFBE subjects.

Among the healthy volunteer groups, the plasma ciprofloxacin median Tmax was significantly shorter with the Linhaliq prototype formulation (i.e. containing FCI) vs. CFI alone and Cmax was considerably higher for the prototype formulations. The figure and table below show that NCFBE subjects had lower systemic ciprofloxacin exposures vs. healthy volunteers after receipt of treatment B, with a GMR for AUC0-t of 0.7 (p=0.0198), which the applicant states to be due to a more central pattern of deposition due to airway obstruction in NCFBE patients.

Mean plasma concentrations over time by treatment (linear), study ARD-3100-0801.

Figure 11.2 **Mean plasma concentrations over time by treatment (linear)**



PK parameters following inhalation of Linhaliq prototype formulation, study ARD 3100-0801.

Treatments (Product; Nebulizer Loaded Dose; Estimated Lung Dose)[1]	Nebulizer; Compressor	Subjects (No.(M/F) Type Age: Mean (range)	Sample	Mean Parameters (+/- SD)				
				C_{max} (ng/mL)	T_{max} (hr)	$AUC_{0-\infty}$ (ng/mL x hr)	$T_{1/2}$ (hr)	C_{min} (ng/mL)
CFI; 67.5 mg; 0.59 mg/kg[3]	PARI LC Sprint neb; AKITA	8 (5M/3F) Healthy volunteer	Plasma	66.6±27.2	1.5	776±157	10.8±1.2	NR*
Linhaliq prototype; 99.9 mg; 0.86 mg/kg[4]	PARI LC Sprint neb; AKITA			169.2±55.2	0.02	920±189	9.4±1.5	NR
Linhaliq prototype; 66.6 mg; 0.95 mg/kg[5]	Apixneb; AKITA			253.8±78.7	0.03	1415±250	8.7±1.5	NR
Linhaliq prototype; 99.9 mg; 0.86 mg/kg[4]	PARI LC Sprint neb; AKITA	6 (2M/4F) NCFBE Patients		87.0±28.1	0.12	700±207	9.7±2.0	NR

Ciprofloxacin concentrations in sputum in the NCFBE patients were higher than plasma concentrations (mean at 2 hours 110 µg/g sputum vs. mean plasma Cmax 87.0 ng/mL) and mean values were in the range 12-110 µg/g from 2-22 h post-dose.

ARD-3150-1201 and ARD-3150-1202 (ORBIT-3 and -4)

Intensive sampling in a subset of subjects was conducted in the PK-substudy of ARD-3150-1201 (n=16) in which the final Linhaliq formulation was administered to NCFBE patients. After inhaled dosing of Linhaliq, ciprofloxacin was rapidly absorbed with a median (range) time to maximum plasma concentration of 1.37 h (0-6.33 h) after dosing. Median Tmax in sputum was 0.75 h (0.58-6.47 h). See also PK in target population below.

The absolute bioavailability of inhaled ciprofloxacin has not been determined.

Distribution

Linhaliq delivers high concentrations of ciprofloxacin directly to the airways of the lung. Following oral and IV administration, protein binding of ciprofloxacin is low (20-30%) and has a large steady state distribution volume of 2-3 L/kg body weight.

Elimination

At steady state, after 7 days of once-daily oral inhalation of Linhaliq, the mean terminal elimination half-life of ciprofloxacin in plasma was 9.2 hours (ARD-3105-1201). After oral administration, ciprofloxacin is largely excreted unchanged both renally and, to a smaller extent, faecally. Renal clearance is between 180-300 mL/kg/h and the total body clearance is between 480-600 mL/kg/h. Ciprofloxacin undergoes both glomerular filtration and tubular secretion.

Low concentrations of four metabolites have been reported with oral ciprofloxacin, which were identified as: desethyleneciprofloxacin (M 1), sulphociprofloxacin (M 2), oxociprofloxacin (M 3) and formylciprofloxacin (M 4).

Dose proportionality and time dependency

Dose-proportionality has not been evaluated for the final Linhaliq formulation. Three dose levels of liposomal ciprofloxacin (CFI alone) were administered in Study ARD-3100-0701, following single-doses of 150, 300 and 450 mg to healthy volunteers. There was an indication of slightly less than dose-proportional increase in AUC and Cmax with increasing single-doses, which was most evident for Cmax. For AUC a 450 mg dose resulted in a dose-adjusted AUC of approx. 70-80% compared to the 150 mg dose. For Cmax a 450 mg dose resulted in a dose-adjusted Cmax of approx. 60% compared to the 150 mg dose.

There are no indications of time dependent pharmacokinetics of ciprofloxacin.

Intra- and inter-individual variability

Following inhalation of Linhaliq in NCFBE patients, inter-individual variability of ciprofloxacin in plasma was approx. 90% and 60% for AUC and Cmax respectively. In sputum the inter-individual variability was approx. 90% for both AUC and Cmax (ARD-3105-1201).

Pharmacokinetics in the target population

Rich plasma and sputum data were obtained from the ARD-3150-1201 PK-substudy in 16 subjects. Based on the data from the PK-substudy, both non-compartmental and popPK analyses were presented.

A comparison of plasma and sputum PK parameters following administration of Linhaliq compared to literature data for oral and IV ciprofloxacin is presented in Table 1.

Table 1. Comparison of plasma and sputum PK parameters (NCA and popPK analysis) following administration of Linhaliq to oral and IV ciprofloxacin (literature data)

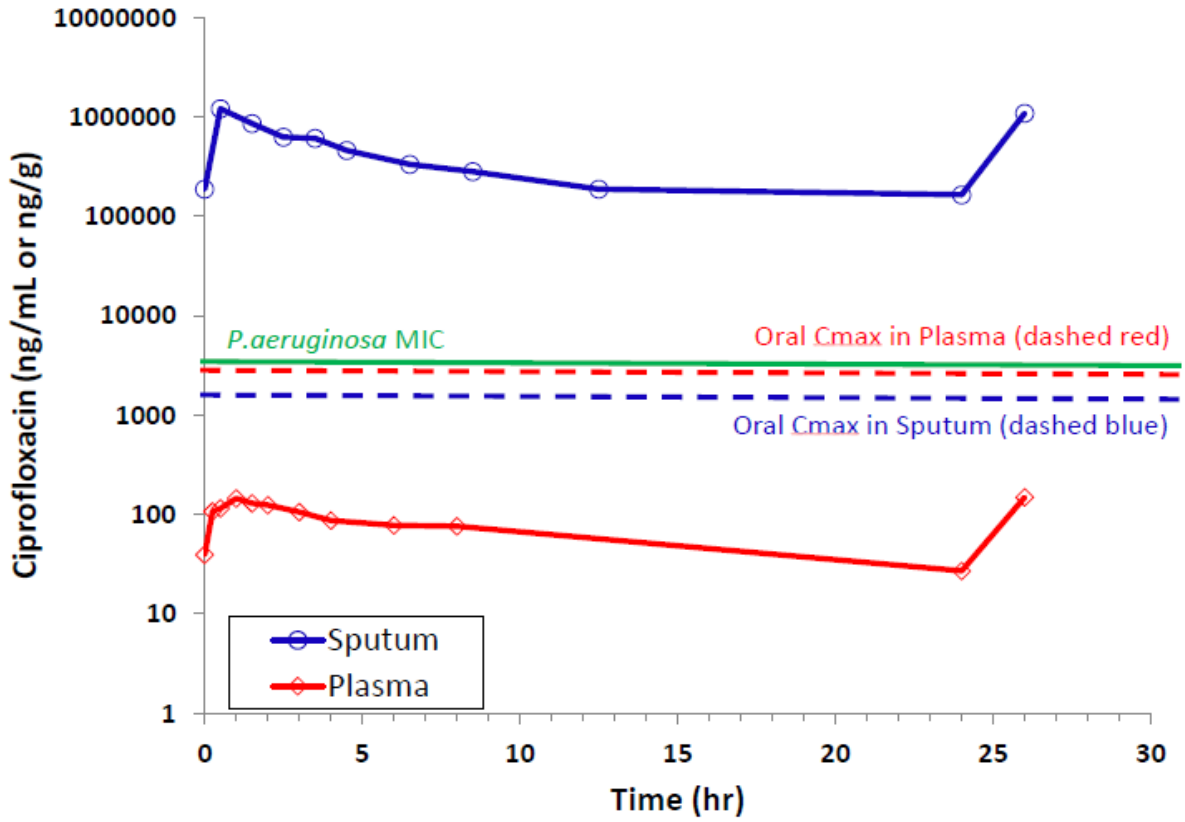
	Linhaliq (189 mg, qd, inhaled use)				Registered Ciprofloxacin (Bayer)					
	Study ARD-3150-1201 PK Substudy		Study ARD-3150-1201 and ARD-3150-1202 Population PK Modelling		Oral Ciprofloxacin (500 mg) q12h		Oral Ciprofloxacin (750 mg) q12h		IV Ciprofloxacin (400 mg) q12h	IV Ciprofloxacin (400 mg) q8h
Biomaterial	*Plasma*	*Sputum*	*Plasma*	*Sputum*	*Plasma*	*Sputum*[1]	*Plasma*	*Sputum*[1]	*Plasma*	*Plasma*
$AUC_{0\text{-}tau}$ (mean) Plasma: µg·hr/mL Sputum: µg·h/g)	2.034	17500	1.708	13134	13.7†	6.8	31.6**	8.7	12.7†	32.9**
C_{max} (mean) Plasma: µg/mL Sputum: µg/g	0.1950	2193	0.1311	806.5	2.97	1.3	3.59	1.6	4.56	4.07
C_{min} (mean) Plasma: µg/mL Sputum: µg/g	0.04127	167.6	0.04253	338.0	NR	ND	NR	ND	NR	NR
T_{max} (h) (median)	1.370	0.75	ND	ND	ND	ND	1-2	ND	ND	ND

$AUC_{0\text{-}tau}$; * $AUC_{0\text{-}t}$; † $AUC_{0\text{-}12h}$; ** $AUC_{0\text{-}24h}$
NR/ND: Not reported/not determined
[1] Sputum data from Davies et al., 1986

In comparison to published data for administration of typical oral doses of ciprofloxacin, the observed mean peak sputum concentrations after inhalation of Linhaliq substantially exceed the sputum concentration observed during high dose oral therapy (Cmax of 1.3 µg/mL for 500 mg oral (bid) and 1.6 to 1.9 µg/mL for 750 mg oral (bid) dose; Ritrovato and Deeter, 1991). Given that reported minimum inhibitory concentrations (MIC) for ciprofloxacin for P. aeruginosa susceptible and resistant strains are <2 µg/mL and >4 µg/mL, respectively (CLSI, 2017), the concentration of ciprofloxacin in sputum achieved at steady state with repeat once-daily dosing of Linhaliq is more than an order of

magnitude higher than the MIC for P. aeruginosa. Furthermore, Linhaliq (189 mg) given by inhalation (PK Substudy) has at least a 10- fold lower systemic exposure to ciprofloxacin than for 500 or 750 mg bid oral ciprofloxacin (Figure 1).

Figure 1. PK profile of inhaled Linhaliq in sputum (solid blue) and plasma (solid red) as compared to oral ciprofloxacin



Special populations

Following inhalation of Linhaliq, the systemic exposure is low. There is no need for dosage adjustments in special populations based on pharmacokinetic data.

Interactions

No interaction studies have been performed with Linhaliq. Since the systemic exposure of ciprofloxacin is substantially (at least 10 fold) lower as compared to oral or IV administraion of ciprofloxacin at recommended therapeutic doses, the risk of clinically meaningful Linhaliq drug interactions is expected to be lower than that following oral or IV ciprofloxacin.

The following pharmacokinetic drug-drug interactions have been reported for oral and IV ciprofloxacin:

Effects of other drugs on the pharmacokinetics of ciprofloxacin

Probenecid interferes with renal secretion of ciprofloxacin. Co-administration of probenecid and ciprofloxacin increases ciprofloxacin serum concentrations.

Effects of ciprofloxacin on the pharmacokinetics of other drugs

Ciprofloxacin inhibits CYP1A2 and thus may cause increased serum concentration of concomitantly administered substances metabolised by this enzyme. Ciprofloxacin has also been reported to affect the plasma concentrations of methotrexate, phenytoin and sildenafil.

3.3.2. Pharmacodynamics

Primary pharmacology

Mechanism of action

The bactericidal action of ciprofloxacin results from inhibition of the enzymes topoisomerase II (DNA gyrase) and topoisomerase IV, which are required for bacterial DNA replication, transcription, repair, and recombination.

Ciprofloxacin is effective against Gram-negative bacteria (such as *Escherichia coli*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Legionella pneumophila*, *Moraxella catarrhalis*, *Proteus mirabilis*, and *Pseudomonas aeruginosa*), but is less effective against Gram-positive bacteria (such as methicillin-sensitive *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Enterococcus faecalis*) than newer fluoroquinolones.

Ciprofloxacin exhibits concentration-dependant bacterial killing when present at concentrations above the minimum inhibitory concentrations (MIC) (Lode *et al*., 1998). The efficacy is mainly dependent on the relation between the maximum concentration in serum (C_{max}) and the minimum inhibitory concentration (MIC) of ciprofloxacin for a bacterial pathogen and the relation between the area under the curve (AUC) and the MIC.

In vitro efficacy against P. aeruginosa biofilms

Study 8800-1367, Biofilm Inhibitory Concentration (BIC) Assay of Multiple *P. aeruginosa* Clinical Isolates

A number of liposomal compositions of ciprofloxacin, including prototype Linhaliq formulations, CFI, and FCI, were shown to inhibit growth by 2-logs (99% reduction) of *P. aeruginosa* biofilms at ciprofloxacin concentrations ranging from 1.0 – 2.0 µg/mL. However, as the applicant notes, limitations of the study include the fact the total ciprofloxacin exposures are similar across the tested formulations, and there is no clearance mechanism in the model to reflect the *in vivo* situation. Thus, no firm conclusions can be drawn from this study on the efficacy of Linhaliq to inhibit growth of *P. aeruginosa* in biofilms.

In vivo efficacy in cystic fibrosis (CF) *mouse model of P. aeruginosa lung infection*

Study 8800-1368, **Efficacy of Liposomal Preparations of Ciprofloxacin as a Treatment for *P. aeruginosa* Lung Infection in CF Mice**

The efficacy of pulmonary administration (via intranasal (IN) instillation) of different doses of CFI and a prototype Linhaliq formulation containing 50 mg/mL CFI and 24 mg/mL FCI were evaluated in comparison to tobramycin or control diluent in a *P. aeruginosa* lung infection model of clinical exacerbation in Cftr-deficient mice.

Mice were treated daily with CFI at one of three doses via intranasal instillation. The estimated lung doses were: 0.2, 0.4, or 0.9 mg/kg/day, respectively. These doses are estimated to be equivalent to clinical lung doses of 10, 12, and 45 mg/day (based on body weight comparison) in a 50-kg patient. The survival rates among the groups did not differ significantly however results suggest that treatment with the highest dose of CFI increases survival time in CF mice.

A second set of experiments, which consisted of three replicates to increase the sample size, evaluated the efficacy of both the CFI and Linhaliq-prototype (1:1 (v/v) mixture of 50 mg/mL CFI and 30 mg/mL FCI) formulations via intranasal instillation. Mice treated with either Linhaliq-prototype or CFI had higher survival rates and clinical scores compared to mice treated with diluent; however, these results were not statistically significant.

A third experiment compared the efficacy of Linhaliq-prototype (1:1 (v/v) mixture of 50 mg/mL CFI and 30 mg/mL FCI) and CFI versus tobramycin via intranasal instillation. There was a trend that once daily administration of Linhaliq-prototype or CFI resulted in higher survival and clinical scores compared to twice a day administration of TOBI or once a day administration of the negative control (diluent).

The actual concentrations of the antimicrobial formulations delivered to the lungs of the mice are not provided. Furthermore, the extent to which this Cftr-deficient animal model has been validated and standarised and can be extrapolated to inhalation rather than intranasal instillation, and NCFBE rather than CF, is not discussed. No conclusions can be drawn on efficacy of the different formulations from this study.

In vitro Ciprofloxacin Susceptibility Criteria

According to the European Committee on Antimicrobial Susceptibility Testing (EUCAST), strains of *P. aeruginosa* with a ciprofloxacin MIC ≤ 0.5 mg/L are considered susceptible (S) and MIC > 0.5 mg/L resistant (R) (EUCAST May 2018).

According to the Clinical and Laboratory Standards Institute (CLSI) criteria, strains of *P. aeruginosa* with a ciprofloxacin MIC ≤ 1 mg/L are considered susceptible (S), MIC of 2 mg/L intermediate (I), and MIC ≥ 4 mcg/mL resistant (R) (CLSI, 2018).

These criteria apply to systemic ciprofloxacin treatment. There are no interpretive criteria for susceptibility specifically to inhaled ciprofloxacin.

Mechanisms of resistance

Acquired decreases in *in vitro* susceptibility to fluoroquinolones (including ciprofloxacin) arise predominantly through three mechanisms: 1) mutations in defined regions of DNA gyrase or topoisomerase IV, 2) reduction in bacterial cell permeability to fluoroquinolones, and 3) increased active fluoroquinolone efflux from bacteria (Bearden and Danziger, 2001; Dahloff, 2012). These changes generally occur in the bacterial chromosome, but can occasionally be transmitted via plasmid (Dahloff, 2012). All *in vitro* mechanisms of resistance are commonly observed in clinical isolates. The degree of cross-resistance between ciprofloxacin and other fluoroquinolones that results is variable. Resistance mechanisms that inactivate other antibiotics, such as permeation barriers (common in *P. aeruginosa*) and efflux mechanisms, may also affect susceptibility to ciprofloxacin.

Susceptibility of P. aeruginosa strains in the pivotal clinical studies

The *in vitro* susceptibilities of all sputum-derived *P. aeruginosa* isolates from subjects treated with Linhaliq in ARD-3150-1201 (ORBIT-3) and ARD-3150-1202 (ORBIT-4) are presented below in Table 2. The % of resistant *P. aeruginosa* isolates, according to EUCAST and CLSI criteria, for Linhaliq and placebo groups pooled across studies ARD-3150-1201 (ORBIT-3) and ARD-3150-1202 (ORBIT-4) is presented graphically in Figure 2.

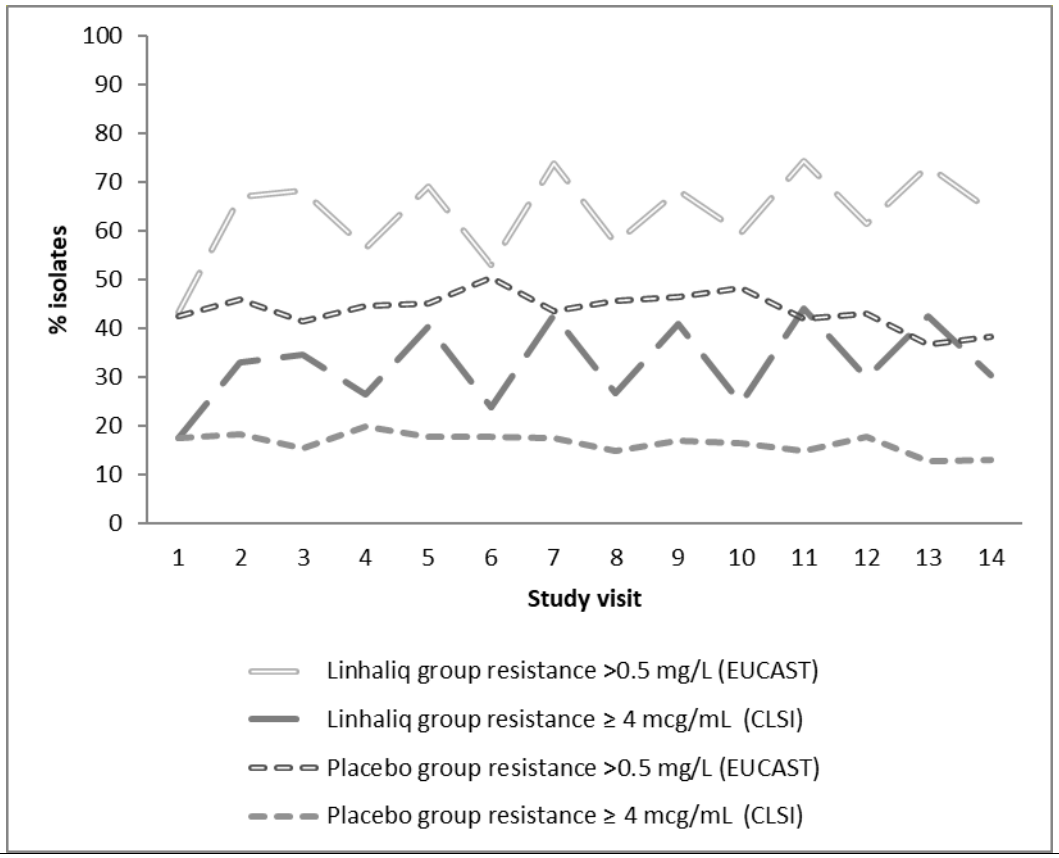
Visits 1, 4, 6, 8, 10, and 12 occurred at the beginning of each On-Treatment period (i.e. the end of each Off-Treatment period). Visits 3, 5, 7, 9 11 and 13 occurred at the end of each On-Treatment period.

Table 2. MIC distribution and proportion of resistant sputum-derived *P. aeruginosa* isolates according to EUCAST and CLSI criteria, by study visit, in subjects treated with Linhaliq in studies ARD-3150-1201 (ORBIT-3) and ARD-3150-1202 (ORBIT-4)

Visit	n	MIC_{50}	MIC_{90}	Range	% resistance >0.5 mg/L (EUCAST)	% resistance ≥ 4 mcg/mL (CLSI)
1 (baseline)	446	0.5	4	≤0.25-128	43	18
2	320	2	8	≤0.25-256	67	33
3	314	2	16	≤0.25-256	68	35
4	387	1	8	≤0.25-64	57	27
5	316	2	16	≤0.25-256	69	41
6	383	1	8	≤0.25-128	53	24
7	318	2	32	≤0.25->256	74	43
8	382	1	8	≤0.25->256	58	27
9	285	2	32	≤0.25->256	68	41
10	381	1	8	≤0.25-256	60	25
11	319	2	32	≤0.25-256	74	44
12	359	1	16	≤0.25->256	62	30
13	296	2	32	≤0.25-256	73	43
14	358	1	16	≤0.25->256	64	30

Table by assessor. Source data: Integrated summary of clinical microbiology 8900-1352, Appendix Table 3.2

Figure 2. % of resistant sputum-derived *P. aeruginosa* isolates, according to EUCAST and CLSI criteria, by study visit, in Linhaliq and placebo groups pooled across ARD-3150-1201 (ORBIT-3) and ARD-3150-1202 (ORBIT-4)



Graph by assessor. Source data: Integrated summary of clinical microbiology 8900-1352, Appendix Table 3.2

Secondary pharmacology

Secondary pharmacodynamic non-Good Laboratory Practice (GLP) studies conducted to evaluate the efficacy of Linhaliq and CFI against non-*P. aeruginosa* infections are not discussed in this assessment.

Prolongation of the QTc interval

Because prolongation of the QT interval is a class effect of fluoroquinolones, including ciprofloxacin, a QT/QTc study was not conducted for Linhaliq. In pooled ARD-3150-1202 and ARD-3150-1201, changes in QTc interval from baseline to Visit 14 (Week 48) of >30 ms or >60 ms occurred more frequently in the placebo group than the Linhaliq group.

3.3.3. Discussion on clinical pharmacology

Pharmacokinetics

Data from the two Phase 3 studies, including the PK-substudy were the only studies using the final Linhaliq formulation, and are thus the most relevant pharmacokinetic studies in the present application. The pharmacokinetic studies aim at characterising the pharmacokinetics in plasma and sputum of orally inhaled ciprofloxacin and are mainly descriptive.

The critical issue for the *efficacy* of Linhaliq is the amount of ciprofloxacin loaded into the nebulizer that reaches the small airways where colonization by *P. aeruginosa* occurs. The applicant did not conduct a scintigraphy study so the distribution of the product, including the proportion of the dose that impacts in the nose and oropharynx, is not known.

The critical issue for *systemic safety* is the amount of ciprofloxacin that reaches the blood which may derive from swallowing material that impacted on the nasal and oropharyngeal mucosal surfaces and/or from absorption of material that reaches the small airways. The very high IIV observed and predicted in subjects with NCFBE likely reflects variability in lung function, affecting the proportion that reaches the airways. The finding that some subjects had ciprofloxacin detected in plasma 4 weeks after the last dose that could not be explained by intervening systemic treatment could suggest that there is very slow complete release of ciprofloxacin from liposomes that impact in the small airways.

Methods

Plasma and sputum ciprofloxacin concentrations were analysed using validated LC/MS/MS methods. The bioanalytical methods for ciprofloxacin in the sputum and in the plasma measure total concentrations of ciprofloxacin as the use of the organic solvents disrupts liposomes. Since only unencapsulated ciprofloxacin is absorbed, the concentrations in plasma reflect unencapsulated ciprofloxacin. The Applicant claims that both encapsulated and unencapsulated ciprofloxacin are thought to exert anti-pseudomonal activity in sputum. Although some data suggests that this may be true, the contribution of free and encapsulated ciprofloxacin to the overall effect in the lung is uncertain.

Rich plasma and sputum data were obtained from the ARD-3150-1201 PK-substudy in 16 subjects and sparse plasma and sputum samples were available from 341 and 358 subjects respectively in the two Phase 3 studies (ARD-3150-1201 and ARD-3150-1202). The Applicant has presented both non-compartmental and PPK analyses. The PPK model was however only based on the rich data from the PK-substudy since the model using the full dataset was not considered valid. Thus, a large amount of data has not been used. This is considered as a major deficiency of the model development. The model

needs to be updated, before it can be used for evaluation of e.g. the effects of different co-variates on the systemic exposure to ciprofloxacin. Question regarding these issues with the model were asked in round 1. As the PPK analysis is considered applicable primarily for evaluation of plasma concentrations and systemic safety, the focus are on the plasma PPK model. The model is not considered useful or needed for assessment of efficacy or dosage. Further evaluation and refinement of the model for sputum concentrations is therefore not considered necessary.

The applicant has not been able to provide an adequate updated PPK mode in round 2. For the model to potentially be deemed adequate, the applicant would have to investigate whether significant covariate may have an impact on the predicted systemic ciprofloxacin exposure using Linhaliq, and the details of the covariate analysis should be provided. A different structure model than a 3-compartment model and different absorption/input are likely needed. A full report of the updated PPK model would need to be provided. However, the issues regarding safety are deemed to be linked to the administration to the lung and long-term safety in the lung rather than due to systemic exposure. Thus, the issues regarding the PPK model are not further pursued.

Plasma exposure

The results from the analysis of ciprofloxacin in *plasma* suggests that the systemic exposure following inhalation of Linhaliq is much lower compared with published data on ciprofloxacin exposure following oral and IV administration. In the PK sub-study in 16 OLEP subjects in ARD-3150-1201 (ORBIT-3), if the applicant is correct about the reasons for the unexpected values in 3 subjects, the plasma ciprofloxacin Tmax after the 7th daily dose was 1.37 h and levels then steadily declined over the dosing interval, although multiple peaks were observed for some individuals. The inter-individual variability (IIV) was high with CV% values for Cmin, Cmax and $AUC_{0\text{-}tau}$ of 148.8%, 59.4% and 93.2%, respectively. This may reflect variable degrees of underlying lung disease affecting how much material reaches the small airways.

The highest Cmax in these 16 subjects was 488 ng/mL and the highest AUC was 8250 ng.h/mL. Using the PPK model the predicted highest Cmax was 540 ng/mL and predicted highest AUC was 11,300 ng.h/mL. Based on these observed and predicted maximum values, the plasma Cmax values expected with Linhaliq are very considerably less than those associated with oral or intravenous dosing (e.g. even with a 250 mg oral dose Cmax is reported to be ~1200 ng/mL). In contrast, the maximum AUC expected with Linhaliq is close to values reported with 500 mg q12h PO or 400 mg q12h IV.

However, when the mean values expected with Linhaliq are compared with systemic dosing there is a much greater comfort margin. Using the PK sub-study or the PPK-predicted values, Cmax is <10% of the values reported for 500 mg oral and 400 mg IV doses while AUC is about 10%.

Another issue to consider is that the absorption of ciprofloxacin from the gut is negatively affected by cations and concomitant use of various antacids. The applicant has investigated the plasma ciprofloxacin exposure in subjects with concomitant administration of cations. Overall it appears that the concomitant administration of cations may not have significant impact on the PK parameters or plasma ciprofloxacin exposure, although it seems that a slight decrease in ciprofloxacin exposure was observed at individual level.

Sputum exposure

The Applicant claims that the high concentration of ciprofloxacin in *sputum* (above MIC) supports the proposed posology. There are however several uncertainties regarding the validity of the sputum concentrations and its relevance in the benefit-risk evaluation. As stated previously, the use of a bioanalytical method which cannot distinguish between free and liposome bound ciprofloxacin adds to

the uncertainty regarding the validity of sputum concentrations. Moreover, variability in sputum concentrations is high and only 16 subjects were included in the final PK evaluation. In addition to this, sputum samples were collected after a deep cough in order to cough up sputum from deeper regions of the lungs. Sputum samples may hence be a mixture of ciprofloxacin delivered both to the upper respiratory tract (mouth/larynx) to deeper parts of the lungs. Therefore, it is not evident that all of the ciprofloxacin found in sputum has really reached the deeper compartments of the lung and the site of action. Ciprofloxacin concentrations in sputum are therefore not considered reliable but since these data are not considered useful nor needed for assessment of efficacy or dosage these issues are not further pursued.

Other issues

The applicant has investigated both between-subject variability and between-occasion variability using the PPK modelling. Overall moderate to high variability has been observed.

There was no placebo group in the early safety and PK studies, which greatly limits the interpretation of the safety data. The PK observations from these studies may be summarised as follows:

In healthy subjects given escalating single CFI doses containing up to 405 mg ciprofloxacin base, there was an approximate dose proportional increase in plasma Cmax and AUC with increasing dose. The t½ ranged between 10 and 15 hours, consistent with release from liposomal ciprofloxacin. Multiple dose administration at 270 mg/day did not show changes in Cmax, Cmin, AUC_{0-t} or Tmax with day and steady state was reached after the third dose.

In CF patients given 270 mg/day, plasma Cmax ranged from 75-300 ng/mL in 4 subjects sampled. The mean was comparable to the mean Cmax on day 3 in healthy subjects given the same dose (160 ng/mL). AUCs also showed ~4-fold range between subjects. This was the first study to show that high but variable sputum concentrations could be achieved.

The first study with a prototype Linhaliq formulation (ARD-3100-0801) showed the effect of adding FCI, with a median Tmax that was significantly shorter and a higher Cmax vs. CFI alone. The Tmax with CFI/FCI was only a few minutes, which is too short for Cmax to be explained by orally absorbed swallowed material and seems rather improbable to result from fast absorption from lower airways. It appears that different blood sampling times were scheduled between the Study ARD-3100-0801 and PK Substudy ORBIT-3. Particularly an immediately post-dose sample was taken in the Study ARD-3100-0801 while the first sampling time was 0.25 hour post dose in the PK Substudy. This may explain the different Tmax observed between the studies. However, the early Cmax was not characterised in the PK Substudy and an underestimation of the total exposure of ciprofloxacin may not be excluded. The applicant should further discuss the impact of the missed early Cmax in the PK Substudy ORBIT-3 on the overall characterisation of the pharmacokinetics of ciprofloxacin using Linhaliq **(OC)**. Importantly, study ARD-3100-0801 showed that mean plasma concentrations were lower for the NCFBE patients vs. healthy volunteers who received the same single CFI/FCI dose, with a GMR for AUC of ~0.7.

The applicant's Summary of Biopharmaceutics states that the AKITA dosing system used in ARD-3100-0801 about doubled the delivery efficacy of the PARI LC Sprint nebulizer.

Without further elaboration, it is stated that the Linhaliq prototype formulation loaded dose in Group B (equivalent to 99.9 mg ciprofloxacin) provided an estimated lung dose comparable to that using the PARI LC Sprint nebulizer system in ORBIT-2 -3 and -4 to deliver Linhaliq (loaded dose 189 mg ciprofloxacin). In the 6 NCFBE subjects given a single dose, the mean Cmax was 87 ng/mL and the mean AUC_{0-inf} was 700 ng.h/mL. In the PK sub-study of ORBIT-3 the mean Cmax on day 7 was ~200

ng/mL and the mean AUC_{0-t} was ~2000 ng.h/mL. The applicant provided a discussion of the different Cmax values observed between the study ARD-3100-0801 and PK Substudy using the PPK modelling. It appears that accumulation may be expected at steady state, although the expected time dependency has not been discussed in terms of total systemic exposure, and early studies with CFI did not suggest significant risk of accumulation. The applicant claims that in ORBIT-2, ORBIT-3 and ORBIT-4, the total loaded dose per day in Linhaliq was 189 mg ciprofloxacin but 50% of the emitted dose is lost because the nebuliser produces the aerosol continuously whereas the patient inspires only about one half of the time. However robust data were not provided to adequately support this approximation. This should be further discussed. Moreover, the differences in AUC and Cmax observed between the study ARD-3100-0801 and PK Substudy should be further discussed as well as the expected time dependency **(OC)**.

In the ORBIT-3 PK sub-study, the volume of distribution was not discussed as it was not possible to calculate this parameter for most subjects. In the PPK model, the estimated central (Vc/F) and peripheral (Vp/F) volume of distribution was 1780 L and 1300 L, respectively. Moreover, in the ORBIT-3 PK sub-study, the half-life has been calculated in approximately 40% of the patients due to high plasma concentrations measured in the late part of the time-concentration curve. These data could not be considered completely adequate due to the reduced number of available data (N=6). Based on the presented data, the CL/F estimated in the PPK is approximately consistent with the CL calculated in the PK sub-study. Moreover, the AUCextra appears >20% of the AUCinf for some subjects. This may be due to an insufficient number of scheduled blood sampling times and did not allow an accurate characterisation of the elimination of ciprofloxacin.

In the ORBIT-3 PK sub-study, one subject was excluded from plasma PK analysis due to extremely high concentrations at 6 and 8 h post Day 7 dose. However, co-administration of systemic ciprofloxacin has been not recorded and the plasma concentration at 24 h post Day 7 dose may appear inconsistent with the k_e of ciprofloxacin. General pharmacokinetic characteristics of ciprofloxacin are well known from administration of oral and intravenous formulations. A summary of the most relevant literature data, in order to justify the claimed wordings in the SmPC, would normally have been expected for a complete mixed application. This was not provided. The general pharmacokinetic sections of the proposed SmPC are however in accordance with the SmPC for Ciproxin which has been harmonised via an Art 30 referral. Regarding drug-drug interactions, the risk of clinically relevant interactions is likely lower for Linhaliq than for oral/IV ciprofloxacin.

Pharmacodynamics

The applicant's Clinical Overview states that Linhaliq has been designed rationally to provide both immediately available and slow release ciprofloxacin "*in concentrations in the lung that exceed the MIC throughout the 24-hour dosing interval*".

High ciprofloxacin MICs were measured for *P. aeruginosa* sputum-derived isolates obtained from patients at baseline, which further increased during the treatment with Linhaliq. Meanwhile, MICs remained at similar levels throughout the study period in the placebo groups. There is a theoretical concern that organisms with increased ciprofloxacin MICs would not be treatable with fluoroquinolones should they cause a clinical infection. *In vitro* susceptibilities of bacterial species other than *P. aeruginosa* were not collected during ORBIT-3 or ORBIT-4. Overall, 47.3% of patients enrolled in ORBIT-3 or ORBIT-4 were treated with systemic fluoroquinolones (primarily ciprofloxacin), and amongst these patients there was no indication that treatments for lung infection were less effective in subjects randomized to receive Linhaliq. Furthermore, the incidence rate of pneumonias was similar between patients randomized to receive Linhaliq and those randomized to receive placebo. Finally, there was no evidence from the studies of an increased bacterial infection incidence outside of the

respiratory tract among patients randomized to receive Linhaliq. This issue is not further pursued. The selection of resistant organisms with long-term use remains a potential risk for Linhaliq.

3.3.4. Conclusions on clinical pharmacology

Overall, the pharmacokinetics of ciprofloxacin following administration of Linhaliq has been sufficiently characterised. There are however a few outstanding issues that need to be discussed (**LoOI**).

The mechanism of action of and mechanisms of resistance to ciprofloxacin are already well established. The selection of resistant organisms with long-term use remains a potential risk for Linhaliq.

3.3.5. Clinical efficacy

Dose-response studies and main clinical studies

Dose selection studies

No conventional dose-response studies have been performed.

The 6 ml Linhaliq dose was chosen for the Phase 3 programme based on 1) equipotent anti-pseudomonal activity in patients (subjects with NCFBE chronically infected with *P. aeruginosa*) of 3 and 6 mL doses of CFI given for 28 days in proof-of-concept studies ARD-3100-0702 and -0703 and 2) the good microbiological response (reduction in the density of *P. aeruginosa*), as well as good tolerability and safety of the same dosing regimen, in the Phase 2b study ARD-3150-0902 (ORBIT-2).

The 28-day on/off cyclic dosing regimen concept originates from Cystic Fibrosis (CF) standards of care, and was previously discussed during Scientific Advice (EMA/CHMP/SAWP/727418/2011). The use of 28-day "off" periods is believed to avoid continuous selection of resistant strains by permitting re-establishment of wild-type susceptible strains (Ramsey *et al.*, 1999). The regimen was chosen on the basis of a reduction in *P. aeruginosa* sputum density using this regimen in ORBIT-2, associated with a positive impact on PE frequency, without any clinically meaningful emergence of resistant organisms.

Main clinical studies

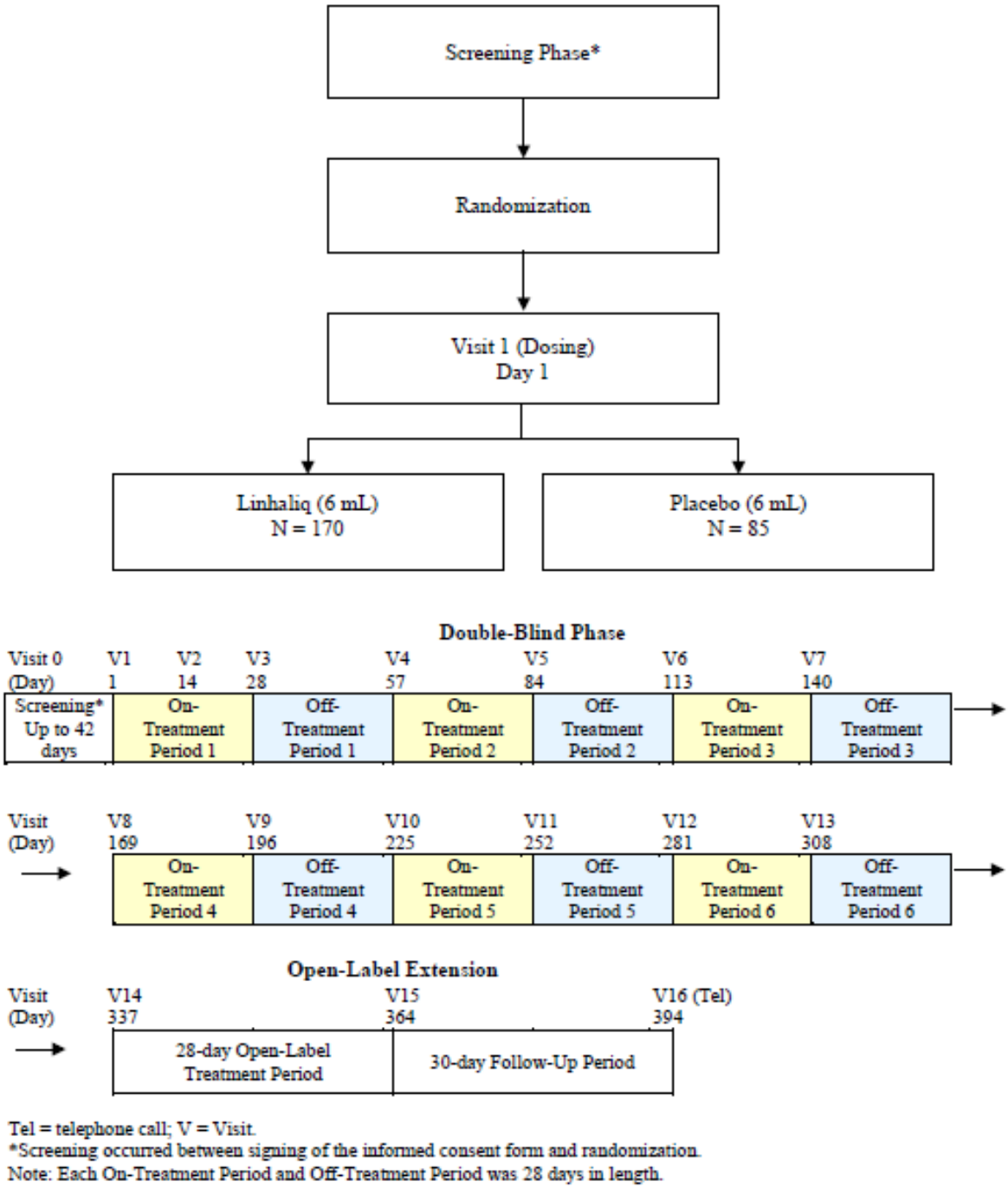
Design

Studies ARD-3150-1201 (ORBIT-3) and ARD-3150-1202 (ORBIT-4) were identical, multicentre, randomised, double-blind, placebo-controlled studies to evaluate the safety and efficacy of daily nebulised Linhaliq for six treatment cycles (28 days On-Treatment, 28 days Off-treatment per cycle) in 278 and 304 adult NCFBE patients, respectively, colonised with *P. aeruginosa* and with at least 2 PEs requiring antibiotics in the 12 months preceding the study.

While eligible subjects were to have a history of at least 2 PEs treated with antibacterial agents within the last 12 months, this does not mean that they were colonized with *P. aeruginosa* at the time of those prior exacerbations. In addition, evidence of truly chronic colonization (e.g. over at least 6 months pre-study) was not required. A minority of patients in ORBIT-3 and 4 did not have *P. aeruginosa* isolated at Visit 1, however all patients, as required by the trial protocol, had *P. aeruginosa* isolated at screening visit and a history of prior *P. aeruginosa* isolation, and were considered chronically infected. Despite this, less than 70% of all enrolled patients had *P. aeruginosa* isolated from every respiratory specimen cultures at any time point during the trials. Overall, 2.1% of all enrolled patients failed to ever have *P. aeruginosa* isolated from their post-screening specimens. Of these, 9 patients were randomised to Linhaliq and 2 patients were randomised to placebo.

A sample size of 234 patients in each trial was required in order to produce 149 cases for the primary analysis endpoint for the desirable power of 90% and 2-sided alpha level of 0.05, assuming loss to follow up of 10% and exponential survival with 48-week failure rates of 80% placebo, 60% Linhaliq. In order to obtain an adequate safety database, the target sample size was increased to 255 per trial.

Figure 3. Study design for identical Phase 3 studies ARD-3150-1201 (ORBIT-3) and ARD-3150-1202 (ORBIT-4).



Tel = telephone call; V = Visit.
*Screening occurred between signing of the informed consent form and randomization.
Note: Each On-Treatment Period and Off-Treatment Period was 28 days in length.

Source: ARD-3150-1201 Clinical Study Report.

Subjects

Key inclusion criteria

- Confirmed diagnosis of NCFBE on CT.
- Documented history of at least 2 PEs treated with courses of antibiotics within the last 12 months.
- FEV1 ≥ 25% of predicted values at the Screening Visit (Visit 0).
- Positive documented *P. aeruginosa* in a sputum/deep-throat swab culture (or BAL or bronchoscopic specimen) prior to the Screening Visit (Visit 0); or at least two positive sputum samples or deep-throat swabs collected 3–4 or more weeks apart from each other during the Screening Phase.
- Positive *P. aeruginosa* in the sputum/deep-throat swab culture collected at the Screening Visit (Visit 0) with at least one *P. aeruginosa* isolate non-resistant (susceptible or intermediate) to ciprofloxacin.

Each subject remained on their prescribed standard medications and therapeutic treatment regimens, to which Linhaliq or placebo (randomisation 2:1) was added, with no instructions given regarding time intervals with respect to study therapy. However, information about the timing of bronchodilator versus spirometry was captured in the eCFR.

Subjects were excluded if they received any IV, oral, or inhaled anti-pseudomonal antibiotic within 28 days prior to Visit 1, except for macrolides (erythromycin, clarithromycin, or azithromycin) taken chronically at a stable dose. During the studies, the use of antibiotics with known activity against *P. aeruginosa* for any purpose other than to treat a PE were considered a potential major protocol deviation.

Treatments

The investigational study drugs used during the Double-Blind Phase were Linhaliq and Placebo Liposomes for Inhalation (PLI).

Linhaliq consisted of equal volumes of CFI, 50 mg/mL and FCI, 20 mg/mL (expressed as ciprofloxacin hydrochloride salt) or CFI 45 mg/mL and FCI 18 mg/mL (expressed as ciprofloxacin base). The mixture of 3 mL CFI and 3 mL FCI in the nebulizer reservoir yielded one 6 mL dose of Linhaliq (total 189 mg/6 mL, expressed as ciprofloxacin free base).

The placebo product, PLI, consisted of equal volumes of empty Control Liposomes for Inhalation (CLI) and 0.9% Saline for Inhalation (SI). The lipid concentration of CLI (5 mg/mL total lipids) represented approximately 5.8% of that for CFI, (85.7 mg/mL total lipids), to avoid any potential confounding biological effects of liposomes. Neither isotonic saline nor distilled water would have been able to provide the required visual blinding. It is conceivable that if Linhaliq had been tested against patients receiving no placebo treatment, the result in favour of Linhaliq might have been stronger, because isotonic saline alone shows beneficial effects in NCFBE patients (Nicholson *et al.*, 2012). However, without further data, the extent of this effect cannot be appreciated or adjusted for.

All subjects received the same 6 mL doses of study drug for administration by oral inhalation, either Linhaliq 6 mL (189 mg/6 ml dose as ciprofloxacin free base) or PLI 6 mL, as assigned according to a 2:1 randomisation scheme stratified by sex, smoking status and baseline number of PEs (2-3, 4-7, >7), for the Double-Blind Phase of 48 weeks. Dosage was not based on weight or adjusted for age.

The applicant has stated that the nebulizers used in different geographical regions were essentially the same (PARI LC® Sprint nebulizer with the blue insert powered by a compressor including the PARI TurboBOY S or SX in Europe, Israel and Australia or the PARI Vios® in North America and Asia). These devices have been shown to have the same performance versus aerosol characteristics, despite the different power supply voltage among geographic regions.

Medication that subjects took other than the study drug was considered a *concomitant medication*. Dosing of concomitant medications was expected to be stabilized before screening and to remain constant during the course of the study, whenever possible. Treatment with tizanidine was not allowed, since concomitant administration of ciprofloxacin with tizanidine is contraindicated due to a known drug-drug interaction.

Controlled medications e.g. oral, inhaled, or IV antibiotics (including macrolides and anti-pseudomonal antibiotics), Corticosteroids, Bronchodilators, Mucolytics and Inhaled hypertonic saline or inhaled mannitol were accepted for treatment of a PE, but otherwise regarded as a protocol deviation to be discussed with the Medical Monitor, if possible, prior to use.

Objectives

The primary objective of both studies was to evaluate the efficacy of Linhaliq compared to placebo in the treatment of chronic lung infections with *P. aeruginosa* in patients with NCFBE by evaluating the time to the first PE in the Double-Blind Phase.

The secondary objectives were to evaluate the following:

- Efficacy of Linhaliq compared to placebo as assessed by clinical outcomes (including number of PEs), pulmonary function, patient-reported outcomes, and exercise testing in the Double-Blind Phase.
- Microbiological response in the Double-Blind Phase and Open-Label Extension.
- Safety and tolerability of Linhaliq compared to placebo in the Double-Blind Phase.
- Safety and tolerability of Linhaliq in the Open-Label Extension.

Efficacy endpoints

The primary efficacy endpoint in the two Phase 3 studies was the time to first PE from the date of randomisation to Week 48. An independent Pulmonary Exacerbation Blinded Adjudication Committee (PEBAC) was established to adjudicate, in a blinded manner, all cases of discrepancies between the investigator's assessment and the protocol-defined criteria for a PE. PE was diagnosed according to a set of sponsor-defined criteria, with sensitivity analyses using British Thoracic Society (BTS) criteria.

Key clinical secondary endpoints were:

1. Number of PEs per subject from baseline (day of randomisation) to Week 48.
2. Number of severe PEs per subject from baseline (day of randomisation) to Week 48.
3. Change in Respiratory Symptoms scale score of the QoL-B from baseline (Day 1) to Week 48.

The objectives and efficacy endpoints of the two identical studies are acceptable.

A *PE was defined* by the protocol by the presence of four or more specific abnormal respiratory signs or symptoms with an onset date and an end date. An abnormality was defined as a change from the subject's baseline in the following nine symptoms, signs, or laboratory findings (O'Donnell *et al*., 1998):

- Change in sputum production (consistency, colour, volume, or haemoptysis).
- Increased dyspnoea (chest congestion or shortness of breath).
- Increased cough.
- Fever (≥38°C).
- Increased wheezing.
- Decreased exercise tolerance, malaise, fatigue, or lethargy.
- Forced expiratory volume in 1 second (FEV1) or forced vital capacity (FVC) decreased 10% from a previously recorded value.

- Radiographic changes indicative of a new pulmonary process.
- Changes in chest sounds.

The *severity of PEs* was defined by protocol as follows:

- Mild: Adjustments in treatment, including increase in frequency of current therapy but excluding the use of antibiotics or no increase in the dose of macrolides.
- Moderate: Treatment with oral or inhaled antibiotics, or increase in the dose of macrolides.
- Severe: Treatment with IV antibiotics and/or hospitalization.

All cases of discrepancies between an investigator's assessment and the protocol-defined criteria for a PE were required to be adjudicated in a blinded manner by the PE Blinded Adjudication Committee (PEBAC), which provided a final blinded assessment as to whether a protocol-defined PE had occurred.

The onset date of the PE was the first point at which 4 or more abnormalities from a pre-defined list of 9 symptoms, signs or laboratory findings occurred concurrently in the subject at one point in time.

Table 1. Mean and Range of Number of PE Signs and Symptoms in the Primary Analysis

Study	ORBIT-3		ORBIT-4	
	Linhaliq	Placebo	Linhaliq	Placebo
Number of primary PEs	108	54	114	64
Mean # of PE signs and symptoms	5.0	5.0	5.1	4.9
Range of PE signs and symptoms				
High	9	8	8	8
Low	4	4	2	3

Source: Applicant's Clinical Responses, Table 44.

There were 5 PEs in 4 subjects in ORBIT-4 where there was inconsistency between the investigator's report on PE and re-adjudication on PE. These were re-adjudicated in a blinded manner by the PEBAC, according to study protocol.

Analyses

The analysis populations were:

- Intent-to-Treat (ITT) Population: all randomised subjects
- Full Analysis (FA) Population: all randomised who received at least one dose of study drug
- Per Protocol (PP) Population: FA subjects with no major protocol deviations, as per the Sponsor's documented blinded adjudication prior to database lock, based on the actual treatment received

All primary and secondary analyses were initially conducted using the FA population that consisted of all randomised subjects who had received at least one dose of study drug. Sensitivity analyses were conducted using the PP and ITT populations.

For the EU, the primary analysis for the primary endpoint (time from randomisation to the first PE) employed a non-stratified weighted log-rank statistic assuming a lag time of 2.5 months. This differed from the US, where the primary analysis was a stratified unweighted log-rank test, stratified for the randomisation stratification factors. A Kaplan-Meier plot of the time to the first PE by treatment was constructed for the FA population. The change of EU primary analysis method from an unweighted log-rank test (used in the estimation of sample size) to a weighted log-rank test occurred while the studies were ongoing, but prior to unblinding, and was discussed within the 2016 scientific advice follow-up

procedure. The applicant claimed that a treatment lag could be expected based on a numbers of factors. However, when data had been analysed the applicant concluded that a treatment time-lag did not exist.

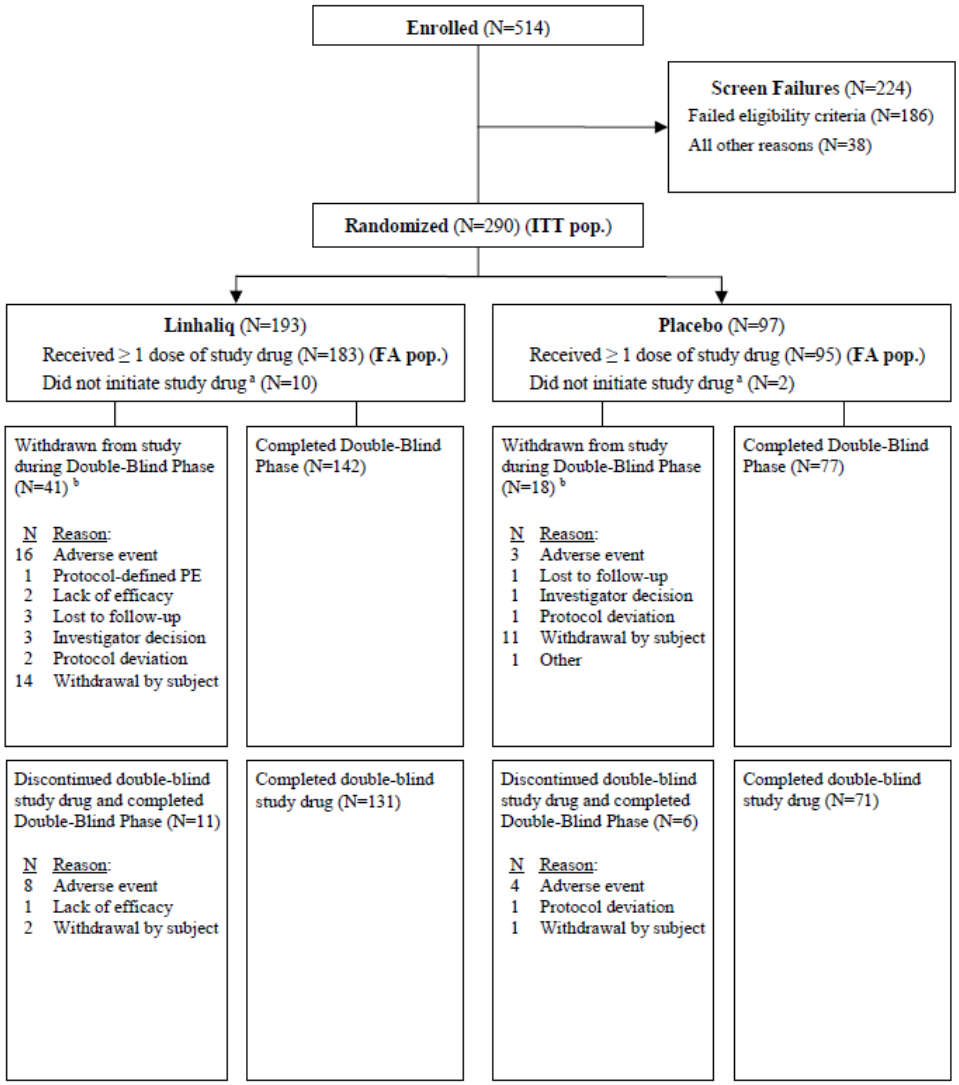
No imputation of missing data was made for the primary analysis of time to first PE. Subjects who had no PE between Day 1 and Visit 14 were censored according to pre-defined censoring rules. Patients lost to follow-up were censored.

Secondary analyses were conducted using stratified negative binominal regression (PE-related endpoints) and MMRM (change in Respiratory Symptoms Scale score of the QoL-B). No imputation of missing data was made for the secondary and other efficacy analyses.

To maintain the Type I error at the overall 2-sided 0.05 significance level a combination of hierarchical and step-down approaches was used. Besides for the three first secondary endpoints, no adjustments for multiplicity were made to other endpoints.

Participant flow

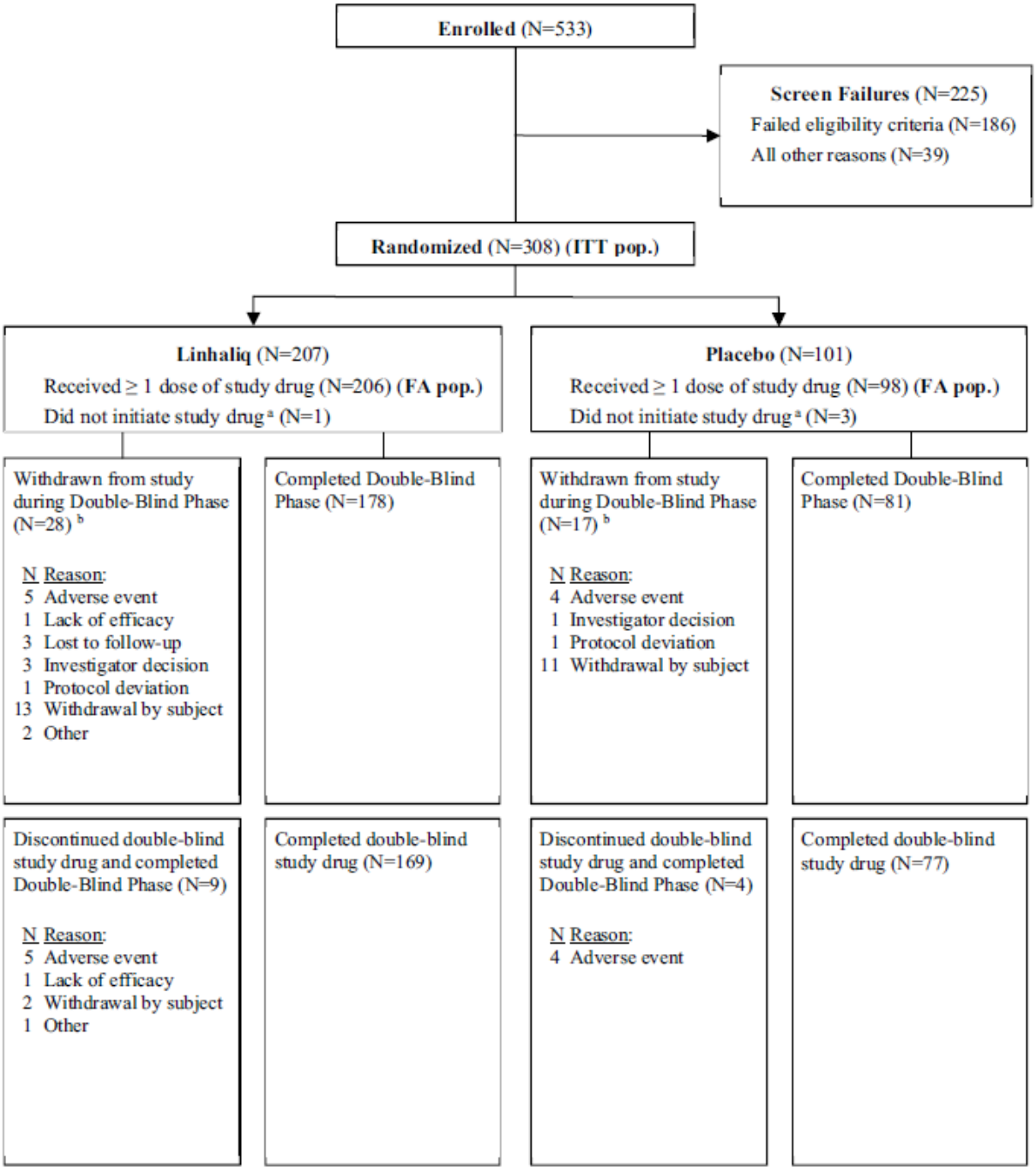
Figure 4. Subject disposition in the Double-blind phase of study ARD-3150-1201 (ORBIT-3)



FA = Full Analysis population; ITT = Intent-to-Treat population; PE = pulmonary exacerbation.
[a] Twelve subjects were randomized but not dosed (10 subjects randomized to Linhaliq and two subjects randomized to placebo).

Source: ARD-3150-1201 Clinical Study Report.

Figure 5. Subject disposition in the Double-blind phase for study ARD-3150-1202 (ORBIT-4)



FA = Full Analysis population; ITT = Intent-to-Treat population; PE = pulmonary exacerbation.
[a] Four subjects were randomized but not dosed (1 subject randomized to Linhaliq and 3 subjects randomized to placebo).
[b] Six subjects died during Double-Blind Phase (2 and 4 subjects in the Linhaliq and placebo groups, respectively).
Source: Table 14.1.1

Data on the number of subjects recruited to each study site could not be found in the applicant's submission. Without this information it is not possible to evaluate whether recruitment was evenly distributed across sites, or whether any study site(s) dominated in the study population (**LoOI**).

Demographics and baseline characteristics

Overall there were no major differences between the groups in demographic and baseline characteristics in either ARD-3150-1201 (ORBIT-3) or ARD-3150-1202 (ORBIT-4). Average baseline spirometry values were slightly better in the 1202 (ORBIT-4) study population than in the 1201 (ORBIT-3) study population: with average baseline FVC % predicted 74.2% vs 69.7%, and average baseline FEV_1 % predicted 61.7 vs 57.4. This may suggest that the 1202 (ORBIT-4) study population had on average less severe NCFBE. The population in ORBIT-4 was slightly younger, less likely to be of the typical white female demographic, to have had slightly fewer exacerbations at baseline.

Approximately 80% of subjects reported initiating (or modifying the dosage of) concomitant medications during the Double-Blind Phase across all groups in both studies.

The stratification factors at randomisation were sex, number of PEs in the 12 months before enrolment and smoking status. However, since very few current smokers were enrolled it was proposed and agreed ((Co-) Rapporteur meetings, 18 October 2017 and 14 November 2017) that smoking status could be removed as a stratification factor for all pre-specified SAP analyses. Further, with only very few enrolled with >7 PEs in the prior 12 month (1.1% (3/278)); in stratified analyses this stratification factor had two instead of three strata (2-3 or ≥4 PEs in the prior 12 months).

Study numbers

Table 2. Analysis populations in the Double-blind phase for studies ARD-3150-1201 (ORBIT-3) and ARD-3150-1202 (ORBIT-4)

Study	**ARD-3150-1201 (ORBIT-3)**		**ARD-3150-1202 (ORBIT-4)**	
Analysis population	**Linhaliq**	**Placebo**	**Linhaliq**	**Placebo**
Intention to Treat	193 (100%)	97 (100%)	207 (100%)	101 (100%)
Full (FA)	183 (94.8%)	95 (97.9%)	206 (99.5%)	98 (97.0%)
Per Protocol	145 (75.1%)	78 (80.4%)	176 (85.0%)	76 (75.0%)
Safety	183 (94.8%)	95 (97.9%)	206 (99.5%)	98 (97.0%)

The most frequent protocol deviation concerned use of anti-pseudomonal antibiotics for treatment of a respiratory condition other than PE as adjudicated by the PEBAC (10-12% across groups). The second most frequent deviation concerned non-concordance, i.e. subjects missing >6 consecutive doses in a cycle or not completing at least 3 treatment cycles (2-9% across groups).

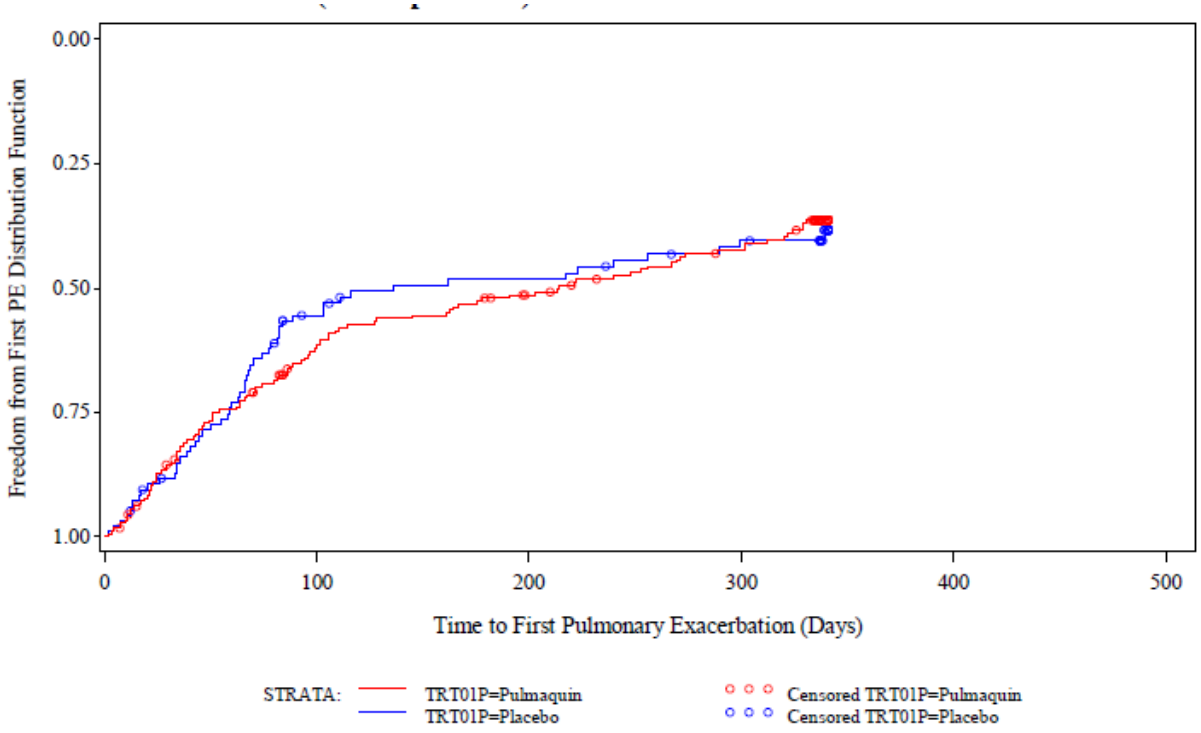
Primary analysis - **ARD-3150-1201 (ORBIT-3)**

In the FA population, 108 subjects (59.0%) in the Linhaliq group experienced at least one PE by Week 48, as compared with 54 subjects (56.8%) in the placebo group. The median time to first PE was 214 days in the Linhaliq group and 136 days in the placebo group; a difference of 78 days.

Analysis of the primary endpoint (FA population) using the pre-specified non-stratified weighted log-rank test demonstrated a treatment effect hazard ratio (95% CI) of 0.92 (0.62, 1.35); (p=0.4020).

Sensitivity analyses of the primary endpoint in the ITT and PP populations were also consistent with the result of the primary analysis in the FA population.

Figure 6. Time to the First PE by Week 48, K-M Plot stratified by Treatment (FA Population) for study ARD-3150-1201 (ORBIT-3)



Source: ARD-3150-1201 Clinical Study Report
Source: Figure 14.2.1.1.1

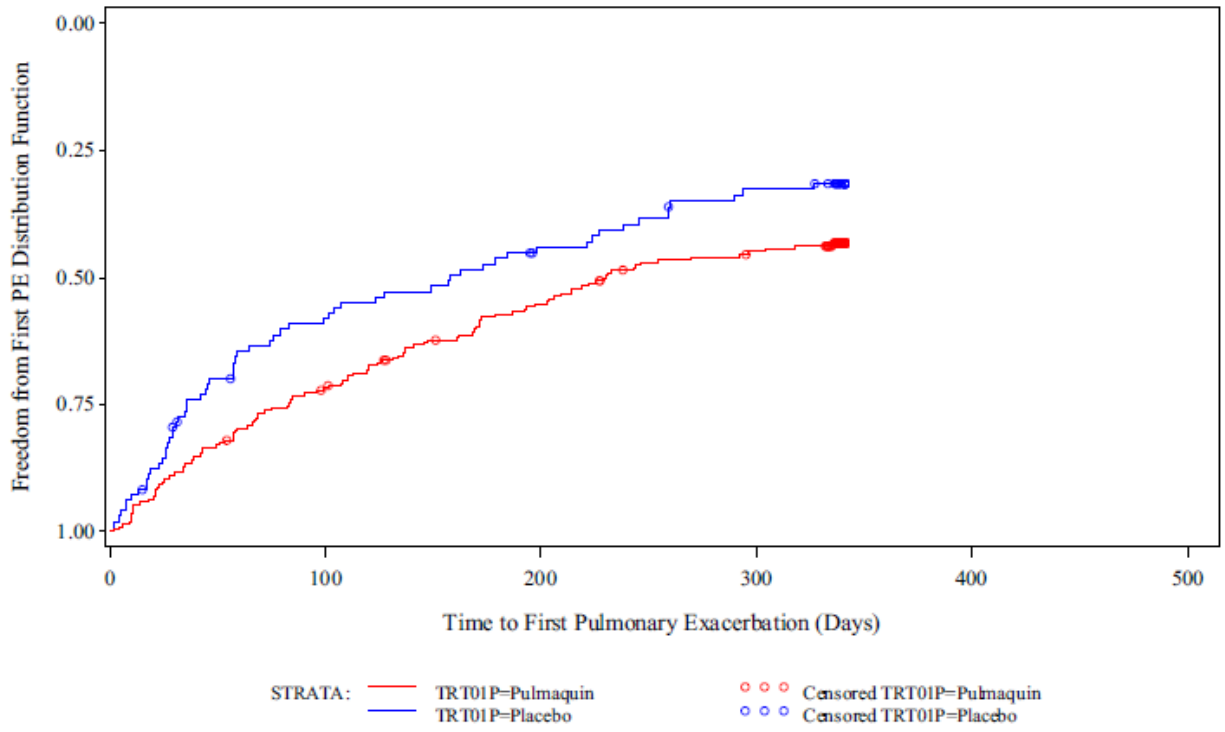
Primary analysis - **ARD-3150-1202 (ORBIT-4)**

114 subjects (55.3%) in the Linhaliq group experienced at least one PE by Week 48, as compared with 64 subjects (65.3%) in the placebo group. The median time to first PE was 230 days in the Linhaliq group and 158 days in the placebo group; a difference of 72 days.

Analysis of the primary endpoint (FA population) using the pre-specified non-stratified weighted log-rank test demonstrated a non-statistically significant treatment effect hazard ratio (95% CI) of 0.82 (0.56, 1.20); (p=0.1674).

Sensitivity analysis of the primary endpoint in the PP population was also not statistically significant.

Figure 7. Time to the First PE by Week 48, K-M Plot by Treatment (FA Population) in study ARD-3150-1202 (ORBIT-4)



Source: Figure 14.2.1.1.1

Source: ARD-3150-1202 Clinical Study Report

Secondary analyses – studies ARD-3150-1201 (ORBIT-3) and ARD-3150-1202 (ORBIT-4)

As summarised in Table 5, study ARD-3150-1202 (ORBIT-4) demonstrated statistically significant differences between groups for first secondary and second secondary efficacy endpoints (frequency of exacerbations):

- The Linhaliq group had a mean of 0.98 PEs per subject by Week 48 compared with 1.47 PEs per subject in the placebo group; risk ratio (95% CI) 0.63 (0.48, 0.82); (p=0.0006).
- The Linhaliq group had a mean of 0.14 severe PEs per subject by Week 48 compared with 0.30 severe PEs per subject in the placebo group; risk ratio (95% CI) 0.40 (0.22, 0.74); (p=0.0031).

In ARD-3150-1201 (ORBIT-3), however, there were no statistically significant differences between groups for first secondary and second secondary efficacy endpoints (frequency of exacerbations):

- The Linhaliq group had a mean of 1.09 PEs per subject by Week 48 compared with 1.31 PEs per subject in the placebo group; risk ratio (95% CI) 0.85 (0.65, 1.12); (p=0.2565).
- The Linhaliq group had a mean of 0.22 severe PEs per subject by Week 48 compared with 0.28 severe PEs per subject in the placebo group; risk ratio (95% CI) 0.80 (0.42, 1.51); (p=0.309).

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment.

Table 3. Summary of efficacy for study ARD-3150-1201 (ORBIT-3)

Title: A Multicenter, Randomised, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Pulmaquin® in the Management of Chronic Lung Infections with *P. aeruginosa* in Subjects with Non-Cystic Fibrosis Bronchiectasis, including 28 Day Open-Label Extension and Pharmacokinetic Substudy			
Study identifier	**ARD-3150-1201 (ORBIT-3)**		
Design	Phase II, randomised, double-blind, placebo-controlled study to assess the efficacy, safety and PK of Linhaliq in adult patients with NCFBE and chronic lung infections with *P. aeruginosa*		
	Duration of main phase:	48 weeks	
	Duration of Run-in phase:	not applicable	
	Duration of Extension phase:	4 weeks	
Hypothesis	Superiority		
Treatments groups	Linhaliq	Linhaliq (3 mL CFI, 45 mg/mL + 3 mL Free Ciprofloxacin for Inhalation [FCI]. OD for 28 d followed by no treatment for 28 d, 6 cycles, 193 subjects randomised	
	Placebo	Placebo, OD for 28 d followed by no treatment for 28 d, 6 cycles, 97 subjects randomised	
Endpoints and definitions	Primary endpoint	Time to first PE from randomisation to Week 48	
	Key Secondary endpoints	Number of PEs from baseline to Week 48 Number of severe PEs from baseline to Week 48 Change in Respiratory Symptoms scale score from baseline to Week 48	
Database lock	DB DBL 21 Sep 2016 OLE DBL 18 Nov 2016		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point	FA population - all randomised subjects who received at least one dose of study drug; Week 48		
Descriptive statistics and effect estimate	Treatment group	Linhaliq	Placebo
	Number of subjects	183	95
		Primary Efficacy Endpoint	
	Time to first PE (95% CI)	214 days (114, 289)	136 days (81, 339)
	Hazard ratio (95% CI) *(Non-stratified weighted log-rank test)*	0.92 (0.62, 1.35) *P*=0.4020	
		Key Secondary Efficacy Endpoints	
	Mean number of PEs baseline to Week 48	1.09	1.31
	Risk ratio (95% CI) *(Stratified negative binomial regression)*	0.85 (0.65, 1.12) *P*=0.2565	
	Mean number of severe PEs from baseline to Week 48	0.22	0.28

	Risk ratio (95% CI) *(Stratified negative binomial regression)*	0.80 (0.42, 1.51) *P*=0.3098	
	LS mean change in Respiratory Symptoms scale score (with sputum colour Q) from baseline to Week 48 (95% CI)	2.10 (-0.46, 4.65)	3.71 (0.32, 7.11)
	(MMRM)	-1.62 (-5.66, 2.43) *P*=0.4328	

Table 4. Summary of efficacy for study ARD-3150-1202 (ORBIT-4)

Title: A Multicenter, Randomised, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Pulmaquin® in the Management of Chronic Lung Infections with *P. aeruginosa* in Subjects with Non-Cystic Fibrosis Bronchiectasis, including 28 Day Open-Label Extension			
Study identifier	**ARD-3150-1202 (ORBIT-4)**		
Design	Phase III, randomised, double-blind, placebo-controlled study to assess the efficacy, safety and PK of Linhaliq in adult patients with NCFBE and chronic lung infections with *P. aeruginosa*		
	Duration of main phase:	48 weeks	
	Duration of Run-in phase:	not applicable	
	Duration of Extension phase:	4 weeks	
Hypothesis	Superiority		
Treatments groups	Linhaliq	Linhaliq (3 mL CFI, 45 mg/mL + 3 mL Free Ciprofloxacin for Inhalation [FCI]. OD for 28 d followed by no treatment for 28 d, 6 cycles, 193 subjects randomised	
	Placebo	Placebo, OD for 28 d followed by no treatment for 28 d, 6 cycles, 97 subjects randomised	
Endpoints and definitions	Primary endpoint	Time to first PE from randomisation to Week 48	
	Key Secondary endpoints	Number of PEs from baseline to Week 48 Number of severe PEs from baseline to Week 48 Change in Respiratory Symptoms scale score from baseline to Week 48	
Database lock	DB DBL 7 Oct 2016 OLE DBL 22 Nov 2016		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point	FA population - all randomised subjects who received at least one dose of study drug; Week 48		
Descriptive statistics and effect estimate	Treatment group	Linhaliq	Placebo
	Number of subjects	206	98
		Primary Efficacy Endpoint	
	Time to first PE (95% CI)	230 days (187, NA)	158 days (79, 238)

	Hazard ratio (95% CI) *(Non-stratified weighted log-rank test)*	0.82 (0.56, 1.20) *P*=0.1674	
		Key Secondary Efficacy Endpoints	
	Mean number of PEs baseline to Week 48	0.98	1.47
	Risk ratio (95% CI) *(Stratified negative binomial regression)*	0.63 (0.48, 0.82) *P*=0.0006	
	Mean number of severe PEs from baseline to Week 48	0.14	0.30
	Risk ratio (95% CI) *(Stratified negative binomial regression)*	0.40 (0.22, 0.74) *P*=0.0031	
	LS mean change in Respiratory Symptoms scale score (with sputum colour Q) from baseline to Week 48 (95% CI)	7.73 (5.37, 10.10)	6.90 (3.58, 10.21)
	(MMRM)	0.84 (-2.97, 4.65) *P*=0.6662	

Clinical studies in special populations

Table 5. Study Subjects Aged 65-74, 75-84 and 85+ in Controlled and Non-controlled Trials

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Controlled Trials			
ARD-3150-1202	112 / 304	50 / 304	3 / 304
ARD-3150-1201	108 / 278	57 / 278	4 / 278
ARD-3150-0902	24 / 42	3 / 42	0 / 42
ARD-3150-0901	32 / 95	13 / 95	2 / 95
Non Controlled trials			
ARD-3100-0701	0 / 20	0 / 20	0 / 20
ARD-3100-0801	4 / 15	1 / 15	0 / 15
ARD-3100-0702	0 / 22	0 / 22	0 / 22
ARD-3100-0703	7 / 36	4 / 36	0 / 36

Source: Applicant's Clinical Responses, Table 47.

The clinical programme enrolled a reasonable number of subjects aged 65-74 and 75-84, but few patients aged 85+. This is not unexpected from the nature of the condition and the severity of disease required as per inclusion criteria for enrolment in the Phase 2 and 3 studies.

Analysis performed across trials (pooled analyses AND meta-analysis)

Table 6. Key Efficacy Analyses of PE Endpoints in Studies ARD-3150-1202 (ORBIT-4) and ARD-3150-1201 (ORBIT-3) (FA Populations, Individual and Pooled)

	ARD-3150-1202		ARD-3150-1201		Pooled	
	Linhaliq (N=206)	Placebo (N=98)	Linhaliq (N=183)	Placebo (N=95)	Linhaliq (N=389)	Placebo (N=193)
Number of subjects with a PE	114 (55.3%)	64 (65.3%)	108 (59.0%)	54 (56.8%)	222 (57.1%)	118 (61.1%)
Primary endpoint: Time to first PE						
Median (days)	230	158	214	136	222	157
Stratified unweighted Treatment Effect Hazard Ratio (95% CI), and p-value (log-rank test)	0.72 (0.53, 0.97) p=0.0323		0.99 (0.71, 1.38) p=0.9743		0.82 (0.65,1.02) p=0.0741	
Non-stratified weighted Treatment Effect Hazard Ratio (95% CI), and p-value (log-rank test	0.82 (0.56, 1.20) p = 0.1674		0.92 (0.62, 1.35) p=0.4020		NA[a]	
Secondary endpoint: Number of PEs per subject						
Mean	0.98	1.47	1.09	1.31	1.03	1.39
Risk Ratio, p-value (stratified negative binomial regression)	0.63 (0.48, 0.82) p=0.0006		0.85 (0.65, 1.12) P=0.2565		0.73 (0.60, 0.88) p=0.0011	
Secondary endpoint: Number of Moderate or Severe PEs per subject						
Mean	0.78	1.27	0.86	1.13	0.82	1.20
Risk Ratio, p-value (stratified negative binomial regression)	0.58 (0.44, 0.77) p=0.0001		0.78 (0.58, 1.05) p=0.0998		0.67 (0.55, 0.82) p=0.0001	
Secondary endpoint: Number of Severe PEs per subject						
Mean	0.14	0.30	0.22	0.28	0.18	0.29
Risk Ratio, p-value (stratified negative binomial regression)	0.40 (0.22, 0.74) p=0.0031		0.80 (0.42, 1.51) p=0.4827		0.58 (0.37, 0.89) p=0.0141	

The stratification factors where applicable are sex and previous number of exacerbations in the past 12 months prior to randomisation.

[a] Analysis not available

Source: ARD-3150-1202 Table 14.2.1, Table 14.2.3.1.1, Table 14.2.3.2.3, Table 14.2.3.2.1; ARD-3150-1201 Table 14.2.1, Table 14.2.3.1.1, Table 14.2.3.2.3, Table 14.2.3.2.1; ISE Table 2.1.1, Table 2.3.1.1, Table 2.3.2.1.1, Table 2.3.2.1.

Source: Module 2.5 Clinical Overview

Pooled primary analysis was only provided using a stratified un-weighted log-rank analysis (as opposed to the pre-specified non-stratified weighted log-rank test), and resulted in a statistically non-significant result. However, it is noted that for the secondary efficacy endpoints of number of PEs, number of severe PEs, and number of moderate or severe PEs, pooled analysis demonstrated a statistically significant effect in favour of Linhaliq.

Supportive study

Study ARD-3150-0902 (ORBIT-2) was a phase 2, multicentre, randomised, double-blind, placebo-controlled study comparing the safety and efficacy of a formulation consisting of liposomal and free ciprofloxacin for inhalation with placebo in subjects with NCFBE and chronic lung infections with *P. aeruginosa*.

The primary objective of the study was to determine whether the microbiological efficacy of ARD-3150 was superior to placebo by evaluating changes in *P. aeruginosa* $\log_{10}$ CFU/g sputum.

Secondary endpoints included; microbiological efficacy, time to, number of patients experiencing, severity of, and time to resolve PEs, spirometry changes, safety and tolerability and QoL.

This study demonstrated statistically significant superiority of Linhaliq over placebo for the primary efficacy endpoint of change in sputum *P. aeruginosa* load from baseline to Day 28. This microbiological treatment effect is supported by statistically non-significant (borderline) superiority of Linhaliq over placebo for secondary efficacy endpoints of time to first PE (reduction of 76 days, point estimate) and number of patients initiating antibiotics (twice as many in the placebo group).

The final formulation of Linhaliq was used in this phase 2 study. However, the study design differed in many ways from that used for the Phase 3 programme, including total duration of treatment (3 treatment cycles), discontinuation of patients following first PE since randomisation (meaning no estimate of the effect of treatment on overall frequency of PEs is possible), and use of a microbiological rather than PE-related primary efficacy endpoint. Because of these differences, the results of this study provide microbiological proof-of-concept, and can offer only limited support to the results of the Phase 3 results.

Product usability testing

The applicant has provided two labelling comprehension studies for the Linhaliq instructions for use of nebulization system in the treatment of non-cystic fibrosis bronchiectasis. The main study 8900-1348 is described below and commented. Study 8900-1349 was a preliminary study and is not further discussed.

Study 8900-1348: Labelling comprehension study for the Linhaliq instructions for use of nebulization system in the treatment of non-cystic fibrosis bronchiectasis.

Forty (40) subjects were recruited to participate in a labeling comprehension study of the Linhaliq nebulizer system between June 6 and June 14, 2017. The Applicant attempted to meet an enrolment target of 30 NCFBE subjects, including 15 nebulizer naïve subjects. The study also intended to enrol approximately 25% of subjects with lower literacy by recruiting 50% of subjects reporting high school diploma only or less than high school level of education. In total, 20 subjects with a diagnosis of non-cystic fibrosis bronchiectasis (NCFBE) and 20 subjects with COPD as surrogates were enrolled in this study. The enrolled study sample in terms of age and gender approximated what is estimated for the intended user population of NCFBE. There were two study cohorts, nebulizer experienced (N=25) and nebulizer naïve (N=15).

Dosing performance with the Linhaliq nebulizer system is summarised below:

- Six (6) subjects of the study sample of 40 or 15% did not correctly perform the Linhaliq dose preparation.

- Of the 6 subjects who made a critical dose preparation error, 3 (50%) did so as a direct result of opening the inner carton box from the bottom and thus not locating the Instructions for Use (IFU). They attempted dose preparation without the Instructions for Use (IFU).
- Of the 3 remaining subjects who performed a critical error, 2 out of the 3 did not read or open the IFU, and 1 was confused by the vial top and did not successfully open it (a low literacy subject).
- There was no difference in performing critical dosing tasks between the nebulizer experienced and nebulizer naïve cohorts.

The results of this study were useful to inform several possible changes in the Linhaliq IFU text as well as the carton labeling (inner box label and outer box label) to improve user performance:

- Revise the IFU to enhance user understanding:
  - Revise Step 4 images with removal of the first vial image; addition of new image which shows lifting of the ringed tab up with text referring to it as "pull ringed tab up and out;" and, a more accurate portrayal of the stopper and its removal.
  - Address action to be taken if ringed tab breaks.
  - Describe how far and how hard to push in the wing tip tubing into the air compressor, such as, "Ensure both attachments are snug." Also, clarify that wingtip connection at both ends of the tubing are the same, i.e. universal, such as "the universal wingtip."
  - Describe if mixing or shaking of the nebulizer is necessary after additional of both vials. For example, "Do not shake the nebulizer. Contents do not need mixing."
- Revise outer box and inner labeling and/or packaging design:
  - Streamline 28-day outer packaging labeling content and remove redundancies, and revise reference to "56 Single-Use Vials."
  - In the alternative, consider a simplistic multipack design where all four inner cartons and the IFU are clearly visible, such as a clear top box.
  - Streamline inner 7-day carton labeling to remove redundancies.
  - Consider revising packaging design to avoid confusion with box orientation and ensure contents are opened from the top.
  - Eliminate "week" specific labeling on inner cartons as almost all subjects removed inner cartons from the top of the box and not the side dispenser.

The results of study 8900-1348 indicate that 15% of users could not correctly prepare the Linhaliq dose, which seems quite high. Almost all errors arose from failing to locate, open or read the Instructions for Use. The applicant summarises several possible changes to the Instructions for Use, outer box and inner labelling that were considered in response to these results but has not confirmed which (if any) of these changes were implemented to produce the packaging and labelling proposals submitted in the application. Moreover, the applicant has not presented any data to support that the changes implemented as a results of this study actually resulted in a higher proportion of users being able to correctly prepare the dose (**LoOI**).

3.3.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical efficacy of Linhaliq in the management of NCFBE patients with chronic lung infection with *P. aeruginosa* has been assessed in one Phase 2 study and two Phase 3 studies.

No traditional dose-response studies have been conducted.

Study ARD-3150-0902 (ORBIT-2) was a phase 2, multicentre, randomised, double-blind, placebo-controlled study comparing the safety and efficacy of Linhaliq with placebo in subjects with NCFBE and chronic lung infections with *P. aeruginosa* (FA population = 42). This study used a microbiological primary efficacy endpoint (change in sputum *P. aeruginosa* load from baseline to Day 28), supported by clinical secondary efficacy endpoints. Patients were discontinued from study drug following their first PE after baseline; therefore, frequency of PE was not measured.

Studies ARD-3150-1201 (ORBIT-3) and ARD-3150-1202 (ORBIT-4) were identical, phase 3, multicentre, randomised, double-blind, placebo-controlled studies comparing the safety and efficacy of 48 weeks treatment with Linhaliq (6 cycles of 28 days On-treatment followed by 28 days Off-treatment) as compared to placebo, in subjects with NCFBE and chronic lung infections with *P. aeruginosa* (FA populations = 278 and 304, respectively), with a pharmacokinetic sub-study completed during a 28-day open-label extension of study ARD-3150-1201 (ORBIT-3). The primary efficacy endpoint was time to first PE from the date of randomisation to Week 48, with key secondary efficacy endpoints of number of PEs, number of severe PEs and Change in Respiratory Symptoms scale score of the QoL-B from baseline (Day 1) to Week 48, and a number of additional microbiological and clinical efficacy endpoints.

An independent Pulmonary Exacerbation Blinded Adjudication Committee (PEBAC) was established to adjudicate, in a blinded manner, all cases of discrepancies between the investigator's assessment and the protocol-defined criteria for a PE. The PEBAC operated according to a written charter and held the same responsibilities for both studies. The analysis of the primary endpoint, as well as the analysis of e.g. the first two secondary endpoints, was based on a combination of final adjudicated assessments (by PEBAC) and non-adjudicated PEs as assessed by the investigator.

For each study, the sample size calculations were based on 48-week failure rates of 80% for placebo, and 60% for Linhaliq. The one SAP submitted (EU SAP version 1.0, dated 20 September 2016) was valid for both studies and states that analyses described were prospectively defined prior to database lock. With the dates for database lock clarified for the two phase 3 studies, this has now been confirmed.

While the phase 3 studies were ongoing, the impact on power of an expected treatment lag was investigated based on results from two studies, among them the Linhaliq phase 2b study (ARD-3150-0902 (ORBIT-2)), where the Kaplan-Meier (KM) estimated survival curves showed no appreciable separation for the first 1 month. This did not lead to any changes in sample size (/number of required events), but was used to justify a weighted log-rank statistic (instead of an unweighted/standard log-rank test) in the analysis of the primary endpoint. However, when the phase 3 data had been un-blinded analysed, the applicant concluded that a treatment time-lag did not exist. No explanation is provided for why this phenomenon, predicted from the Phase 2b data, was not consistently observed in ORBIT-3 and -4, despite using very similar inclusion and exclusion criteria.

Whilst the choice of a (standard) log-rank test was considered acceptable as initially specified, the final decision to revert to this strategy after changing to the weighted test was made after having seen

phase 3 study results; this implies a multiplicity issue that weakens the strength of statistical evidence. For the purpose of the regulatory assessment of efficacy, the methodology as pre-specified in an amendment prior to un-blinding of the data is considered the primary analysis.

In the primary endpoint analysis subjects who had no PE between Day 1 and Visit 14 were censored according to pre-defined censoring rules. Several sensitivity analyses were planned and have been performed including e.g. worst case analyses with imputation of events (PEs) at the time-point for study withdrawal in the Linhaliq arm alone. The sensitivity analyses are overall supported as considered covering a number of aspects in relation to e.g. reasons for missingness. Primary analyses were performed on the FA population excluding subjects that were not dosed. This concerned >5% of Linhaliq subjects in study 1201 (ORBIT-3) but only few subjects, whereof more in the placebo than Linhaliq arm, in study 1202 (ORBIT-4). However, ITT analyses were also pre-defined and have been presented. Multiplicity adjustment was planned and concerned the three most important/key secondary endpoints. No imputation of missing data was made for the secondary and other efficacy analyses.

In ORBIT-3 the rate of discontinuation from study drug was slightly higher in the Linhaliq vs. placebo group. AEs and subject decision to withdraw, likely due to no perceived benefit, were the commonest reasons to discontinue Linhaliq while subject decision was the commonest reason to withdraw in the placebo group. In ORBIT-4 the discontinuation rates were lower than in ORBIT-3 and slightly lower in the Linhaliq vs. placebo group. Subject decision was the commonest reason to withdraw in both groups.

Efficacy data and additional analyses

Key results

Study ARD-3150-0902 (ORBIT-2) demonstrated statistically significant superiority of Linhaliq over placebo for the primary efficacy endpoint of change in sputum *P. aeruginosa* load from baseline to Day 28. These results provided microbiological proof-of-concept to take forward to Phase 3 development. The observed lag in treatment effect (approximately 1 month) on time to PE observed between Linhaliq and placebo groups was taken into consideration in the statistical analysis plan for studies ARD-3150-1201 (ORBIT-3) and ARD-3150-1202 (ORBIT-4).

In studies ARD-3150-1201 (ORBIT-3) and ARD-3150-1202 (ORBIT-4), treatment with Linhaliq resulted in a prolongation of the median time to first PE by more than 2 months, but neither study met the required level of statistical significance ($p<0.05$) for the primary analysis using the pre-specified non-stratified weighted log-rank test. There were high baseline ciprofloxacin MICs among *P. aeruginosa* isolates obtained from patients in studies ARD-3150-1201 (ORBIT-3) and ARD-3150-1202 (ORBIT-4), which further increased during the treatment with Linhaliq. Meanwhile, MICs in patients receiving placebo remained at baseline levels throughout both studies.

Post hoc database review

The Rapporteurs raised concerns at D120 regarding an in-house, unblinded review and modification of the analysis datasets for studies ARD-3150-1201 (ORBIT-3) and ARD-3150-1202 (ORBIT-4), highlighted by review of the dossier by FDA.

Following database lock and unblinding of patient level data, the Applicant identified programming errors in the analysis datasets, whereby certain PE events had been identified or classified inaccurately. This prompted the Applicant to undertake a Systematic Review of all PE events. Patient source data, generated from the locked study databases by an independent CRO, were manually

reviewed by unblinded personnel. It is not clear whether this decision was made prior to or after it was known that both studies, on the basis of the original analysis, had failed to meet their primary objective. The decision to review source level data was, however, certainly made after unblinding and must be assumed to be data-driven. Had the analysis results been favourable for the application, perhaps no such additional scrutiny would have been applied.

No Standard Operating Procedure was created for this process. In total, 10 PE events in 9 patients that had been programmatically identified from the original dataset, where evaluation against the protocol definition of PE was manually deemed to be incorrect, were re-adjudicated by the original PEBAC in a blinded manner. This led to changes to the PEBAC dataset and analysis datasets managed by the two CROs, but not to the locked clinical trial databases containing individual patient source data. Re-analysis using the post-Re-adjudication analysis datasets resulted in a p-value <0.05 in ORBIT-4 (although only analysis using a stratified un-weighted log-rank test is presented, as opposed to the pre-specified non-stratified weighted log-rank test), due to minus one PE event in the Linhaliq arm and plus one PE event in placebo arm. It is now unclear whether the EU primary analysis (using the pre-specified non-stratified weighted log-rank test) as presented in the dossier is based on the Original or Re-adjudication analysis datasets (**LoOI**).

Table 7. Pre-and Post Re-Adjudication Changes in Primary Endpoint

Trial	Endpoint	Data pre re-adjudication	Data post re-adjudication
ORBIT-3	Patients with at least 1 PE during the trial	106 (LIN), 54 (PBO)	108 (LIN), 54 (PBO)
	P-value (Time to 1st PE)[a,c]	0.931	0.974
	Mean number of PEs per subject	1.08 (LIN), 1.26 (PBO)	1.09 (LIN), 1.31 (PBO)
	P-value [b,c]	0.336	0.257
	Mean number of severe PEs per subject	0.22 (LIN), 0.27 (PBO)	0.22 (LIN), 0.28 (PBO)
	P-value [b,c]	0.502	0.483

ORBIT-4	Patients with at least 1 PE during the trial	115 (LIN), 63 (PBO)	114 (LIN), 64 (PBO)
	P-value (Time to 1st PE) [a,c]	0.0525	0.032
	Mean number of PEs per subject	0.99 (LIN), 1.46 (PBO)	0.98 (LIN), 1.47 (PBO)
	P-value [b,c]	0.001	0.0006
	Mean number of severe PEs per subject	0.14 (LIN), 0.29 (PBO)	0.14 (LIN), 0.30 (PBO)
	P-value [b,c]	0.005	0.003

LIN=Linhaliq arm; PBO=placebo arm
Red bolded font indicates a change from the pre re-adjudication value.
Models include prior PEs (2-3 vs. ≥4) and sex as stratification factors.
[a] Time to first PE stratified unweighted log rank test, and [b]Stratified negative binomial model.
[c] Excludes a single patient in each Phase 3 trial that was randomised as having had two prior PEs but was later corrected by the investigator to one prior PE. This patient was by error excluded from the FA and ITT populations for each trial by the statistical CRO. Since the stratification by prior PEs did not have a <2 stratum and following the intent-to-treat principle, Aradigm believes that this patient should have been included for the primary TTFPE analysis

Concerns regarding the above process were raised by FDA upon review of the dossier, and an independent Third Party Evaluation was requested, using the locked clinical trial databases and original PE adjudication database. A third party CRO created a new set of programs that identified 31 cases where data were discordant, an even larger number than was identified by the applicant's own Systematic Review. This suggests that yet again in this third analysis, different approaches or rules were being applied to programmatically identified PE events from patient source data (**LoOI**). These were re-adjudicated by an entirely new PEBAC, blinded to subject and site identification, although it is unclear whether they were also blinded to treatment arm, previous adjudication result etc. (**LoOI**). The third-party analysis across secondary efficacy and sensitivity analyses were slightly more favourable outcome of the TTFPE and other secondary or supportive PE endpoints:

Table 8. Time to the First PE by Week 48 (ORBIT-3, ORBIT-4) – Third Party Evaluation analyses vs. Post-Systematic Review and Re-Adjudication analyses – FA Population

	ORBIT-3 – TPE		ORBIT-3 – Original		ORBIT-4 – TPE		ORBIT-4 – Original	
	Linhaliq	Placebo	Linhaliq	Placebo	Linhaliq	Placebo	Linhaliq	Placebo
	(N = 183)	(N = 95)	(N = 183)	(N = 95)	(N = 206)	(N = 98)	(N = 206)	(N = 98)
Weighted log-rank test – All PEs								
Number of subjects with a PE	108 (59.0%)	55 (57.9%)	108 (59.0%)	54 (56.8%)	113 (54.9%)	64 (65.3%)	114 (55.3%)	64 (65.3%)
Number of subjects who did not have a PE (censored)	75 (41.0%)	40 (42.1%)	75 (41.0%)	41 (43.2%)	93 (45.1%)	34 (34.7%)	92 (44.7%)	34 (34.7%)
Quartiles (95% CI) (days) [a]								
25th percentile	51 (37, 80]	59 (36, 69)	51 (37, 80)	59 (36, 69)	83 (57, 113)	36 (26, 58)	83 (57, 113)	36 (26, 58)
50th percentile	214 (114, 289)	136 (81, 299)	214 (114, 289)	136 (81, 339)	231 (187, NA)	158 (79, 238)	230 (187, NA)	158 (79, 238)
75th percentile	NA	NA	NA	NA	NA	NA (290, NA)	NA	NA (290, NA)
Treatment effect hazard ratio (95% CI) [b]		0.88 [0.60, 1.30]		0.92 (0.62, 1.35)		0.81 [0.55, 1.18]		0.82 (0.56, 1.20)
Non-stratified weighted log-rank test assuming maximum lag of 2.5 months								
P-value [c]		0.53		0.40		0.14		0.17
Unweighted log-rank test – All PEs	(N = 183)	(N = 95)	(N = 183)	(N = 95)	(N = 206)	(N = 98)	(N = 206)	(N = 98)
Number of subjects with a PE	108 (59.0%)	55 (57.9%)	108 (59.0%)	54 (56.8%)	113 (54.9%)	64 (65.3%)	114 (55.3%)	64 (65.3%)
Number of subjects who did not have a PE (censored)	75 (41.0%)	40 (42.1%)	75 (41.0%)	41 (43.2%)	93 (45.1%)	34 (34.7%)	92 (44.7%)	34 (34.7%)
Quartiles (95% CI) (days) [a]								
25th percentile	51 (37, 80]	59 (36, 69)	51 (37, 80)	59 (36, 69)	83 (57, 113)	36 (26, 58)	83 (57, 113)	36 (26, 58)
50th percentile	214 (114, 289)	136 (81, 299)	214 (114, 289)	136 (81, 339)	231 (187, NA)	158 (79, 238)	230 (187, NA)	158 (79, 238)
75th percentile	NA	NA	NA	NA	NA	NA (290, NA)	NA	NA (290, NA)
Treatment effect hazard ratio (95% CI) [b]		0.97 (0.70, 1.34)		0.99 (0.71, 1.38)		0.70 (0.52, 0.96)		0.72 (0.53, 0.97)
Stratified unweighted log-rank test								
P-value [c]		0.84		0.97		0.024		0.032

Note: Time to the first PE = date of documentation of first PE – randomization date + 1.
A hazard ratio < 1 indicates a lower risk with Linhaliq compared with placebo.
[a] Percentiles computed using only treatment effect as a stratification factor.
[b] The treatment effect hazard ratio is calculated by performing a stratified, unweighted Cox Proportional Hazard model.
[c] Stratified unweighted log-rank test using the stratification factors sex and previous number of exacerbations in the past 12 months prior to randomization.
Source TPE: ORBIT-3 Table 14.2.1.R; ORBIT-4 Table 14.2.1.R; ORBIT-3 Table 14.2.1.1.R; ORBIT-4 Table 14.2.1.1.R
Source Original: ORBIT-3 Table 14.2.1; ORBIT-4 Table 14.2.1; ORBIT-3 Table 14.2.2.1; ORBIT-4 Table 14.2.2.1

It is not possible to conclude that either the Re-adjudication analysis datasets or the Third Party Evaluation analysis datasets are more acceptable than the Original analysis datasets, given the *post hoc*, unblinded nature of the reviews conducted, the absence of an SOP for the Applicant's Systematic Review, and the discrepancies between the number of PE events counted in each new evaluation. Therefore, a quandary presents as to which of the three analyses is deemed the "true" conclusion for these studies, and it seems most likely that there are errors in all three. Finally, the Applicant has not yet submitted the pooled data analyses made by the Third Party Evaluation (**LoOI**).

The Applicant states that no GCP concerns were raised by the FDA, however, for full understanding of FDA's concern on GCP issues, the full report of inspection from FDA should be provided (**LoOI**). Furthermore, though it is stated that the FDA in principle agreed with the TPE protocol, the Independent Statistical Analysis Plan, and the charter, their final position is not known and should be clarified (**LoOI**).

Sub-group analyses

FEV1% predicted

Sub-group analysis for subjects with lowest and highest FEV1% predicted at screening, as requested by the Rapporteurs, shows a similar treatment effect observed in each of these sub-groups. However, considerable concerns regarding the integrity of the analyses based on post-database lock re-adjudications currently outweigh this issue, which is not further pursued.

Table 9. PE rate per Subject Overall and for Lowest and Highest Quartile Subgroup Baseline FEV1% Predicted, ORBIT-3

	Overall		Baseline FEV1% Predicted Group: ≤ 25th Percentile (N=81)		≥75th Percentile (N=61)	
	Linhaliq (N=183)	**Placebo** (N=95)	**Linhaliq** (N=55)	**Placebo** (N=26)	**Linhaliq** (N=41)	**Placebo** (N=20)
Number of PEs per Subject						
Mean	1.09	1.31	1.25	1.54	0.63	1.15
Risk Ratio, and p-value (stratified negative binomial regression)	0.85 (0.65, 1.12) p=0.2565		0.96 (0.62 , 1.49) p=0.8604		0.60 (0.30, 1.17) p= 0.1313	
Number of Moderate or Severe PEs per Subject						
Mean	0.86	1.13	1.04	1.27	0.49	1.05
Risk Ratio, and p-value (stratified negative binomial regression)	0.78 (0.58, 1.05) p=0.0998		1.00 (0.59, 1.70) p=0.9897		0.51 (0.24, 1.05) p=0.0691	
Number of Severe PEs per Subject						
Mean	0.22	0.28	0.42	0.31	0.1	0.2
Risk Ratio, and p-value (stratified negative binomial regression)	0.80 (0.42, 1.51) p=0.4827		1.71 (0.69, 4.21) p=0.2466		NA (NA, NA) NA	

Source: ORBIT-3 Table 14.2.3.1.1, Table 31.90.1, Table 14.2.3.2.3, Table 31.90.2, Table 14.2.3.2.1, Table 31.90.2.1

Table 10. PE rate per Subject Overall and for Lowest and Highest Quartile Subgroup Baseline FEV1% Predicted, ORBIT-4

	Overall		Baseline FEV1% Predicted Group: ≤ 25th Percentile (N=72)		Baseline FEV1% Predicted Group: ≥75th Percentile (N=93)	
	Linhaliq (N=206)	Placebo (N=98)	Linhaliq (N=45)	Placebo (N=27)	Linhaliq (N=65)	Placebo (N=28)
Number of PEs per Subject						
Mean	0.98	1.47	1.09	1.78	0.72	0.89
Risk Ratio, and p-value (stratified negative binomial regression)	0.63 (0.48, 0.82) p=0.0006		0.51 (0.34, 0.77) p=0.0014		0.85 (0.46, 1.56) p=0.5997	
Number of Moderate or Severe PEs per Subject						
Mean	0.78	1.27	0.98	1.44	0.57	0.86
Risk Ratio, and p-value (stratified negative binomial regression)	0.58 (0.44, 0.77) p=0.0001		NA (NA, NA) NA		0.71 (0.39, 1.27) p=0.2450	
Number of Severe PEs per Subject						
Mean	0.14	0.3	0.31	0.56	0.08	0.07
Risk Ratio, and p-value (stratified negative binomial regression)	0.40 (0.22, 0.74) p=0.0031		0.43 (0.18, 1.03) p=0.0589		1.30 (0.24, 6.91) p=0.7579	

Source: ORBIT-4 Table 14.2.3.1.1, Table 31.90.1, Table 14.2.3.2.3, Table 31.90.2, Table 14.2.3.2.1, Table 31.90.2.1

Study site

ORBIT-3 Site 1200 dosed 28 patients, by far the largest single site number, followed by ORBIT-3 site 1201 with 12 patients. In ORBIT-4 the highest enrolling site 0551 dosed 11 patients. All other sites in ORBIT-3 and ORBIT-4 dosed less than 10 patients. Given the high enrolment numbers for site 1200, sensitivity analyses were conducted for the primary and secondary PE endpoints for site 1200 alone and ORBIT-3 minus site 1200 patients. Overall, the primary and secondary PE analyses for Site 1200 in ORBIT-3 showed a better outcome in the placebo group that the Linhaliq group. Due to multiple sites enrolling few subjects, no robust conclusions regarding between-site differences can be drawn for either study.

Differences between ORBIT-3 and 4

The applicant has performed a number of post-hoc analyses to investigate the similarities and differences between the studies.

Macrolide use prior to study randomisation was not used as a stratification factor in ORBIT-3 and 4. The difference between the groups in the percentages of patients who received macrolide treatment prior to randomization in the ORBIT-3 trial was striking; in contrast, there was a lesser difference, favouring the opposite direction, between the groups in ORBIT-4:

Table 11. Number and Percentage of Patients Using Macrolides Prior to Randomization and On-Study (Double-Blind Phase), Full Analysis Population

		Macrolide Use Prior to Randomization		Macrolide Use On-Study (Double-Blind Phase)	
		n	%	n	%
ORBIT-3	Linhaliq (n=183)	43	23.5	22	11.4
	Placebo (n=95)	13	13.7	18	18.6
ORBIT-4	Linhaliq (n=206)	34	16.5	37	17.9
	Placebo (n=98)	24	24.5	19	18.8

If pre-randomization macrolide use is an indirect indicator of NCFBE disease severity (as asserted by the Applicant), then the observed imbalance will favour the placebo group in ORBIT-3 (thus decreasing the apparent treatment effect size) and the Linhaliq group in ORBIT-4 (thus increasing the apparent treatment effect size).

In ORBIT-3 the baseline FEV1% predicted was about 5% points lower than in ORBIT-4. The rate of decline in lung function in NCFBE patients is about a relative 1-2% decrease in FEV1 per year (King, 2011). Also, more patients in ORBIT-3 than in ORBIT-4 were on bronchodilators during the trials. These data may indicate that ORBIT-3 patients appeared to have had more advanced disease than ORBIT-4 patients, and, in addition, ORBIT-3 Linhaliq patients had worse pulmonary disease than ORBIT-3 placebo patients.

However, if it is accepted that higher baseline use of macrolides (and/or lower baseline FEV1% or higher baseline use of bronchodilators) indicates sicker patients, the two study populations are in fact not comparable, which poses a problem for pooled analysis of the studies and for the Applicant's claims regarding the totality of the data.

Finally, it seems plausible that on-study macrolides may be somewhat efficacious and therefore could have negated the efficacy observed for Linhaliq. However, it is not possible to fully evaluate or adjust for this potential effect. Moreover, considerable concerns regarding the integrity of the analyses based on post-database lock re-adjudications currently outweigh this issue, which his not further pursued.

3.3.7. Conclusions on clinical efficacy

A Major Objection on clinical efficacy remains (**LoOI**). The clinical efficacy of Linhaliq versus placebo has not been demonstrated in either of the two identically designed Phase 3 studies, neither of which meet their pre-specified primary endpoint (taking into account the pre-specified use of a non-stratified weighted log-rank test).

The preferential use of a stratified non-weighted log-rank test, being decided *post hoc* after unblinding of the data, is unavoidably data driven and therefore not accepted for primary analysis. While the Applicant's argument may be true that, despite similar inclusion and exclusion criteria, the Phase 3 studies failed to enrol a similar study population to that in which a treatment effect was observed in Phase 2, this argument leads to two possible conclusions, both of which are problematic for this application: either that the Phase 3 programme failed to enrol a study population sufficiently representative of the target population, or that, if the study population is considered acceptable, the Phase 3 studies failed to demonstrate convincing evidence of efficacy in the intended target population.

Concerns remain regarding the integrity of the Re-adjudication and Third Party Evaluation analyses conducted by the applicant after database lock, given the *post hoc*, unblinded nature of the reviews conducted, the absence of an SOP for the Applicant's Systematic Review, and the discrepancies between the number of PE events counted in each new evaluation. It is not possible at present to conclude that either the Re-adjudication analysis datasets or the Third Party Evaluation analysis datasets are more acceptable than the Original analysis datasets**.**

The Applicant asserts that data generated in ORBIT-3 and 4 support the conclusion of a clinically relevant and important benefit to patients with NCFBE and chronic lung infection with *P. aeruginosa*, on the basis that Time to First PE is not the most clinically relevant endpoint, despite this being pre-specified (and accepted) as the primary endpoint for the Phase 3 studies. No convincing argument is made as to why trends in PE frequencies observed in the pooled dataset are concluded to be clinically meaningful for the target population, in particular to the extent that the clinical benefit reflected in the

point estimates might be expected to outweigh considerable, unresolved uncertainties regarding the accuracy of estimation, given that efficacy has not been demonstrated with sufficient statistical certainty.

A number of details relating to the *post hoc* review and re-adjudication processes conducted by the Applicant and by a Third Party, which were not provided in the Applicant's responses to the D120 LoQ, should be clarified (**LoOI**). Clarification of these points is required for completion but is not considered sufficient to resolve the outstanding Major Objection.

3.3.8. Clinical safety

The overall clinical development program to support the safety of Linhaliq comprises eight clinical studies in healthy volunteers and patients with NCFBE who were dosed with either Linhaliq, precursors of Linhaliq or Ciprofloxacin for Inhalation (CFI), the liposomal component of Linhaliq.

A tabulation of the study designs, subject populations, safety parameters assessed, study treatments, and number of subjects in the Safety Population for each study is provided below. The overall clinical development program randomised 815 subjects (764 subjects with NCFBE, 22 subjects with cystic fibrosis, and 29 healthy volunteers).

Clinical Studies that Contributed to the Safety Evaluation of Linhaliq

Study Number and Phase	Study Design	No. of Safety Population Subjects, Sex (M, F), Age Range	Safety and Tolerability Parameters Evaluated[a]	Dose, Duration
Linhaliq Studies				
ARD-3150-1202 (ORBIT-4) (Phase 3)	Multinational, multicentre, randomised, double-blind, placebo-controlled study to evaluate the safety and efficacy of Linhaliq compared with placebo in the management of chronic *P. aeruginosa* lung infections in subjects with NCFBE with a history of PEs	304 (206 Linhaliq, 98 placebo) 107 M, 197 F 18-90 years	Physical examinations, AEs, vital signs, ECGs, pulmonary function tests (spirometry), clinical laboratory tests, DLCO	Linhaliq (6 mL, 189 mg) or placebo (3 mL CLI + 3 mL normal saline) was administered by inhalation once daily during six 56-day treatment cycles. Each treatment cycle consisted of 28 days of study drug treatment (on-treatment period) followed by 28 days of no study drug treatment (off-treatment period). Study drug was delivered via a PARI LC® Sprint nebulizer with a PARI Vios®, TurboBOY® S, or TurboBOY® SX compressor.
ARD-3150-1202 Open-Label Extension (OLE)	Multinational, multicentre, 28-day OLE with Linhaliq to extend the safety database	235 (prior DBP treatment group: Linhaliq, 164; placebo, 71)	Physical examinations, AEs, vital signs, ECGs, pulmonary function tests (spirometry), clinical laboratory tests	Linhaliq (6 mL, 189 mg) was administered by inhalation once daily for 28 days. Study drug was delivered via a PARI LC® Sprint nebulizer with a PARI Vios®, TurboBOY® S, or TurboBOY® SX compressor.
ARD-3150-1201 (ORBIT-3) (Phase 3)	Multinational, multicentre, randomised, double-blind, placebo-controlled study to evaluate the safety and efficacy of Linhaliq compared with placebo in the management of chronic *P. aeruginosa* lung infections in subjects with NCFBE with a history of PEs	278 (183 Linhaliq, 95 placebo) 84 M, 194 F 21-87 years	Physical examinations, AEs, vital signs, ECGs, pulmonary function tests (spirometry), clinical laboratory tests, DLCO	Linhaliq (6 mL, 189 mg) or placebo (3 mL CLI + 3 mL normal saline) was administered by inhalation once daily during six 56-day treatment cycles. Each treatment cycle consisted of 28 days of study drug treatment (on-treatment period) followed by 28 days of no study drug treatment (off-treatment period). Study drug was delivered via a PARI LC® Sprint nebulizer with a PARI Vios®, TurboBOY® S, or TurboBOY® SX compressor.

Study Number and Phase	Study Design	No. of Safety Population Subjects, Sex (M, F), Age Range	Safety and Tolerability Parameters Evaluated[a]	Dose, Duration
ARD-3150-1201 OLE	Multinational, multicentre, 28-day OLE with Linhaliq to extend the safety database	195 (prior DBP treatment group: Linhaliq, 127; placebo, 68)	Physical examinations, AEs, vital signs, ECGs, pulmonary function tests (spirometry), clinical laboratory tests	Linhaliq (6 mL, 189 mg) was administered by inhalation once daily for 28 days. Study drug was delivered via a PARI LC® Sprint nebulizer with a PARI Vios®, TurboBOY® S, or TurboBOY® SX compressor.
ARD-3150-0902 (ORBIT-2) (Phase 2b)	International, multicentre, randomised, double-blind, placebo-controlled study designed to evaluate the safety and efficacy of Linhaliq in subjects with NCFBE	42 (20 Linhaliq, 22 placebo) 19 M, 23 F 35-83 years	Physical examinations, AEs, vital signs, ECGs, clinical laboratory tests	Linhaliq (6 mL, 189 mg) or placebo (3 mL CLI + 3 mL normal saline) was administered by inhalation once daily during three 56-day treatment cycles. Each treatment cycle consisted of 28 days of study drug treatment (on-treatment period) followed by 28 days of no study drug treatment (off-treatment period). Study drug was delivered via a PARI LC® Sprint nebulizer with a PARI TurboBOY® S compressor.
ARD-3100-0801 (Phase 1)	Single-centre, randomised, crossover study in healthy adults and subjects with NCFBE	15 (9 healthy, 6 NCFBE) 7 M, 8 F 20-77 years	Physical examinations, AEs, vital signs, ECGs, clinical laboratory tests, pulmonary function tests (spirometry), tolerability (taste and tolerability questionnaire, cough and/or irritation after treatment, nebulization time)	Healthy subjects: (a) 1.5 mL CFI (67.5 mg) + 1.5 mL normal saline delivered via an AKITA Jet nebulizer (PARI LC Sprint Jet nebulizer with AKITA dosing unit); (b) 2 mL Linhaliq prototype (66.6 mg) delivered via an AKITA Apixneb nebulizer (PARI proprietary mesh nebulizer with AKITA dosing unit); (c) 3 mL Linhaliq prototype (99.9 mg) delivered via an AKITA Jet nebulizer. Crossover design with single doses separated by at least 5 days. Subjects with NCFBE: 3 mL Linhaliq prototype delivered via an AKITA Jet nebulizer. All subjects: Reference compound: tobramycin solution (TOBI®) administered the evening before commencing each administration of CFI or Linhaliq prototype.

Study Number and Phase	Study Design	No. of Safety Population Subjects, Sex (M, F), Age Range	Safety and Tolerability Parameters Evaluated[a]	Dose, Duration
CFI-Only Studies				
ARD-3100-0701 (Phase 1)	Open-label, single escalating dose (Cohorts 1-3) and multiple-dose (Cohort 4) study in healthy adults	20 14 M, 6 F 20-52 years	AEs, vital signs, ECGs, pulmonary function tests (spirometry), oxygen saturation (pulse oximetry), tolerability, clinical laboratory tests	CFI delivered via a PARI LC® Sprint nebulizer and PARI TurboBOY® S compressor Cohorts 1-3: single dose (135, 270, or 405 mg) Cohort 4: once daily for 7 days (270 mg)
ARD-3100-0702 (Phase 2a)	Multicentre, single-arm, multiple-dose study in subjects with cystic fibrosis	22 15 M, 7 F 19-44 years	AEs, laboratory values, vital signs, spirometry changes, physical examination findings and ECGs	6 mL CFI (270 mg) delivered via a PARI LC® Sprint nebulizer and PARI TurboBOY® S compressor Once daily for 14 days
ARD-3100-0703 (Phase 2a)	Multicentre, two-arm, multiple-dose study in subjects with NCFBE	39[b] 14 M, 25 F 46-80 years	Physical examinations, AEs, vital signs, ECGs, pulmonary function tests (spirometry), clinical laboratory tests, daily patient diary (breathing, general wellbeing, cough, chest pain, cold/flu symptoms, appearance of sputum, change in treatment/ management of symptoms)	3 mL CFI (135 mg) + 3 mL saline for inhalation or 6 mL CFI delivered via a PARI LC® Sprint nebulizer and PARI TurboBOY® S compressor Once daily for 28 days
ARD-3100-0901 (Phase 2b)	International, multicentre, randomised, double-blind, placebo-controlled study in subjects with NCFBE	95[c] (62 CFI, 33 placebo) 28 M, 67 F 24-88 years	AEs, laboratory values, vital signs, physical examination findings and ECGs	2 mL CFI (100 mg), 3 mL CFI (150 mg), placebo (2 mL CLI), or placebo (3 mL CLI) once daily for 28 days. Study drug was delivered via a PARI LC® Sprint nebulizer and PARI TurboBOY® S compressor

AE = adverse event; CFI = Ciprofloxacin for Inhalation; DBP = Double-Blind Phase; DLCO = Diffusing Capacity of the Lung for Carbon Monoxide; ECG = electrocardiogram; F = female; M = male; NCFBE = non-cystic fibrosis bronchiectasis; OLE = Open-Label Extension; PE = pulmonary exacerbation; PK = pharmacokinetic.
Except where noted, the Safety population consisted of all subjects who received at least one dose of study drug. Treatment assignment was based on the treatment actually received.

[a] Pulmonary function tests (spirometry) and DLCO were also assessed as exploratory efficacy measures in ARD-3150-1202 and ARD-3150-1201.

[b] The Safety population for ARD-3100-0703 was defined as all subjects who were enrolled and provided informed consent. Three subjects included in the Safety population for ARD-3100-0703 did not receive any study drug: 1 subject had neutropenic sepsis requiring hospitalization and 2 subjects had a PE before dosing. Therefore, only 36 subjects were exposed to study drug.

[c] The Safety population for ARD-3100-0901 was defined as the 95 randomised subjects who received at least one dose of study drug (Linhaliq or placebo).

The safety assessment below will focus on the pooled safety dataset from the double-blind phase of the two identical phase 3 studies (ORBIT-3 and ORBIT-4).

Patient exposure

The studies for the summary of clinical safety randomised 815 subjects (764 subjects with NCFBE, 22 subjects with cystic fibrosis, and 29 healthy volunteers). A total of 562 subjects were exposed to Linhaliq or Linhaliq prototype at doses of 2 to 6 mL; 148 subjects were exposed to CFI only; and 33 subjects were exposed to placebo (CLI) only. Of the total of 624 NCFBE subjects randomised to the to-be-marketed dose of Linhaliq, 409 were exposed in the double-blind phase to Linhaliq and 215 subjects were exposed to placebo. In the open-label extensions of the two Phase 3 trials, an additional 139 NCFBE subjects (originally randomised to placebo) were exposed to Linhaliq. Overall, a total of 548 NCFBE subjects were exposed to Linhaliq in the Phase 2b and Phase 3 trials.

This section focuses on the studies conducted in NCFBE patients with the formulation proposed for marketing, comprising pooled data for 582 subjects from the double-blind phase of the placebo-controlled ARD 3150-1202 and ARD 3150-1201 Phase 3 studies, with supporting data from an additional 42 subjects in the placebo-controlled ARD 3150-0902 Phase 2b study and from the 28 day open-label extension phase of the aforementioned Phase 3 studies.

Table 12. Study Drug Exposure and Compliance in the Double-Blind Phase of ARD-3150-1202, ARD-3150-1201, and Pooled (Safety Population), and in the ARD-3150-1202 and ARD-3150-1201 Open-Label Extensions

	Double-Blind Phase						Open-Label Extension	
	ARD-3150-1202		ARD-3150-1201		Pooled		ARD-3150-1202	ARD-3150-1201
	Linhaliq (N = 206)	Placebo (N = 98)	Linhaliq (N = 183)	Placebo (N = 95)	Linhaliq (N = 389)	Placebo (N = 193)	Total (N = 235)	Total (N = 195)
Total Number of Vials Dispensed								
Mean (SD)	307.5 (77.24)	296.7 (88.24)	281.2 (99.75)	290.0 (92.05)	295.1 (89.39)	293.4 (89.96)	56.0 (0.00)	56.0 (0.14)
Min, Max	56, 392	56, 392	56, 392	56, 392	56, 392	56, 392	56, 56	54, 56
Total Number of Vials Taken (Method A) [a]								
Mean (SD)	298.0 (82.39)	286.8 (95.81)	270.5 (107.22)	280.8 (98.14)	285.1 (95.75)	283.8 (96.75)	54.3 (7.35)	54.1 (7.96)
Min, Max	6, 336	6, 350	2, 336	4, 378	2, 336	4, 378	2, 56	4, 56
Study Drug Compliance (%) [b]								
< 40%	3 (1.5%)	3 (3.1%)	6 (3.3%)	3 (3.2%)	9 (2.3%)	6 (3.1%)	4 (1.7%)	5 (2.6%)
≥ 40% to < 60%	4 (1.9%)	2 (2.0%)	6 (3.3%)	2 (2.1%)	10 (2.6%)	4 (2.1%)	2 (0.9%)	1 (0.5%)
≥ 60% to < 80%	8 (3.9%)	4 (4.1%)	8 (4.4%)	2 (2.1%)	16 (4.1%)	6 (3.1%)	5 (2.1%)	3 (1.5%)
≥ 80% to < 90%	12 (5.8%)	6 (6.1%)	16 (8.7%)	7 (7.4%)	28 (7.2%)	13 (6.7%)	6 (2.6%)	4 (2.1%)
≥ 90%	179 (86.9%)	83 (84.7%)	147 (80.3%)	81 (85.3%)	326 (83.8%)	164 (85.0%)	218 (92.8%)	180 (92.3%)

SD = standard deviation.
[a] Total number of vials taken (Method A) = total number of vials dispensed – total number of unused vials returned.
[b] Compliance is calculated as the total actual vials taken by Method A during Double-Blind Phase (or Open-Label Extension), divided by total number of vials dispensed during Double-Blind Phase (or Open-Label Extension), multiplied by 100.
Source: ARD-3150-1202 Table 14.3.1.1, ARD-3150-1201 Table 14.3.1.1, ISS Table 2.1, ARD-3150-1202 OLE Table 14.4.1.2, ARD-3150-1202 OLE Table 14.4.1.2

A safety database including a total of 548 NCFBE subjects (409 in double-blind phase) exposed to Linhaliq in the dose proposed for marketing is considered adequate.

Adverse events

Adverse events (AEs) were collected following completion of the informed consent process; however, all AEs described in this Summary of Clinical Safety are treatment emergent unless otherwise indicated. AE data presented in this Summary of Clinical Safety are consistent with the Medical

Dictionary for Regulatory Activities (MedDRA) coding dictionary used at the time each study was originally analysed and reported in the individual CSRs.

In general, an AE was defined as any untoward medical occurrence in a subject that might or might not have had a causal relationship with the study drug. An AE therefore included any unfavourable and unintended sign (including abnormal laboratory findings), symptom, or disease temporally associated with the use of a study drug, whether or not considered related to the study drug. Separately, a serious adverse event (SAE) included, but was not limited to, an event that was fatal, was life-threatening, required inpatient hospitalization or prolongation of an existing hospitalization, resulted in a persistent or significant disability or incapacity, or was a congenital anomaly or birth defect in a pregnancy outcome. In addition, medically important events that did not result in any of the previously listed outcomes, but nevertheless were judged by the investigator to jeopardize the subject and required medical intervention to prevent said outcome, were also considered SAEs. Individual studies may have included additional information associated with the definition and collection of AEs and SAEs; see the individual CSRs for specific details.

Adverse events of special interest (AESI) were any irritation of the airway represented by either verbatim or preferred terms, which included bronchial hyperreactivity, bronchospasm, increased cough, dry throat, dysphonia, dyspnoea, oropharyngeal pain, painful respiration, pharyngeal oedema, pleuritic pain, respiratory tract irritation, tachypnoea, throat irritation, upper airway cough syndrome, wheezing, pleurisy, throat ache, laryngitis, pharyngitis, and itchy (itching) throat.

Integrated safety dataset

Table 13. Overall Summary of AEs in the Double-Blind Phase of ARD-3150-1202, ARD-3150-1201, and Pooled (Safety Population)

	ARD-3150-1202		ARD-3150-1201		Pooled	
	Linhaliq (N = 206)	Placebo (N = 98)	Linhaliq (N = 183)	Placebo (N = 95)	Linhaliq (N = 389)	Placebo (N = 193)
Subjects who had an AE	179 (86.9%)	95 (96.9%)	164 (89.6%)	87 (91.6%)	343 (88.2%)	182 (94.3%)
Subjects who had an AE related to study drug	58 (28.2%)	35 (35.7%)	78 (42.6%)	32 (33.7%)	136 (35.0%)	67 (34.7%)
Subjects who had an AE leading to study drug discontinuation (with action taken "study drug withdrawn")	10 (4.9%)	7 (7.1%)	24 (13.1%)	9 (9.5%)	34 (8.7%)	16 (8.3%)
Subjects who had an AE leading to withdrawal from study	5 (2.4%)	4 (4.1%)	16 (8.7%)	3 (3.2%)	21 (5.4%)	7 (3.6%)
Subjects who had an SAE	35 (17.0%)	28 (28.6%)	56 (30.6%)	24 (25.3%)	91 (23.4%)	52 (26.9%)
Subjects who had an SAE related to study drug	1 (0.5%)	1 (1.0%)	6 (3.3%)	1 (1.1%)	7 (1.8%)	2 (1.0%)
Subjects who had an AE with severity of: [a]						
Mild	36 (17.5%)	18 (18.4%)	32 (17.5%)	18 (18.9%)	323 (83.0%)	167 (86.5%)
Moderate	104 (50.5%)	50 (51.0%)	86 (47.0%)	49 (51.6%)	265 (68.1%)	140 (72.5%)
Severe	39 (18.9%)	27 (27.6%)	46 (25.1%)	20 (21.1%)	85 (21.9%)	47 (24.4%)
Subjects who had an AE related to study drug with severity of: [b]						
Mild	34 (16.5%)	18 (18.4%)	38 (20.8%)	16 (16.8%)	118 (30.3%)	53 (27.5%)
Moderate	22 (10.7%)	14 (14.3%)	30 (16.4%)	15 (15.8%)	57 (14.7%)	32 (16.6%)
Severe	2 (1.0%)	3 (3.1%)	10 (5.5%)	1 (1.1%)	12 (3.1%)	4 (2.1%)
Subjects who had a fatal AE	1 (0.5%)	2 (2.0%)	5 (2.7%)	3 (3.2%)	6 (1.5%)	5 (2.6%)
Subjects who had an AESI	150 (72.8%)	78 (79.6%)	133 (72.7%)	67 (70.5%)	283 (72.8%)	145 (75.1%)
Subjects who had a related AESI	31 (15.0%)	16 (16.3%)	41 (22.4%)	18 (18.9%)	72 (18.5%)	34 (17.6%)

AE = adverse event; AESI = adverse event of special interest; SAE = serious adverse event.
[a] For the pooled data: number of unique subjects with any event at the severity of mild, moderate or severe.
[b] For the pooled data: number of unique subjects with any related event at a severity of mild, moderate, or severe.
Source: ARD-3150-1202 Table 14.3.1.2, Table 14.3.2.1, and Table 14.3.2.2; ARD-3150-1201 Table 14.3.1.2, Table 14.3.2.1, and Table 14.3.2.2; ISS Table 3.1.1, Table 3.1.3, Table 3.2.1, and Table 3.2.2

Given that the 1201 and 1202 studies were of identical design and were performed in similar time frames and geographic locations, the differences between the respective Linhaliq arms in overall rates of AEs related to study drug (42.6% vs 28.2%), AEs leading to study drug discontinuation (13.1% vs 4.9%), AEs leading to withdrawal of study (8.7% vs 2.4%), overall SAE rate (30.6% vs 17.0%) and rate of fatal AEs (2.7% vs 0.5%) are striking. The Applicant has clarified that patients in ORBIT-3 in general had more advanced disease than ORBIT-4 at enrolment, which could explain the differences in AE frequencies between the Linhaliq arms of the studies. Differences in distribution of geographic locations (US/Oceania vs Eastern Europe/South America), and hence potential differences in clinical characteristics of the patients de facto recruited to the studies, could be the root cause of these observations.

Another possible issue is the choice of liposome-containing placebo. For analysis of safety and tolerability the optimal placebo is probably isotonic saline, but it is acknowledged that effective blinding could require a liposome-containing comparator. However, there is no clinical data to support that the liposomal placebo is without safety or tolerability issues and this could affect the assessment in comparison to Linhaliq. The Applicant has clarified the reasons for choosing a liposome-containing comparator rather than isotonic saline. It is agreed that a surfactant-like composition of the liposomes could provide an immunologically inert vehicle for drug delivery, but the "no difference observed" arguments in comparison to placebo and the expected course of NCFBE disease is not supported by any calculations to estimate the largest possible difference that could go undetected in the ORBIT studies. However, the chosen approach is acceptable.

Table 14. AEs Occurring in ≥ 2% of Subjects in Either Pooled Treatment Group in the Double-Blind Phase of ARD-3150-1202, ARD-3150-1201, and Pooled (Safety Population)

	ARD-3150-1202		ARD-3150-1201		Pooled	
System Organ Class / Preferred Term	Linhaliq (N = 206) Subjects n (%)	Placebo (N = 98) Subjects n (%)	Linhaliq (N = 183) Subjects n (%)	Placebo (N = 95) Subjects n (%)	Linhaliq (N = 389) Subjects n (%)	Placebo (N = 193) Subjects n (%)
Subjects who had an AE	179 (86.9%)	95 (96.9%)	164 (89.6%)	87 (91.6%)	343 (88.2%)	182 (94.3%)
Respiratory, thoracic and mediastinal disorders	157 (76.2%)	85 (86.7%)	138 (75.4%)	73 (76.8%)	295 (75.8%)	158 (81.9%)
Cough	137 (66.5%)	71 (72.4%)	114 (62.3%)	55 (57.9%)	251 (64.5%)	126 (65.3%)
Dyspnoea	107 (51.9%)	55 (56.1%)	104 (56.8%)	48 (50.5%)	211 (54.2%)	103 (53.4%)
Sputum increased	99 (48.1%)	64 (65.3%)	82 (44.8%)	44 (46.3%)	181 (46.5%)	108 (56.0%)
Wheezing	84 (40.8%)	49 (50.0%)	69 (37.7%)	35 (36.8%)	153 (39.3%)	84 (43.5%)
Increased viscosity of bronchial secretion	43 (20.9%)	25 (25.5%)	23 (12.6%)	12 (12.6%)	66 (17.0%)	37 (19.2%)
Haemoptysis	27 (13.1%)	18 (18.4%)	31 (16.9%)	9 (9.5%)	58 (14.9%)	27 (14.0%)
Oropharyngeal pain	10 (4.9%)	13 (13.3%)	9 (4.9%)	7 (7.4%)	19 (4.9%)	20 (10.4%)
Rhinorrhoea	11 (5.3%)	9 (9.2%)	3 (1.6%)	6 (6.3%)	14 (3.6%)	15 (7.8%)
Respiratory tract congestion	9 (4.4%)	8 (8.2%)	7 (3.8%)	1 (1.1%)	16 (4.1%)	9 (4.7%)
Sputum discoloured	5 (2.4%)	7 (7.1%)	8 (4.4%)	4 (4.2%)	13 (3.3%)	11 (5.7%)
Nasal congestion	5 (2.4%)	3 (3.1%)	6 (3.3%)	4 (4.2%)	11 (2.8%)	7 (3.6%)
Dysphonia	6 (2.9%)	1 (1.0%)	3 (1.6%)	7 (7.4%)	9 (2.3%)	8 (4.1%)
Productive cough	9 (4.4%)	1 (1.0%)	5 (2.7%)	0 (0%)	14 (3.6%)	1 (0.5%)
Respiratory failure	4 (1.9%)	4 (4.1%)	5 (2.7%)	2 (2.1%)	9 (2.3%)	6 (3.1%)
Rhonchi	3 (1.5%)	4 (4.1%)	6 (3.3%)	1 (1.1%)	9 (2.3%)	5 (2.6%)
Throat irritation	4 (1.9%)	3 (3.1%)	4 (2.2%)	2 (2.1%)	8 (2.1%)	5 (2.6%)
Pleuritic pain	6 (2.9%)	1 (1.0%)	3 (1.6%)	0 (0%)	9 (2.3%)	1 (0.5%)
Asthma	0 (0%)	2 (2.0%)	3 (1.6%)	2 (2.1%)	3 (0.8%)	4 (2.1%)
Sinus congestion	3 (1.5%)	0 (0%)	0 (0%)	4 (4.2%)	3 (0.8%)	4 (2.1%)

System Organ Class / Preferred Term	ARD-3150-1202		ARD-3150-1201		Pooled	
	Linhaliq (N = 206) Subjects n (%)	Placebo (N = 98) Subjects n (%)	Linhaliq (N = 183) Subjects n (%)	Placebo (N = 95) Subjects n (%)	Linhaliq (N = 389) Subjects n (%)	Placebo (N = 193) Subjects n (%)
General disorders and administration site conditions	119 (57.8%)	70 (71.4%)	118 (64.5%)	63 (66.3%)	237 (60.9%)	133 (68.9%)
Fatigue	71 (34.5%)	49 (50.0%)	71 (38.8%)	40 (42.1%)	142 (36.5%)	89 (46.1%)
Exercise tolerance decreased	54 (26.2%)	33 (33.7%)	44 (24.0%)	22 (23.2%)	98 (25.2%)	55 (28.5%)
Pyrexia	42 (20.4%)	25 (25.5%)	48 (26.2%)	31 (32.6%)	90 (23.1%)	56 (29.0%)
Malaise	36 (17.5%)	14 (14.3%)	16 (8.7%)	15 (15.8%)	52 (13.4%)	29 (15.0%)
Chest pain	11 (5.3%)	4 (4.1%)	12 (6.6%)	5 (5.3%)	23 (5.9%)	9 (4.7%)
Chest discomfort	9 (4.4%)	7 (7.1%)	10 (5.5%)	3 (3.2%)	19 (4.9%)	10 (5.2%)
Asthenia	3 (1.5%)	1 (1.0%)	8 (4.4%)	3 (3.2%)	11 (2.8%)	4 (2.1%)
Oedema peripheral	1 (0.5%)	6 (6.1%)	7 (3.8%)	1 (1.1%)	8 (2.1%)	7 (3.6%)
Pain	4 (1.9%)	3 (3.1%)	6 (3.3%)	1 (1.1%)	10 (2.6%)	4 (2.1%)
Chills	2 (1.0%)	4 (4.1%)	2 (1.1%)	0 (0%)	4 (1.0%)	4 (2.1%)
Investigations	134 (65.0%)	61 (62.2%)	112 (61.2%)	51 (53.7%)	246 (63.2%)	112 (58.0%)
Forced expiratory volume decreased	70 (34.0%)	33 (33.7%)	62 (33.9%)	19 (20.0%)	132 (33.9%)	52 (26.9%)
Breath sounds abnormal	61 (29.6%)	28 (28.6%)	42 (23.0%)	17 (17.9%)	103 (26.5%)	45 (23.3%)
Forced vital capacity decreased	48 (23.3%)	24 (24.5%)	37 (20.2%)	14 (14.7%)	85 (21.9%)	38 (19.7%)
Sputum abnormal	24 (11.7%)	15 (15.3%)	22 (12.0%)	12 (12.6%)	46 (11.8%)	27 (14.0%)
Pulmonary function test decreased	1 (0.5%)	1 (1.0%)	19 (10.4%)	11 (11.6%)	20 (5.1%)	12 (6.2%)
Chest x-ray abnormal	7 (3.4%)	2 (2.0%)	5 (2.7%)	4 (4.2%)	12 (3.1%)	6 (3.1%)
Weight decreased	1 (0.5%)	3 (3.1%)	4 (2.2%)	2 (2.1%)	5 (1.3%)	5 (2.6%)

System Organ Class / Preferred Term	ARD-3150-1202		ARD-3150-1201		Pooled	
	Linhaliq (N = 206) Subjects n (%)	Placebo (N = 98) Subjects n (%)	Linhaliq (N = 183) Subjects n (%)	Placebo (N = 95) Subjects n (%)	Linhaliq (N = 389) Subjects n (%)	Placebo (N = 193) Subjects n (%)
Infections and infestations	104 (50.5%)	61 (62.2%)	87 (47.5%)	50 (52.6%)	191 (49.1%)	111 (57.5%)
Sputum purulent	52 (25.2%)	37 (37.8%)	34 (18.6%)	13 (13.7%)	86 (22.1%)	50 (25.9%)
Nasopharyngitis	13 (6.3%)	6 (6.1%)	8 (4.4%)	5 (5.3%)	21 (5.4%)	11 (5.7%)
Pneumonia	8 (3.9%)	0 (0%)	12 (6.6%)	7 (7.4%)	20 (5.1%)	7 (3.6%)
Sinusitis	13 (6.3%)	4 (4.1%)	4 (2.2%)	5 (5.3%)	17 (4.4%)	9 (4.7%)
Urinary tract infection	10 (4.9%)	3 (3.1%)	9 (4.9%)	2 (2.1%)	19 (4.9%)	5 (2.6%)
Upper respiratory tract infection	9 (4.4%)	1 (1.0%)	10 (5.5%)	1 (1.1%)	19 (4.9%)	2 (1.0%)
Rhinitis	5 (2.4%)	4 (4.1%)	5 (2.7%)	3 (3.2%)	10 (2.6%)	7 (3.6%)
Lower respiratory tract infection	0 (0%)	2 (2.0%)	7 (3.8%)	6 (6.3%)	7 (1.8%)	8 (4.1%)
Oral candidiasis	3 (1.5%)	4 (4.1%)	6 (3.3%)	1 (1.1%)	9 (2.3%)	5 (2.6%)
Influenza	2 (1.0%)	4 (4.1%)	4 (2.2%)	3 (3.2%)	6 (1.5%)	7 (3.6%)
Viral infection	3 (1.5%)	2 (2.0%)	0 (0%)	2 (2.1%)	3 (0.8%)	4 (2.1%)
Vulvovaginal candidiasis	2 (1.0%)	4 (4.1%)	1 (0.5%)	0 (0%)	3 (0.8%)	4 (2.1%)
Nervous system disorders	78 (37.9%)	40 (40.8%)	75 (41.0%)	32 (33.7%)	153 (39.3%)	72 (37.3%)
Lethargy	49 (23.8%)	20 (20.4%)	39 (21.3%)	18 (18.9%)	88 (22.6%)	38 (19.7%)
Headache	23 (11.2%)	14 (14.3%)	21 (11.5%)	11 (11.6%)	44 (11.3%)	25 (13.0%)
Dysgeusia[a]	13 (6.3%)	7 (7.1%)	19 (10.4%)	6 (6.3%)	32 (8.2%)	13 (6.7%)
Dizziness	13 (6.3%)	4 (4.1%)	15 (8.2%)	5 (5.3%)	28 (7.2%)	9 (4.7%)
Gastrointestinal disorders	49 (23.8%)	31 (31.6%)	43 (23.5%)	27 (28.4%)	92 (23.7%)	58 (30.1%)
Nausea	14 (6.8%)	7 (7.1%)	16 (8.7%)	4 (4.2%)	30 (7.7%)	11 (5.7%)
Diarrhoea	14 (6.8%)	10 (10.2%)	7 (3.8%)	9 (9.5%)	21 (5.4%)	19 (9.8%)
Vomiting	6 (2.9%)	4 (4.1%)	9 (4.9%)	3 (3.2%)	15 (3.9%)	7 (3.6%)
Abdominal pain	5 (2.4%)	5 (5.1%)	8 (4.4%)	0 (0%)	13 (3.3%)	5 (2.6%)
Constipation	5 (2.4%)	2 (2.0%)	5 (2.7%)	3 (3.2%)	10 (2.6%)	5 (2.6%)
Abdominal pain upper	3 (1.5%)	5 (5.1%)	8 (4.4%)	0 (0%)	6 (1.5%)	5 (2.6%)
Dry mouth	1 (0.5%)	4 (4.1%)	3 (1.6%)	2 (2.1%)	4 (1.0%)	6 (3.1%)
Gastrooesophageal reflux disease	5 (2.4%)	1 (1.0%)	1 (0.5%)	3 (3.2%)	6 (1.5%)	4 (2.1%)

System Organ Class / Preferred Term	ARD-3150-1202		ARD-3150-1201		Pooled	
	Linhaliq (N = 206) Subjects n (%)	Placebo (N = 98) Subjects n (%)	Linhaliq (N = 183) Subjects n (%)	Placebo (N = 95) Subjects n (%)	Linhaliq (N = 389) Subjects n (%)	Placebo (N = 193) Subjects n (%)
Musculoskeletal and connective tissue disorders	50 (24.3%)	24 (24.5%)	43 (23.5%)	20 (21.1%)	93 (23.9%)	44 (22.8%)
Arthralgia	13 (6.3%)	5 (5.1%)	10 (5.5%)	4 (4.2%)	23 (5.9%)	9 (4.7%)
Back pain	8 (3.9%)	3 (3.1%)	13 (7.1%)	3 (3.2%)	21 (5.4%)	6 (3.1%)
Pain in extremity	8 (3.9%)	2 (2.0%)	11 (6.0%)	1 (1.1%)	19 (4.9%)	3 (1.6%)
Myalgia	4 (1.9%)	7 (7.1%)	5 (2.7%)	2 (2.1%)	9 (2.3%)	9 (4.7%)
Musculoskeletal chest pain	8 (3.9%)	1 (1.0%)	4 (2.2%)	2 (2.1%)	12 (3.1%)	3 (1.6%)
Musculoskeletal pain	5 (2.4%)	0 (0%)	3 (1.6%)	3 (3.2%)	8 (2.1%)	3 (1.6%)
Neck pain	1 (0.5%)	4 (4.1%)	2 (1.1%)	1 (1.1%)	3 (0.8%)	5 (2.6%)
Injury, poisoning and procedural complications	29 (14.1%)	13 (13.3%)	17 (9.3%)	14 (14.7%)	46 (11.8%)	27 (14.0%)
Laceration	5 (2.4%)	2 (2.0%)	3 (1.6%)	3 (3.2%)	8 (2.1%)	5 (2.6%)
Contusion	5 (2.4%)	0 (0%)	2 (1.1%)	5 (5.3%)	7 (1.8%)	5 (2.6%)
Fall	5 (2.4%)	0 (0%)	4 (2.2%)	2 (2.1%)	9 (2.3%)	2 (1.0%)
Skin and subcutaneous tissue disorders	25 (12.1%)	16 (16.3%)	22 (12.0%)	8 (8.4%)	47 (12.1%)	24 (12.4%)
Rash	7 (3.4%)	3 (3.1%)	6 (3.3%)	2 (2.1%)	13 (3.3%)	5 (2.6%)
Pruritus	3 (1.5%)	4 (4.1%)	6 (3.3%)	1 (1.1%)	9 (2.3%)	5 (2.6%)
Cardiac disorders	13 (6.3%)	6 (6.1%)	15 (8.2%)	7 (7.4%)	28 (7.2%)	13 (6.7%)
Atrial fibrillation	4 (1.9%)	2 (2.0%)	4 (2.2%)	2 (2.1%)	8 (2.1%)	4 (2.1%)
Palpitations	5 (2.4%)	2 (2.0%)	0 (0%)	3 (3.2%)	5 (1.3%)	5 (2.6%)
Ear and labyrinth disorders	11 (5.3%)	9 (9.2%)	16 (8.7%)	3 (3.2%)	27 (6.9%)	12 (6.2%)
Ear pain	4 (1.9%)	5 (5.1%)	3 (1.6%)	0 (0%)	7 (1.8%)	5 (2.6%)
Psychiatric disorders	10 (4.9%)	7 (7.1%)	11 (6.0%)	9 (9.5%)	21 (5.4%)	16 (8.3%)
Depression	2 (1.0%)	1 (1.0%)	3 (1.6%)	3 (3.2%)	5 (1.3%)	4 (2.1%)
Insomnia	0 (0%)	3 (3.1%)	2 (1.1%)	4 (4.2%)	2 (0.5%)	7 (3.6%)
Vascular disorders	15 (7.3%)	3 (3.1%)	11 (6.0%)	5 (5.3%)	26 (6.7%)	8 (4.1%)
Hypertension	9 (4.4%)	3 (3.1%)	3 (1.6%)	3 (3.2%)	12 (3.1%)	6 (3.1%)
Blood and lymphatic system disorders	4 (1.9%)	4 (4.1%)	9 (4.9%)	3 (3.2%)	13 (3.3%)	7 (3.6%)
Anaemia	4 (1.9%)	0 (0%)	5 (2.7%)	1 (1.1%)	9 (2.3%)	1 (0.5%)
Immune system disorders	6 (2.9%)	1 (1.0%)	5 (2.7%)	0 (0%)	11 (2.8%)	1 (0.5%)
Seasonal allergy	4 (1.9%)	0 (0%)	4 (2.2%)	0 (0%)	8 (2.1%)	0

AE = adverse event.
Coding is based on MedDRA 18.1. At each level of summarization, subjects reporting more than one AE are counted only once.
[a] The PT of dysgeusia was used to map events such as "taste" or "bitter taste with study drug inhalation" and does not indicate a neurological disorder.
Source: ARD-3150-1202 Table 14.3.1.3, ARD-3150-1201 Table 14.3.1.3, ISS Table 3.1.2

Overall, the safety profile of Linhaliq does not significantly differ from placebo when comparing the pooled study groups. In study 1201, there is a substantial difference between Linhaliq and placebo groups in FEV decrease with rates of 33.9% and 20.0%, respectively, while no such difference is seen in study 1202. An increased risk of long-term bronchopulmonary adverse drug reactions may need a far longer observation time than the span of the ORBIT studies, to clearly emerge. Therefore, the bronchopulmonary long-term safety of Linhaliq should be further clarified in a post-approval safety study (**LoOI**).

Also, in the pooled Linhaliq group, the rates of upper respiratory tract and urinary tract infections are more common than in subjects receiving placebo, but this is likely a coincidence as the total rate of infections and infestations favor the Linhaliq group. As to immunological events, see the separate section below.

When viewing the SmPC section 4.8, it is however not completely clear how the Applicant has processed the AE data to generate the ADR table. Section 4.8 of the SmPC (see SmPC comment) should be updated and justified according to SmPC guidelines. Hence, in addition to an updated table, a separate MAA assessment of possibility of causality for each proposed ADR is required. When looking at the present table, it seems rather likely that some of the listed terms are simply reported AEs, not ADRs. The Applicant has performed a complete review of the ADRs previously listed and is now proposing a very reductionistic approach for SmPC section 4.8, relying heavily on the investigator's assessment on whether the presented AEs were related to study drug or not, and excluding those that

could be related to the underlying disease. This strategy is endorsed regarding AEs where a causal relationship between the medicinal product and the adverse event is not a reasonable possibility, for example those related to levels of systemic ciprofloxacin exposure that are very far from what is seen with Linhaliq. However, all AEs related to the airways and thorax should be reintroduced as ADRs and listed in Section 4.8 even if they could be attributable to underlying disease or are similarly frequent in the (liposome-containing) placebo arm. A new ADR table should be presented using the principles described above (and could be deducted from the initial question), with annotation to clearly indicate all changes from the original version submitted (**LoOI**).

Adverse events of special interest (AESI)

AESI are defined as any irritation of the airway, are summarized for individual studies and the pooled dataset below. AESI were reported at a similar overall rate between the pooled Linhaliq and placebo groups (72.8% and 75.1%, respectively), and no SOC or individual PT was reported notably more frequently in the Linhaliq group versus the placebo group. Importantly, AEs of bronchospasm, throat irritation, respiratory tract irritation, laryngitis, and pharyngitis were reported at a similar rate between Linhaliq and placebo groups. No AE occurred at a 5% greater rate in the pooled Linhaliq group than the placebo group.

AEs of bronchospasm were reported in an equal percentage of subjects in both groups (1.3% Linhaliq, 1.0% placebo): 5 events in 5 Linhaliq subjects and 2 events in 2 placebo subjects.

Table 15. AESI in the Double-Blind Phase of ARD-3150-1202, ARD-3150-1201, and Pooled (Safety Population)

	ARD-3150-1202		ARD-3150-1201		Pooled	
System Organ Class / Preferred Term	Linhaliq (N = 206) Subjects n (%) [No. of Events]	Placebo (N = 98) Subjects n (%) [No. of Events]	Linhaliq (N = 183) Subjects n (%) [No. of Events]	Placebo (N = 95) Subjects n (%) [No. of Events]	Linhaliq (N = 389) Subjects n (%) [No. of Events]	Placebo (N = 193) Subjects n (%) [No. of Events]
Subjects who had an AESI	150 (72.8%) [738]	78 (79.6%) [504]	133 (72.7%) [690]	67 (70.5%) [365]	283 (72.8%) [1428]	145 (75.1%) [869]
Respiratory, thoracic and mediastinal disorders	150 (72.8%) [713]	78 (79.6%) [490]	130 (71.0%) [661]	66 (69.5%) [350]	280 (72.0%) [1374]	144 (74.6%) [840]
Cough	137 (66.5%) [286]	71 (72.4%) [193]	114 (62.3%) [284]	55 (57.9%) [138]	251 (64.5%) [570]	126 (65.3%) [331]
Dyspnoea	107 (51.9%) [241]	55 (56.1%) [151]	104 (56.8%) [205]	48 (50.5%) [114]	211 (54.2%) [446]	103 (53.4%) [265]
Wheezing	84 (40.8%) [152]	49 (50.0%) [115]	69 (37.7%) [130]	35 (36.8%) [71]	153 (39.3%) [282]	84 (43.5%) [186]
Oropharyngeal pain	10 (4.9%) [13]	13 (13.3%) [19]	9 (4.9%) [11]	7 (7.4%) [8]	19 (4.9%) [24]	20 (10.4%) [27]
Dysphonia	6 (2.9%) [6]	1 (1.0%) [1]	3 (1.6%) [3]	7 (7.4%) [7]	9 (2.3%) [9]	8 (4.1%) [8]
Throat irritation	4 (1.9%) [4]	3 (3.1%) [6]	4 (2.2%) [10]	2 (2.1%) [2]	8 (2.1%) [14]	5 (2.6%) [8]
Pleuritic pain	6 (2.9%) [7]	1 (1.0%) [1]	3 (1.6%) [3]	0	9 (2.3%) [10]	1 (0.5%) [1]
Pleurisy	2 (1.0%) [2]	0	4 (2.2%) [6]	3 (3.2%) [5]	6 (1.5%) [8]	3 (1.6%) [5]
Bronchospasm	1 (0.5%) [1]	1 (1.0%) [2]	4 (2.2%) [5]	1 (1.1%) [1]	5 (1.3%) [6]	2 (1.0%) [3]
Upper airway cough syndrome	0	1 (1.0%) [1]	2 (1.1%) [2]	1 (1.1%) [1]	2 (0.5%) [2]	2 (1.0%) [2]
Pharyngeal erythema	1 (0.5%) [1]	1 (1.0%) [1]	0	1 (1.1%) [1]	1 (0.3%) [1]	2 (1.0%) [2]
Choking sensation	0	0	2 (1.1%) [2]	0	2 (0.5%) [2]	0
Pharyngeal oedema	0	0	0	1 (1.1%) [1]	0	1 (0.5%) [1]
Respiratory tract irritation	0	0	0	1 (1.1%) [1]	0	1 (0.5%) [1]
General disorders and administration site conditions	19 (9.2%) [22]	11 (11.2%) [13]	21 (11.5%) [25]	8 (8.4%) [11]	40 (10.3%) [47]	19 (9.8%) [24]
Chest pain	11 (5.3%) [12]	4 (4.1%) [4]	12 (6.6%) [15]	5 (5.3%) [5]	23 (5.9%) [27]	9 (4.7%) [9]
Chest discomfort	9 (4.4%) [10]	7 (7.1%) [9]	10 (5.5%) [10]	3 (3.2%) [6]	19 (4.9%) [20]	10 (5.2%) [15]

Overall, the AESI rates are comparable between the pooled Linhaliq and placebo groups. Regarding bronchospasm, the rate is numerically higher in the Linhaliq 1201 group (2.2%) compared to the Linhaliq 1202 group (0.5%) as well as the placebo groups (1.1% and 1.0%, respectively). However,

the difference in not of a magnitude where random effects can be excluded and the risk of bronchospasm is not considered to significantly affect the benefit/risk balance for Linhaliq.

Serious adverse events and deaths

SAEs occurring in ≥ 2% of subjects in either pooled treatment group in the double-blind phases of ARD-3150-1202 and ARD-3150-1201, and pooled, are summarized below.

No SAE occurred at a 2% greater rate in the Linhaliq group than the placebo group. SAEs occurring at a 2% greater rate in the placebo group than the Linhaliq group were increased sputum (3.1% placebo, 0.5% Linhaliq), lower respiratory tract infection (3.1% placebo, 0.5% Linhaliq), and dyspnoea (6.7% placebo, 4.4% Linhaliq).

Table 16. SAEs Occurring in ≥ 2% of Subjects in Either Pooled Treatment Group in the Double-Blind Phase of ARD-3150-1202, ARD-3150-1201, and Pooled (Safety Population)

System Organ Class / Preferred Term	ARD-3150-1202		ARD-3150-1201		Pooled	
	Linhaliq (N = 206) Subjects n (%) [No. of Events]	Placebo (N = 98) Subjects n (%) [No. of Events]	Linhaliq (N = 183) Subjects n (%) [No. of Events]	Placebo (N = 95) Subjects n (%) [No. of Events]	Linhaliq (N = 389) Subjects n (%) [No. of Events]	Placebo (N = 193) Subjects n (%) [No. of Events]
Subjects who had an SAE	35 (17.0%) [57]	28 (28.6%) [56]	56 (30.6%) [95]	24 (25.3%) [70]	91 (23.4%) [152]	52 (26.9%) [126]
Respiratory, thoracic and mediastinal disorders	16 (7.8%) [23]	14 (14.3%) [27]	30 (16.4%) [44]	13 (13.7%) [21]	46 (11.8%) [67]	27 (14.0%) [48]
Dyspnoea	6 (2.9%) [7]	5 (5.1%) [7]	11 (6.0%) [16]	8 (8.4%) [9]	17 (4.4%) [23]	13 (6.7%) [16]
Respiratory failure	3 (1.5%) [3]	4 (4.1%) [4]	5 (2.7%) [5]	0	8 (2.1%) [8]	4 (2.1%) [4]
Haemoptysis	2 (1.0%) [2]	1 (1.0%) [3]	7 (3.8%) [7]	1 (1.1%) [2]	9 (2.3%) [9]	2 (1.0%) [5]
Sputum increased	1 (0.5%) [1]	2 (2.0%) [4]	1 (0.5%) [1]	4 (4.2%) [4]	2 (0.5%) [2]	6 (3.1%) [8]
Infections and infestations	12 (5.8%) [13]	11 (11.2%) [13]	16 (8.7%) [19]	15 (15.8%) [22]	28 (7.2%) [32]	26 (13.5%) [35]
Pneumonia [a]	7 (3.4%) [7]	0	7 (3.8%) [8]	6 (6.3%) [6]	14 (3.6%) [15]	6 (3.1%) [6]
Lower respiratory tract infection	0	1 (1.0%) [1]	2 (1.1%) [2]	5 (5.3%) [10]	2 (0.5%) [2]	6 (3.1%) [11]
General disorders and administration site conditions	3 (1.5%) [4]	4 (4.1%) [6]	5 (2.7%) [5]	5 (5.3%) [8]	8 (2.1%) [9]	9 (4.7%) [14]
Pyrexia	2 (1.0%) [2]	2 (2.0%) [2]	1 (0.5%) [1]	3 (3.2%) [3]	3 (0.8%) [3]	5 (2.6%) [5]

SAE = serious adverse event.
Coding is based on MedDRA 18.1 or higher. At each level of summarization, subjects reporting more than one AE are counted only once. Only system organ classes with at least one preferred term occurring in ≥ 2% of subjects in either pooled treatment group are listed.
[a] See Section 2.1.4.4, Adverse Events of Pneumonia.
Source: ARD-3150-1202 Table 14.3.2.3, ARD-3150-1201 Table 14.3.2.3, ISS Table 3.2.3

In ORBIT-3 the safety profile for Linhaliq was not as good as that for placebo and to some extent the differences were centred in the respiratory SOC, linking the lack of efficacy in this trial to the safety profile. Over and above this observation, the data suggest that ciprofloxacin per se may be a bronchial irritant. In contrast, in ORBIT-4, although the actual rates for respiratory SOC AEs were comparable with those in the Linhaliq group in ORBIT-3, the safety profile of Linhaliq was if anything slightly better than that of placebo. The applicant should provide an analysis of all and individual AEs potentially reflecting airways irritation for subsets of patients who did and did not use bronchodilators during the trial. The changes in FEV1 should also be presented by subgroup. These analyses should be conducted for each trial separately. Unfortunately, the timing of bronchodilator use in relation to the assigned daily treatment was not captured and therefore it is not possible to request further analyses in this regard.

The overall rates of SAEs are comparable between the pooled Linhaliq and placebo groups. Similar to the general AE trend, the SAE rate is numerically higher in the Linhaliq arm of the 1201 study also for

a relatively "hard" outcome such as haemoptysis (3.8% vs 1.0%) compared to both the internal placebo arm and Linhaliq 1202 subjects.

Fatal AEs

Eleven subjects in ARD-3150-1202 and ARD-3150-1201 and 1 subject in ARD-3100-0703 had a fatal AE. Most of the AEs leading to death were in the Respiratory, Thoracic and Mediastinal Disorders SOC (64%), as expected for this patient population. All deaths were considered unrelated to study drug. The survival analysis numerically favoured Linhaliq-treated subjects over placebo, with hazard ratios and 95% CIs of 0.79 (0.19, 3.31) in ORBIT-3 and 0.12 (0.01, 1.12) in ORBIT-4.

Table 17. Fatal AEs in the Linhaliq clinical development programme

Subject ID	Study	Age (years)/Sex	MedDRA Preferred Term(s)	Relationship to Study Drug	Study Day	Days Since Last Dose of Study Drug
Linhaliq, 6 mL						
04-1156-006	ARD-3150-1202	63/M	Bronchopneumonia	Unlikely	22	2
03-0017-001	ARD-3150-1201	80/F	Thalamus haemorrhage	Not related	174	146
03-0017-002	ARD-3150-1201	74/M	Loss of consciousness	Not related	247	3
03-0032-002	ARD-3150-1201	69/F	Cardiac arrest Unresponsive to stimuli	Unlikely Unlikely	84	7
03-1113-001	ARD-3150-1201	75/F	Respiratory failure	Not related	72	68
03-1603-003	ARD-3150-1201	67/F	Pneumonia	Unlikely	60	43
Placebo						
04-1552-001	ARD-3150-1202	44/F	Respiratory failure	Not related	152	13
04-1553-004	ARD-3150-1202	58/M	Chronic respiratory failure	Not related	6	4
03-1106-005	ARD-3150-1201	79/M	Pancreatic carcinoma	Not related	238	42
03-1605-009	ARD-3150-1201	64/F	Pneumonia	Not related	374	181
03-2003-003	ARD-3150-1201	50/F	Asphyxia	Not related	11	0
CFI, 3 mL						
608	ARD-3100-0703	61/M	Pneumonia Sepsis Multi-organ failure	Unlikely	40	12

AE = adverse event; CFI = Ciprofloxacin for Inhalation; F = female; M = male; MedDRA = Medical Dictionary for Regulatory Activities.
Source: ISS Table 3.2.8; ARD-3150-1202 Listing 16.2.7.1, Listing 16.2.7.5, and Listing 16.2.4.1; ARD-3150-1201 Listing 16.2.7.1, Listing 16.2.7.5, and Listing 16.2.4.1; ARD-3100-0703 Section 14.5.1, Listing 16.2.7.1, and Listing 16.2.4.1

Additional deaths were reported for 1 subject in ARD-3150-1201, who died during screening (no study drug was administered), as well as 1 Linhaliq and 2 placebo subjects in ARD-3150-1202. One subject (73/M; Linhaliq treatment group) was found dead on Study Day 372. The death (sudden death) was reported to Drug Safety as an AE; however, due to the data cut-off for AEs included in the Double-Blind Phase, this event is not reflected in the AE listings and tables in the CSR. One subject (45/F; placebo treatment group) died from respiratory insufficiency on Study Day 112, and subject 04-2351-013 (48/F; placebo treatment group) died from the "disease for which the subject was receiving study treatment" on Study Day 140.

Laboratory findings

A summary of actual values and changes in baseline in haematology, chemistry and urine analysis laboratory results for pooled ARD-3150-1202 and ARD-3150-1201 has been provided by the MAA but data is not shown in detail in this assessment report as the systemic exposure of ciprofloxacin following Linhaliq inhalation is very limited compared to oral or intravenous administration, for which the safety profile is already well established. As expected, the rate of abnormal laboratory findings in haematology, chemistry or urine analysis is comparable to placebo.

Haematology

Mean haematology values were similar in the Linhaliq group and the placebo group at baseline. No clinically meaningful fluctuations were noted in the mean or median change from baseline results for the clinical haematology analytes at Visits 8 and 14 in either treatment group.

In ARD-3150-1202 and ARD-3150-1201 open-label extensions, mean values for clinical haematology analytes at Visit 15 showed no clinically meaningful changes from baseline (Visit 14)

Chemistry

Mean clinical chemistry values were similar in the Linhaliq group and the placebo group at baseline. No clinically meaningful fluctuations were noted in the mean or median change from baseline results for the clinical chemistry analytes at Visits 8 and 14 in either treatment group.

In ARD-3150-1202 and ARD-3150-1201 open-label extensions, mean values for clinical chemistry analytes at Visit 15 showed no clinically meaningful changes from baseline (Visit 14).

Urinalysis

No clinically meaningful trends were observed in urinalysis results for individual subjects.

Safety in special populations

The Applicant has provided an age-stratification of AEs. Overall, no clear age-related trends were observed.

Table 18. Adverse Events – Age Stratified According to EMA Requirements

MedDRA Terms	Linhaliq				Placebo				Linhaliq+Placebo
	Age <65	Age 65-74	Age 75-84	Age 85+	Age <65	Age 65-74	Age 75-84	Age 85+	TOTAL
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total number of subjects (n)	171	139	75	4	77	81	32	3	582
Serious AEs – Total	31 (18.1%)	39 (28.1%)	19 (25.3%)	2 (50.0%)	20 (26.0%)	20 (24.7%)	10 (31.3%)	2 (66.7%)	143 (24.6%)
- Fatal	1 (0.6%)	3 (2.2%)	2 (2.7%)	0	3 (3.9%)	1 (1.2%)	1 (3.1%)	0	11 (1.9%)
- Hospitalization/prolong existing hospitalization	28 (16.4%)	39 (28.1%)	18 (24.0%)	2 (50.0%)	19 (24.7%)	20 (24.7%)	9 (28.1%)	2 (66.7%)	137 (23.5%)
- Life-threatening	5 (2.9%)	6 (4.3%)	2 (2.7%)	0	4 (5.2%)	2 (2.5%)	1 (3.1%)	0	20 (3.4%)
- Disability/incapacity	1 (0.6%)	2 (1.4%)	0	0	1 (1.3%)	0	1 (3.1%)	0	5 (0.9%)
- Other (medically significant)	13 (7.6%)	14 (10.1%)	6 (8.0%)	1 (25.0%)	8 (10.4%)	9 (11.1%)	4 (12.5%)	2 (66.7%)	57 (9.8%)
AE leading to drop-out	7 (4.1%)	7 (5.0%)	7 (9.3%)	0	3 (3.9%)	3 (3.7%)	1 (3.1%)	0	28 (4.8%)
Psychiatric disorders	10 (5.8%)	6 (4.3%)	5 (6.7%)	0	5 (6.5%)	7 (8.6%)	4 (12.5%)	0	37 (6.4%)
Nervous system disorders	55 (32.2%)	71 (51.1%)	26 (34.7%)	1 (25.0%)	25 (32.5%)	37 (45.7%)	10 (31.3%)	0	225 (38.7%)
Accidents and injuries	7 (4.1%)	23 (16.5%)	12 (16.0%)	0	6 (7.8%)	7 (8.6%)	4 (12.5%)	0	59 (10.1%)
Cardiac disorders	4 (2.3%)	16 (11.5%)	7 (9.3%)	1 (25.0%)	3 (3.9%)	5 (6.2%)	4 (12.5%)	1 (33.3%)	41 (7.0%)
Vascular disorders	11 (6.4%)	11 (7.9%)	4 (5.3%)	0	3 (3.9%)	5 (6.2%)	0	0	34 (5.8%)
Cerebrovascular disorders	0	3 (2.1%)	1 (1.3%)	0	0	0	0	0	4 (0.7%)
Infections and infestations	71 (41.5%)	82 (59.0%)	35 (46.7%)	3 (75.0%)	39 (50.6%)	50 (61.7%)	20 (62.5%)	2 (66.7%)	302 (51.9%)
Anticholinergic syndrome	0	0	0	0	0	0	0	0	0
Quality of life decreased	0	0	0	0	0	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	16 (9.4%)	23 (16.5%)	8 (10.7%)	0	6 (7.8%)	10 (12.3%)	3 (9.4%)	1 (33.3%)	67 (11.5%)
Other AEs appearing more frequently in older patients	Presented in Table 69								

Source: Applicant's responses, Table 68.

Immunological events

The Applicant has not presented a separate section on immunological events. From the overall AE table, it is evident that rates of rash and pruritus are similar between Linhaliq and placebo groups. However, events in the term "Immune system disorders" are unevenly distributed with 11 events (2.8%) in the Linhaliq group and only 1 (0.5%) in subjects receiving placebo. Of these events 8 vs 0 are reported as seasonal allergy in Linhaliq and placebo groups, respectively.

The Applicant states that the imbalance in immune disorder AEs between Linhaliq and placebo groups are caused by an improbable but not impossible difference in pre-existing conditions of allergic reactions between the Linhaliq and placebo groups. However, it is not clear if there is a true difference in pre-existing conditions of if it is the rate of on-treatment events, interpreted as presentations of seasonal allergy, that differs between groups. This should be supported by data on the total number of subjects with pre-existing allergic conditions in the respective group, to provide a denominator and rule out that the observed difference is not triggered by the study drug in patients prone to allergic reactions in general (**LoOI**).

Safety related to drug-drug interactions and other interactions

The Applicant states that no human drug metabolism or drug-drug interaction studies have been conducted with Linhaliq. The systemic pharmacokinetics of oral and IV ciprofloxacin are well characterized, and the drug-drug and metabolic properties of Linhaliq are expected to follow the oral or IV (systemic) formulations. Systemic exposure with Linhaliq is at least an order of magnitude lower compared with therapeutic doses of oral and IV ciprofloxacin. Thus, drug interactions are not expected to occur with Linhaliq to the same extent as with systemic administration of ciprofloxacin. It is expected that any drug-drug interactions will mimic qualitatively those for oral or IV ciprofloxacin, with the expectation that the extent of interactions may be less due to the much lower systemic exposure to ciprofloxacin following administration of Linhaliq via inhalation as compared to the approved dosage regimens of oral and IV ciprofloxacin products.

The line of argumentation provided by the Applicant is supported. The interactions systemic exposure of Linhaliq will qualitatively be similar to other ciprofloxacin products, but dose-dependent interactions will be of less clinical impact for Linhaliq.

Discontinuation due to AEs

ARD-3150-1202 and ARD-3150-1201

Discontinuation rates, and reasons for discontinuation, were similar between the pooled Linhaliq and placebo datasets. In the double-blind phase, AEs leading to discontinuation of study drug (AEs with action taken "study drug withdrawn") by SOC and PT are summarized below for the pooled dataset. Overall, 8.7% of Linhaliq subjects and 8.3% of placebo subjects discontinued study drug due to an AE. The only AE leading to discontinuation of study drug reported for ≥1% of subjects in either treatment group was dyspnoea (2.6% Linhaliq, 2.1% placebo).

Table 19. Treatment-Emergent Adverse Events with Action Taken of Study Drug Withdrawn, by System Organ Class and Preferred Term in the Double-Blind Phase (Safety Population)

	Linhaliq (N=389)		Placebo (N=193)		Total (N=582)	
	Subjects	Events	Subjects	Events	Subjects	Events
Subjects Who Had a TEAE with Action Taken of "Study Drug Withdrawn"	34 (8.7%)	42	16 (8.3%)	18	50 (8.6%)	60
Respiratory, thoracic and mediastinal disorders	21 (5.4%)	25	6 (3.1%)	6	27 (4.6%)	31
Dyspnoea	10 (2.6%)	10	4 (2.1%)	4	14 (2.4%)	14
Bronchospasm	2 (0.5%)	2	1 (0.5%)	1	3 (0.5%)	3
Cough	3 (0.8%)	3	0	0	3 (0.5%)	3
Wheezing	2 (0.5%)	2	0	0	2 (0.3%)	2
Acute Respiratory Failure	1 (0.3%)	1	0	0	1 (0.2%)	1
Bronchial Secretion Retention	1 (0.3%)	1	0	0	1 (0.2%)	1
Choking Sensation	1 (0.3%)	1	0	0	1 (0.2%)	1
Dyspnoea Exertional	1 (0.3%)	1	0	0	1 (0.2%)	1
Haemoptysis	1 (0.3%)	1	0	0	1 (0.2%)	1
Hypoxia	1 (0.3%)	1	0	0	1 (0.2%)	1
Pleuritic Pain	1 (0.3%)	1	0	0	1 (0.2%)	1
Respiratory Failure	0	0	1 (0.5%)	1	1 (0.2%)	1
Sputum Increased	1 (0.3%)	1	0	0	1 (0.2%)	1
Gastrointestinal disorders	3 (0.8%)	3	3 (1.6%)	3	6 (1.0%)	6
Diarrhoea	1 (0.3%)	1	1 (0.5%)	1	2 (0.3%)	2
Nausea	1 (0.3%)	1	1 (0.5%)	1	2 (0.3%)	2
Intestinal Ischaemia	1 (0.3%)	1	0	0	1 (0.2%)	1
Mouth Ulceration	0	0	1 (0.5%)	1	1 (0.2%)	1
Musculoskeletal and connective tissue disorders	4 (1.0%)	7	1 (0.5%)	1	5 (0.9%)	8
Muscular Weakness	2 (0.5%)	2	0	0	2 (0.3%)	2

Note: Coding is based on MedDRA 18.1 or higher.
Note: At each level of summation (overall, system organ class, preferred term), subjects reporting more than one adverse event are counted only once.
Note: Due to lack of coding option for an AE "Taste (abnormal) during inhalation" the events were coded to "Dysgeusia", but this does not represent a neurological disorder in patients.
Source Data: ADSLADD ADAE

Source: Aradigm\ISS\TLFs\Programs\t_ae_disc_saf.sas cchesbrough Run date: 21JUN17 10:26 Source Data Date: 12Jun2017

In the open-label extension, 1.7% and 1.5% of subjects in the ARD-3150-1202 and ARD-3150-1201 OLEs, respectively, discontinued study drug due to an AE. AEs leading to discontinuation of study drug, across the two OLEs, included chest discomfort (2 subjects), dyspnoea (2 subjects), and cough, haemoptysis, and osteoarthritis (1 subject each).

Post marketing experience – N/A

3.3.9. Discussion on clinical safety

The overall rates of adverse events (both severe and none-severe) in the pooled safety dataset for subjects treated with Linhaliq appear to a large extent comparable to placebo. As ciprofloxacin is a substance with a well-established safety profile and the systemic exposure caused by Linhaliq is substantially lower than for conventional ciprofloxacin products, no new safety issues are expected outside of the airways where the drug is administrated. A minor issue is a difference in immunological events between Linhaliq and placebo subjects and the Applicant is requested to provide additional clinical information on these subjects. Another possible issue is the choice of liposome-containing placebo. For analysis of safety and tolerability the optimal placebo is probably isotonic saline, but it is acknowledged that effective blinding could require a liposome-containing comparator.

The phase 3 data show numerically more subjects with decreases of FEV1 in the Linhaliq groups in comparison to placebo, particularly in ORBIT3 (33.9% vs 20.0%), and the absence of statistically significant differences cannot be interpreted as proof of equality. The abovementioned uncertainties, together with the novel approach of administering ciprofloxacin-containing liposomes to the airways, make the long-term aspects of bronchopulmonary safety aspects uncertain. An increased risk of long-term bronchopulmonary adverse drug reactions may need a far longer observation time than the span

of the ORBIT studies, to clearly emerge. Therefore, the bronchopulmonary long-term safety of Linhaliq should be further clarified in a post-approval safety study (see RMP section below).

The adverse events of special interest are all focused on airway reactions. Overall, the AESI rates are comparable between the pooled Linhaliq and placebo groups. Regarding bronchospasm, the rate is numerically higher in the Linhaliq 1201 group (2.2%) compared to the Linhaliq 1202 group (0.5%) as well as the placebo groups (1.1% and 1.0%, respectively). However, the difference is not of a magnitude where random effects can be excluded.

The overall rates of SAEs are comparable between the pooled Linhaliq and placebo groups. Similar to the general AE trend, the SAE rate is numerically higher in the Linhaliq arm of the 1201 study also for a relatively "hard" outcome such as haemoptysis (3.8% vs 1.0%) compared to both the internal placebo arm and Linhaliq subjects in the 1202 study. Discontinuation rates, and reasons for discontinuation, were similar between the pooled Linhaliq and placebo datasets.

All deaths (11 subjects in ARD-3150-1202 and ARD-3150-1201 and 1 subject in ARD-3100-0703) were considered unrelated to study drug.

3.3.10. Conclusions on clinical safety

Overall, Linhaliq seems reasonably safe and well-tolerated in comparison to the empty liposomal vehicle used as placebo. However, the remaining uncertainties, together with the novel approach of administering ciprofloxacin-containing liposomes to the airways, make the long-term aspects of bronchopulmonary safety aspects uncertain. An increased risk of long-term bronchopulmonary adverse drug reactions may need a far longer observation time than the span of the ORBIT studies, to clearly emerge. Therefore, the long-term bronchopulmonary safety of Linhaliq should be further clarified in a post-approval safety study.

A few other concerns remain, where the Applicant is requested to provide clarification or additional data.

3.4. Risk management plan

Safety concerns

The applicant proposed no safety concerns for inclusion in the RMP. However, long-term bronchopulmonary safety should be listed as a Missing Information in the RMP safety specification, and the Applicant should propose post-approval safety study (PASS) to address this issue (**LoOI**).

The adverse effects of systemic exposure to ciprofloxacin are well known and although bronchospasm is a novel risk related to the mode of administration, no additional pharmacovigilance activities or additional risk minimization measures are proposed.

Pharmacovigilance plan

There are no post-authorisation studies planned; this is not considered acceptable as the Applicant should propose post-approval safety study (PASS) to address the missing information on the long term bronchopulmonary safety (LoOI)

Risk minimisation measures

There are no proposed risk minimisation measures; the Applicant should update the section in line with the comments on the safety specifications above. (LoOI)

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.1 could be acceptable if the applicant implements the changes to the RMP as detailed in the endorsed Rapporteur assessment report and in the List of Outstanding Issues in section 6.3.

4. Orphan medicinal products

Orphan designation

N/A

Similarity

N/A

5. Benefit risk assessment

5.1. Therapeutic Context

5.1.1. Disease or condition

The most recently proposed indication is: prevention and reduction of frequent pulmonary exacerbations in non-cystic fibrosis bronchiectasis adult patients who have chronic lung infection with *Pseudomonas aeruginosa*.

5.1.2. Available therapies and unmet medical need

P. aeruginosa colonisation in NCFBE is associated with increased PEs, hospitalisation, reduced FEV_1, poorer quality of life, serious morbidity and reduced life expectancy (Finch *et al.*, 2015; Loebinger *et al.*, 2009; Wilson *et al.*, 1997; Goeminne *et al.*, 2014).

The European Respiratory Society (ERS) guidelines on the management of NCFBE in adults (Polverino *et al.*, 2017) recommend long-term inhaled antibiotic treatment (≥3 months) in NCFBE and chronic *P. aeruginosa* infection in adults experiencing three or more pulmonary exacerbations per year. The guidelines are conditional recommendations for off-label use based only on a moderate level of evidence, as there are currently no authorised medicinal products for the treatment of NCFBE patients with chronic lung infection with *P. aeruginosa*.

Several randomised trials of nebulised antibacterial agents have been conducted in patients with NCFBE. Despite a significant reduction in *P. aeruginosa* bacterial density, most have shown poor tolerability due to bronchospasm even in the context of protective bronchodilators.

5.1.3. Main clinical studies

The clinical efficacy of Linhaliq in the management of NCFBE patients with chronic lung infection with *P. aeruginosa* has been assessed in one Phase 2 study and two Phase 3 studies.

Study ARD-3150-0902 (ORBIT-2) was a Phase 2b study that evaluated the safety and efficacy of once daily nebulised Linhaliq for up to three treatment cycles (28 days On-Treatment, 28 days Off-treatment per cycle) in 42 adult NCFBE patients colonised with *P. aeruginosa* and with at least 2 pulmonary exacerbations (PE) requiring antibiotics in the 12 months preceding the study.

Studies ARD-3150-1201 (ORBIT-3) and ARD-3150-1202 (ORBIT-4) were identical, multicentre, randomised, double-blind, placebo-controlled studies to evaluate the safety and efficacy of daily nebulised Linhaliq for six treatment cycles (28 days On-Treatment, 28 days Off-treatment per cycle) in 278 and 304 adult NCFBE patients, respectively, colonised with *P. aeruginosa* and with at least 2 PEs requiring antibiotics in the 12 months preceding the study.

Each subject remained on their prescribed standard medications and therapeutic treatment regimens for the 48-week duration of the Double-Blind Phase, to which Linhaliq or placebo was added.

5.2. Favourable effects

In study ARD-3150-1201 (ORBIT-3). Treatment with Linhaliq resulted in a numerical prolongation of the median time to first PE by more than 2 months, but did not meet statistical significance for the pre-specified primary efficacy endpoint using the pre-specified statistical analysis method (non-stratified weighted log-rank test); hazard ratio (95% CI) of 0.99 (0.71, 1.38); (p=0.9743) or key secondary efficacy endpoints although the point estimates were in favour of Linhaliq. For the first key secondary endpoint, number of PEs per subject by Week 48, the risk ratio Linhaliq/placebo was; 0.85 (95% CI: 0.65, 1.12); p=0.2565. For the second key secondary endpoint, number of severe PEs per subject by Week 48, the risk ratio Linhaliq/placebo was 0.80 (95% CI: 0.42, 1.51); p=0.3098. There was no effect of active treatment on the proportion of subjects with at least one PE during the double-blind phase (59.0% in the Linhaliq group vs. 56.8% in the placebo group)

In study ARD-3150-1202 (ORBIT-4), treatment with Linhaliq resulted in a prolongation of the median time to first PE by more than 2 months, but did not meet statistical significance for the primary efficacy endpoint using the pre-specified statistical analysis method (non-stratified weighted log-rank test); hazard ratio (95% CI) of 0.82 (0.56, 1.20); (p=0.1674). There was a reduction in the proportion of subjects with at least one PE during the double-blind phase (55.3% in the Linhaliq group vs. 65.3% in the placebo group). Secondary analysis in study ARD-3150-1202 (ORBIT-4) demonstrated a statistically significant difference (37% reduction, point estimate) between Linhaliq and placebo groups for the first secondary efficacy endpoint of number of PEs per subject by Week 48, risk ratio (95% CI) of 0.63 (0.48, 0.82); (p=0.0006); and a statistically significant difference (60% reduction, point estimate) between Linhaliq and placebo groups for the second secondary efficacy endpoint of number of severe PEs per subject by Week 48, risk ratio (95% CI) of 0.40 (0.22, 0.74); (p=0.0031).

5.3. Uncertainties and limitations about favourable effects

The positive trend in primary efficacy outcome seen in studies ARD-3150-1201 (ORBIT-3) and ARD-3150-1202 (ORBIT-4) did not achieve statistical significance in either study according to their pre-specified primary analyses; on the other hand, in the pooled analysis there was an impact on the frequency of PE's (risk ratio 0.73, 95% CI: 0.60, 0.88; p= 0.0011, not corrected for multiplicity).

In ORBIT-4 the treatment effect hazard ratio (95% CI), based on a stratified unweighted log-rank test (primary analysis for the US), was 0.72 (0.53, 0.97); (p=0.0323) in the FA population and 0.78 (0.55, 1.11); (p=0.1610) in the PP population. However, a borderline positive result in what was for the EU only a supportive analysis cannot be used to classify ORBIT-4 as a positive trial.

The applicant has performed a number of post-hoc analyses to investigate the similarities and differences between the two pivotal studies and concluded that there appeared to be imbalances at baseline in FEV1% predicted and the use of bronchodilators and chronic macrolides between placebo and Linhaliq groups, and also a higher use of anti-pseudomonal antibiotics in study 1201 (ORBIT-3). If it is accepted that higher baseline use of macrolides (and/or lower baseline FEV1% or higher baseline

use of bronchodilators) indicates sicker patients, the two study populations are in fact not comparable, which poses a problem for pooled analysis of the studies and for the Applicant's claims regarding the totality of the data. Finally, it seems plausible that on-study macrolides may be somewhat efficacious and therefore could have negated the efficacy observed for Linhaliq. However, it is not possible to fully evaluate or adjust for this potential effect.

Other parameters were identified which apparently differed between study ARD-3150-1201 (ORBIT-3) and study ARD-3150-1202 (ORBIT-4). Overall, the differences between the two trials are not very marked yet there is a consistent indication that the population in ORBIT-4 was slightly younger, less likely to be of the typical white female demographic, to have had slightly fewer exacerbations in the previous year and to have slightly better lung function. Finally, more patients in the placebo groups than in the Linhaliq group took glucocorticoids by any route during the trial; ORBIT-3 34.7% vs 42.3%, ORBIT-4 30.4% vs 41.5%.

A further possible issue adding to uncertainty over the effect size is the choice of placebo. A detailed comparison of CLI and CFI compositions could not be found in the submitted documentation. The concentration of liposomes in CLI is not identical to that in CFI, which would make the comparator neither a true vehicle control, nor an entirely inert placebo control (e.g. "sham" nebuliser containing only NaCl or distilled water). This could have implications for the interpretation of the clinical efficacy results in terms of a difference between Linhaliq and placebo arms. However, without further data, the extent of this effect cannot be appreciated or adjusted for.

Finally, concerns regarding the post-unblinding review and re-adjudication of PE events, and the impact of this process on analysis results, remain incompletely resolved. It is not possible to conclude that either the Re-adjudication analysis datasets or the Third Party Evaluation analysis datasets are more acceptable than the Original analysis datasets, given the post hoc, unblinded nature of the reviews conducted, the absence of an SOP for the Applicant's Systematic Review, and the discrepancies between the number of PE events counted in each new evaluation. Although for the EU the possibly biased re-analyses does not have the effect of changing the outcome of the primary analysis from negative to positive (as the EU primary analysis was still negative for ORBIT-4 in the data presented in the submission), it seems most likely that there are errors in all three analyses, and it may be possible that the "true" results are in fact even less favourable.

5.4. Unfavourable effects

Adverse drug reactions

The overall rates of adverse events (both severe and none-severe) in the pooled safety dataset for subjects treated with Linhaliq appear to a large extent comparable to placebo. As ciprofloxacin is a substance with a well-established safety profile and the systemic exposure caused by Linhaliq is substantially lower than for conventional ciprofloxacin products, no new safety issues are expected outside of the airways where the drug is administrated. A minor issue is a difference in immunological events between Linhaliq and placebo subjects and the Applicant is requested to provide additional clinical information on these subjects. Another possible issue is the choice of liposome-containing placebo. For analysis of safety and tolerability the optimal placebo is probably isotonic saline, but it is acknowledged that effective blinding could require a liposome-containing comparator.

The phase 3 data show numerically more subjects with decreases of FEV1 in the Linhaliq groups in comparison to placebo, particularly in ORBIT3 (33.9% vs 20.0%), and the absence of statistically significant differences cannot be interpreted as proof of equality. The abovementioned uncertainties, together with the novel approach of administering ciprofloxacin-containing liposomes to the airways,

make the long-term aspects of bronchopulmonary safety aspects uncertain. An increased risk of long-term bronchopulmonary adverse drug reactions may need a far longer observation time than the span of the ORBIT studies, to clearly emerge. Therefore, the bronchopulmonary long-term safety of Linhaliq should be further clarified in a post-approval safety study (see RMP section below).

The adverse events of special interest are all focused on airway reactions. Overall, the AESI rates are comparable between the pooled Linhaliq and placebo groups. Regarding bronchospasm, the rate is numerically higher in the Linhaliq 1201 group (2.2%) compared to the Linhaliq 1202 group (0.5%) as well as the placebo groups (1.1% and 1.0%, respectively). However, the difference is not of a magnitude where random effects can be excluded.

The overall rates of SAEs are comparable between the pooled Linhaliq and placebo groups. Similar to the general AE trend, the SAE rate is numerically higher in the Linhaliq arm of the 1201 study also for a relatively "hard" outcome such as haemoptysis (3.8% vs 1.0%) compared to both the internal placebo arm and Linhaliq subjects in the 1202 study. Discontinuation rates, and reasons for discontinuation, were similar between the pooled Linhaliq and placebo datasets.

Selection of increased ciprofloxacin MIC

Linhaliq treatment resulted in a sustained increase in ciprofloxacin MICs of *P. aeruginosa* isolates in patients with NCFBE, from the very first treatment cycle. For Linhaliq subject isolates, the ciprofloxacin MIC50 was 0.5 mcg/mL at baseline and 1 mcg/mL at the end of the study (Visit 14) and the ciprofloxacin MIC90 increased from 4 mcg/mL at baseline to 16 mcg/mL at Visit 14. Meanwhile, MICs of *P. aeruginosa* isolates from patients receiving placebo remained at baseline levels throughout the studies. Thus, Linhaliq treatment appears to select for increased ciprofloxacin MICs in patients with NCFBE.

5.5. Uncertainties and limitations about unfavourable effects

The safety profile of Linhaliq is to a large extent based on the two identical phase 3 studies, ORBIT-3 and ORBIT-4. Although they are of identical design and performed in similar time frames and geographic locations, the safety outcomes are in some respects strikingly different. This makes the aggregation of a safety profile for Linhaliq slightly challenging, and safety data from the individual studies must to some extent be assessed separately as populations might not from all aspects be suitable for pooling.

The phase 3 data show numerically more subjects with decreases of FEV1 in the Linhaliq groups in comparison to placebo, particularly in ORBIT3 (33.9% vs 20.0%), and the absence of statistically significant differences cannot be interpreted as proof of equality. The abovementioned uncertainties, together with the novel approach of administering ciprofloxacin-containing liposomes to the airways, make the long-term aspects of bronchopulmonary safety aspects uncertain. An increased risk of long-term bronchopulmonary adverse drug reactions may need a far longer observation time than the span of the ORBIT studies, to clearly emerge. Therefore, the bronchopulmonary long-term safety of Linhaliq should be further clarified in a post-approval safety study (see RMP section below).

The potential for Linhaliq to select for increased ciprofloxacin MIC has not been not fully characterised by a complement of *in vitro*, *in vivo* and clinical data. The measured MIC values of isolates from the pooled Phase 3 study populations provided descriptive data only, and the precise clinical impact is unknown. Thus, selection of resistance remains a potential risk for Linhaliq.

5.6. Effects Table

Table 20. Effects Table for Linhaliq for prevention and reduction of frequent pulmonary exacerbations in non-cystic fibrosis bronchiectasis adult patients who have chronic lung infection with *Pseudomonas aeruginosa*.

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Prolonged time to first PE by week 48	Median (95% CI)	Days	**Linhaliq** ORBIT-3: 214 (114, 289) ORBIT-4: 230 (187, NA)	**PLI** ORBIT-3: 136 (81, 339) ORBIT-4: 158 (79, 238)	HR (95% CI) 0.92 (0.62, 1.35) p=0.4020 HR (95% CI) 0.82 (0.56, 1.20) p=0.1674	ARD-3150-1201 ARD-3150-1202
Number of PEs per subject by week 48	Mean per subject	N	**Linhaliq** ORBIT-3: 1.09 ORBIT-4: 0.98	**PLI** ORBIT-3: 1.31 ORBIT-4: 1.47	RR (95% CI) 0.85 (0.65, 1.12), p=0.2565 RR (95% CI) 0.63 (0.48, 0.82), p=0.0006	ARD-3150-1201 ARD-3150-1202
Number of severe PEs per subject by week 48	Mean per subject	N	**Linhaliq** ORBIT-3: 0.22 ORBIT-4: 0.14	**PLI** ORBIT-3: 0.28 ORBIT-4: 0.30	RR (95% CI) 0.80 (0.42, 1.51), p=0.4927 RR (95% CI) 0.40 (0.22, 0.74), p=0.0031	ARD-3150-1201 ARD-3150-1202
Unfavourable Effects						
Increased ciprofloxacin MICs in *P. aeruginosa* isolates from baseline to Visit 14	Resistant isolates (EUCAST criteria), pooled ORBIT-3 and -4	%	**Linhaliq** Baseline: 43 Visit 14: 64	**PLI** Baseline: 43 Visit 14: 38	Descriptive only	Day 80 Clinical AR
Bronchospasm	Cumulative AE rate	%	1.3	1.0	Not significant	
FEV decrease	Cumulative AE rate	%	33.9	26.9	Not significant	

Abbreviations: AE = adverse event, CI = confidence interval, EUCAST = European Committee on Antimicrobial Susceptibility Testing, HR = hazard ratio, NA = not available, PE = pulmonary exacerbation, PLI = placebo for inhalation, RR = risk ratio
Notes: Treatment with Linhaliq = 6 mL nebulised daily (28 On-Treatment days, 28 Off-Treatment days per cycle, total of 6 cycles).

5.7. Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

While there are microbiological effects, no relationship has previously been established between microbiological effects and clinical parameters in NCFBE patients. A clinical treatment effect of the absolute size demonstrated in studies ARD-3150-1201 (ORBIT-3) and study ARD-3150-1202 (ORBIT-4) for NCFBE patients with chronic lung infection with *P. aeruginosa*, representing a delay in time to first PE of over 2 months with Linhaliq as compared to placebo is considered modest, and neither of the pivotal studies showed statistically significant effects on its primary endpoint.

No convincing argument is provided as to why the observed trends in PE frequencies are concluded to be clinically meaningful for the target population, in particular to the extent that the clinical benefit reflected in the point estimates might be expected to outweigh considerable, unresolved uncertainties regarding the accuracy of estimation, given that efficacy has not been demonstrated with sufficient statistical certainty. The Applicant asserts that a reduction in PEs, particularly moderate and severe PEs requiring antibiotics and/or hospitalisation, is expected to translate into benefits for Quality of Life, daily symptoms, lung function and mortality, but such assumptions are theoretical, rather than supported by data from the clinical trials. Indeed, the mean on-treatment improvement in QOL-B Respiratory Symptom Scale score was generally +1 to +3 points amongst Linhaliq subjects, and the mean off-treatment deterioration in score was generally 0 to -4 points. This is a very small difference in the context of a 100-point scale, considering the mean baseline score of around 55 points in this study population and the Minimally Important Difference (MID) of around 8 points, calculated either as ½ Standard Deviation or 1 Standard Error of the baseline score as per the QOL-B Evidence Dossier.

The apparent trend for Linhaliq treatment to select for increasing ciprofloxacin MIC among *P. aeruginosa* isolates in patients with NCFBE is of unclear clinical consequence. In the short term, a clinical disadvantage secondary to antibiotic resistance might be expected in situations where a patient develops a clinical infection from an organism with an MIC increased by Linhaliq use. In the longer term, a decreasing susceptibility with treatment over time may gradually reduce, and eventually negate, any treatment effect. Studies conducted to date have only investigated 6 treatment cycles, which may be too short a time period to demonstrate such an effect.

5.7.2. Balance of benefits and risks

In summary while Linhaliq is microbiologically active as anticipated, clinical benefit has not been established across the phase III program. Although Linhaliq appears relatively well tolerated, there is a concern about the potential selection of high ciprofloxacin MICs in patients treated with Linhaliq. In the absence of firmly established clinical efficacy, positive B/R cannot be inferred.

Bronchospasm is known to pose problems for some patients with almost all inhaled treatments, most of which are administered over long periods or lifelong. The cumulative risk of bronchospasm with Linhaliq over a lifetime of treatment might be therefore acceptable, but only in the context of an established treatment effect.

5.7.3. Additional considerations on the benefit-risk balance

There are currently also Major Objections regarding the quality of Linhaliq.

5.8. Conclusions

There are two Major Objections on quality and one Major Objection on clinical efficacy.

The benefit-risk balance of Linhaliq is negative.