EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 July 2020
EMA/473660/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Arikayce liposomal

International non-proprietary name: amikacin

Procedure No. EMEA/H/C/005264/0000

Note

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

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Administrative information

Name of the medicinal product:	Arikayce liposomal
Applicant:	Insmed Netherlands B.V. Stadsplateau 7 3521 AZ Utrecht Netherlands
Active substance:	AMIKACIN SULFATE
International Non-proprietary Name/Common Name:	amikacin
Pharmaco-therapeutic group (ATC Code):	aminoglycoside antibacterials, other aminoglycosides (J01GB06)
Therapeutic indication(s):	Arikayce liposomal is indicated for the treatment of non-tuberculous mycobacterial (NTM) lung infections caused by *Mycobacterium avium* Complex (MAC) in adults with limited treatment options who do not have cystic fibrosis
Pharmaceutical form:	Nebuliser dispersion
Strength:	590 mg
Route of administration:	Inhalation use
Packaging:	Vial (glass)
Package size(s):	28 vials

Table of contents

List of abbreviations

Abbreviation	Definition
6MWT	6-minute walk test
AE	adverse event
AESI	adverse events of special interest
ALIS	amikacin liposome inhalation suspension
ATS/IDSA	American Thoracic Society/Infectious Diseases Society of America
AUC	area under the concentration-time curve
AUC_{0-24}	area under the concentration-time curve from 0 to 24 hours
BID	twice daily
CF	cystic fibrosis
CHMP	Committee for Medicinal Products for Human Use
C_{max}	maximum concentration
COPD	chronic obstructive pulmonary disease
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DPPC	dipalmitoylphosphatidylcholine
eGFR	estimated glomerular filtration rate
EOT	End of Treatment
EU	European Union
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IV	intravenous
LAI	liposomal amikacin for inhalation
MAA	marketing authorization application
MAC	*Mycobacterium avium* Complex
MDR	multidrug regimen
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
MIC_{50}	MIC against 50% of isolates
MIC_{90}	MIC against 90% of isolates

Abbreviation	Definition
MTB	*Mycobacterium tuberculosis*
NaCl	sodium chloride
NE	not estimable
NTM	nontuberculous mycobacteria(l)
ODD	Orphan Drug Designation
PD	pharmacodynamic
PK	pharmacokinetic
PPK	population PK
P aeruginosa	*Pseudomonas aeruginosa*
PT	preferred term
QD	once daily
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SGRQ	St. George's Respiratory Questionnaire
SLIT	sustained release lipid inhalation targeting
SOC	system organ class
spp.	species
TEAE	treatment-emergent adverse event
TOBI	tobramycin solution for inhalation
US	United States

Definitions and Terms	
Converter	A subject who had 3 consecutive monthly MAC-negative sputum cultures
Date of conversion	Date of the first of at least 3 consecutive monthly culture specimens that were MAC negative
Durable sputum culture conversion at 3 months off treatment	3 consecutive monthly MAC-negative sputum cultures by Month 6, sustain the conversion (no positive solid media sputum cultures and no more than 2 consecutive liquid positive cultures) through an additional 12 months of treatment, and continue to sustain the conversion through 3 months off all NTM MAC treatment
Relapse or recurrence after achieving culture conversion	MAC-positive sputum cultures in liquid media (agar negative) for 3 or more consecutive months or having 1 MAC positive sputum culture on solid media (agar positive)
Sputum culture conversion	3 consecutive monthly MAC-negative sputum cultures
Sustained sputum culture conversion	3 consecutive monthly MAC-negative sputum cultures by Month 6, and no positive solid media sputum cultures and no more than 2 consecutive liquid positive cultures through an additional 12 months of treatment, from the start of conversion (first of 3 negative cultures)

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Insmed Netherlands B.V. submitted on 1 July 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Arikayce, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 13 December 2018.

Arikayce was designated as an orphan medicinal product EU/3/14/1259 on 8 April 2014 in the following condition: Treatment of nontuberculous mycobacterial lung disease.

The applicant initially applied for the following indication:

"Arikayce is indicated for the treatment of persistent *Mycobacterium avium* Complex (MAC) lung infection as part of a combination antibacterial drug regimen in adults. Consideration should be given to official guidance on the appropriate use of antibacterial agents."

The name Arikayce was changed to 'Arikayce liposomal' during the procedure. Reference to both names appears throughout the assessment.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Arikayce liposomal as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the Orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: www.ema.europa.eu/en/medicines/human/EPAR/arikayce-liposomal.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision EMEA-C3-000525-PIP01-08 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was not yet completed as some measures were deferred. The PDCO issued an opinion on compliance for the PIP EMEA-C3-000525-PIP01-08-M04.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication. There are no medicinal products authorised in the EU for the indication

claimed for Arikayce liposomal.

New active Substance status

The applicant indicated the active substance amikacin contained in the above medicinal product to be considered as a known active substance.

- Protocol assistance

The applicant received Scientific Advice on 23 January 2014 (EMEA/H/SA/1157/2/2013/SME/II) and 21 May 2015 (EMEA/H/SA/1157/2/FU/1/2015/PA/SME/II) for the development programme supporting the indication granted by CHMP.

The Scientific Advice pertained to the following clinical aspects of the dossier:

- Plan to submit a MAA on the basis of a single pivotal trial.
- Design of study TR02-112 in terms of dose regimen, endpoints, control, sample size, statistical analysis plan and patient population (patients with pulmonary NTM, ages 18 years to 85 years, with either *Mycobacterium avium complex* and/or *Mycobacterium abscessus*, who are culture positive on a stable ATS/IDSA guidelines-based multi-drug regimen for at least 6 months).
- Design of the single arm study TR02-116, in patients with pulmonary NTM, ages 6 years to 85 years, with either *Mycobacterium avium complex* and/or *Mycobacterium abscessus* who are not eligible for study TR02-112 or who are intolerant to their current regimen. Concurrence that study TR-02-116 will be ongoing at the time of submission of the MAA.
- Design of study INS-212 in adult patients with refractory MAC lung infection, in terms of endpoints, population, statistical analysis, collection and handling of the sputum samples for microbiological assessments.
- Overall clinical development plan

Date	Reference
23 January 2014	EMEA/CHMP/SAWP/15124/2014
21 May 2015	EMEA/CHMP/SAWP/310273/2015

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jayne Crowe Co-Rapporteur: Ewa Balkowiec Iskra

The application was received by the EMA on	1 July 2019
The procedure started on	18 July 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	7 October 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	7 October 2019

The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	18 October 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 November 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	26 February 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	25 March 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	17 April 2020
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	30 April 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	25 May 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	9 June 2020
The CHMP agreed on a 2nd list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	25 June 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	29 June 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	2 July 2020
A SAG/Expert group was convened to address questions raised by the CHMP on The CHMP considered the views of the SAG as presented in the minutes of this meeting.	10 July 2020
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	21 July 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Arikayce liposomal on	23 July 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Arikayce liposomal is proposed to be indicated for the treatment of treatment of non-tuberculous mycobacterial (NTM) lung infections caused by *Mycobacterium avium* Complex (MAC) in adults with

limited treatment options who do not have cystic fibrosis. It will be used as part of a combination antibacterial drug regimen.

At the time of this report, there are no approved medications for the NTM indication in the EU.

Non-tuberculous mycobacterial (NTM) lung disease caused by MAC is associated with productive cough, shortness of breath, fatigue, lung function decline and mortality. MAC has been implicated in complications of debilitating lung diseases such as bronchiectasis or chronic obstructive pulmonary disease (COPD). Post-menopausal Caucasian women without apparent predisposing conditions have been reported with increasing frequency to have pulmonary disease associated with MAC.

The morbidity associated with NTM lung diseases is significant and has been reported in the literature to have a 5-year all-cause mortality risk ranging from 5.4% to 39.7%. In retrospective studies from the literature, the failure to achieve negative sputum cultures in patients with MAC lung disease has been associated with higher mortality rates. The 5-year mortality rate in one study was 33.3% for untreated MAC lung disease compared to 22.2% for treated MAC lung disease in patients with definite MAC lung disease. In the treated group, sputum culture conversion was 53.7% compared to 0% in the untreated group.

Another study evaluated the outcomes of patients with macrolide-resistant MAC lung disease and found that the 1-year mortality rate was 34% for patients who remained sputum culture positive compared to 0% for patients who converted to negative. This study also showed a similar trend in the 5-year mortality risk for most patients who reached their 5-year follow-up (63% for patients who remained culture-positive compared to 23% for converters). A recent update in patients with MAC lung disease reported a pooled estimate of 5-year all-cause mortality of 27%, with a high variability across the pooled datasets, ranging from 10% to 48%. Predictors of mortality risk were male sex, presence of comorbidities and advanced patient age.

2.1.2. Epidemiology

The prevalence of human disease attributable to NTM infections has increased over the past few decades. In spite of an increasing body of evidence on its epidemiology, NTM infection, unlike tuberculosis, is not a notifiable disease in most countries and numbers are likely to be underestimated. The incidence of NTM lung disease in the United States (US) doubled from 1997 to 2007 and annual prevalence increased from approximately 20 to 47 cases per 100,000 or 8.2% per year in US Medicare beneficiaries. At least 80% of diagnosed pulmonary NTM infections in the US are caused by MAC. The prevalence of NTM lung infection in the European Economic Area is 0.6 per 10,000 of the population. In Germany, the documented prevalence of NTM pulmonary disease, a non-notifiable disease, increased from 2.3 to 3.3 cases/100,000 population from 2009 to 2014, with a strong association with advanced age and COPD. In addition, pulmonary *M. avium intracellulare* was the main driver of the rise in NTM incidence in England, Wales, and Northern Ireland between 2007 and 2012.

2.1.3. Aetiology and pathogenesis

Mycobacterium avium and *M. intracellulare* (which belong to MAC), are the predominant infective species in NTM pulmonary disease worldwide. The NTM-Network European Trials Group study conducted in 62 laboratories in 30 countries across 6 continents found MAC bacteria predominated in most countries, followed by *M. gordonae* and *M. xenopi*.

2.1.4. Clinical presentation and diagnosis

Fatigue and loss of energy were reported as the most common symptoms by 80% of participants in an informal poll while 40% reported chronic cough and coughing up blood and phlegm. Less commonly, malaise, dyspnoea, fever, haemoptysis and weight loss can occur, usually with advanced MAC lung disease. Evaluation is often complicated by the symptoms of other pulmonary comorbidities.

Pulmonary NTM infections are diagnosed based on at least 2 sputum samples positive for an NTM species or a single positive culture from bronchoscopy or lung biopsy and radiographic criteria for disease and radiographic evidence of bronchiectasis, nodules or cavities per the American Thoracic Society/Infectious Disease Society of America [ATS/IDSA] Statement.

2.1.5. Management

There are no approved treatments specifically for NTM lung disease in the EU. Treatment guidelines have been developed by the ATS/IDSA and the British Thoracic Society, which have since been adopted by various countries globally and incorporated into local guidelines. The current treatment of NTM lung disease is primarily with a multi-drug regimen (MDR) based on the treatment of tuberculosis. The recommendation for patients with MAC is a 3-drug regimen including a macrolide, ethambutol and a rifamycin. Treatment is often for 12 to 18 months and selected based on clinical presentation and disease progression but may exceed 18 months.

Intravenous (IV) amikacin or intramuscular streptomycin are recommended for patients with fibrocavitary disease or severe nodular/bronchiectatic disease and/or previously treated disease. Aminoglycosides are limited by poor penetration into lung tissue after IV administration, poor uptake by alveolar macrophages and the potential for ototoxicity, loss of balance and impaired renal function with high or prolonged systemic exposure.

The goal of treatment is 12 months of negative sputum cultures while on treatment. Culture conversion has been reported to occur in the majority of patients without fibrocavitary disease if they complete a full course of guideline-based treatment. However, in patients who experience treatment failure and/or have more severe underlying conditions such as fibrocavitary disease, culture conversion is more difficult, even with extended treatment, and alternative therapeutic options are limited. The ATS/IDSA guidelines recommend a 3 times weekly regimen of clarithromycin (1,000 mg) or azithromycin (500 mg), rifampicin (600 mg) and ethambutol (25 mg/kg) for most patients with nodular/bronchiectatic MAC lung disease. For patients with fibrocavitary MAC lung disease or severe nodular/bronchiectatic disease, a daily regimen of clarithromycin (500 to 1,000 mg) or azithromycin (250 mg), rifampicin (600 mg) or rifabutin (150 to 300 mg) and ethambutol (15 mg/kg) with consideration of 3 times weekly IV amikacin or streptomycin early in therapy is recommended. Patients should continue treatment for 12 months after sputum culture conversion has been achieved.

The recently updated British Thoracic Society guideline on the management of NTM pulmonary disease provides treatment recommendations similar to the ATS/IDSA guidelines for the NTM species that most commonly fulfil the ATS/IDSA microbiologic criteria for NTM pulmonary disease within the UK, namely MAC, *M. kansasii*, *M. malmoense*, *M. xenopi* and *M. abscessus* complex. The guidance is based on five randomised controlled studies and several non-comparative studies involving individuals (not known to be HIV-positive) with MAC identified in the literature.

In 2020, while this procedure was ongoing, the ERS/ATS/IDSA/ESCMID clinical practice guideline recommended addition of Arikayce to treatment in patients not responding to at least 6 months of currently recommended treatment.

About the product

Amikacin liposome inhalation dispersion (ALIS) is a sterile, white, milky, aqueous, liposomal nebuliser dispersion consisting of amikacin sulfate encapsulated in liposomes, composed of dipalmitoylphosphatidylcholine (DPPC) and cholesterol. The concentration of the active ingredient is expressed in terms of amikacin base and is nominally 70 mg/mL. The liposomes are composed of phospholipids naturally occurring in lung surfactant. DPPC and cholesterol are formulated at a 2:1 weight ratio. The liposomal formulation was developed to provide release of drug in the lung over time, allowing for QD administration.

Aspects of development

On 4 November 2014, Insmed submitted a marketing authorization application (MAA) for ALIS for the treatment of CF patients with chronic infection due to *P. aeruginosa* and for the treatment of patients with NTM lung infections. During the review of the MAA, a draft Similarity Assessment was received which suggested that ALIS and tobramycin inhalation solution (TOBI) Podhaler were similar. Accordingly, Insmed was requested to furnish additional information to elucidate the differences between ALIS and TOBI Podhaler. Insmed chose to withdraw the proposed indication of treatment of CF patients with chronic infection due to *P. aeruginosa.* Instead, Insmed continued to focus on the NTM indication. Accordingly, the regulatory strategy was switched to seek a Conditional Approval for the NTM indication supported by a single Phase 2 study (TR02-112).

TR02-112 did not reach nominal statistical significance for the primary endpoint, which the CHMP considered to have unproven clinical relevance. Following an oral explanation to the CHMP, the evidence of efficacy and safety provided by TR02-112 was considered by the Committee to be insufficient to support approval and Insmed withdrew the MAA on 8 June 2016. The Phase 3 studies INS-212 and INS-312 were ongoing at the time of the withdrawal. This new MAA includes updates to Modules 3, 4 (new in-vitro and in-vivo studies in macrophages) and 5 (INS-212 and 213, with new POPPK analyses) and seeks only an indication for treatment of MAC.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as liposomal nebuliser dispersion containing amikacin sulfate equivalent to 590 mg amikacin as active substance.

Other ingredients are cholesterol*,* dipalmitoyl phosphatidylcholine (DPPC)*,* sodium chloride*,* sodium hydroxide (for pH adjustment), and water for injections.

The product is available in Type I borosilicate glass vial is sealed with a bromobutyl rubber stopper and aluminium seal with a flip-tear off cap as described in section 6.5 of the SmPC.

The finished product is administered by oral inhalation via nebulisation using the Lamira Nebuliser System.

2.2.2. Active Substance

General information

The chemical name of active substance is (2S)-4-amino-N-[(1R,2S,3S,4R,5S)-5-amino-2-[(2S,3R,4S,5S,6R)-4-amino-3,5-dihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy-4-[(2R,3R,4S,5R,6R)-6-(aminomethyl)-3,4,5-trihydroxyoxan-2-yl]oxy-3-hydroxy-cyclohexyl]-2-hydroxy-butan-amide, sulfate (1:2 salt) corresponding to the molecular formula $C_{22}H_{43}N_5O_{13}\cdot 2H_2SO_4$. It has a relative molecular mass of 781.76 and the following structure:

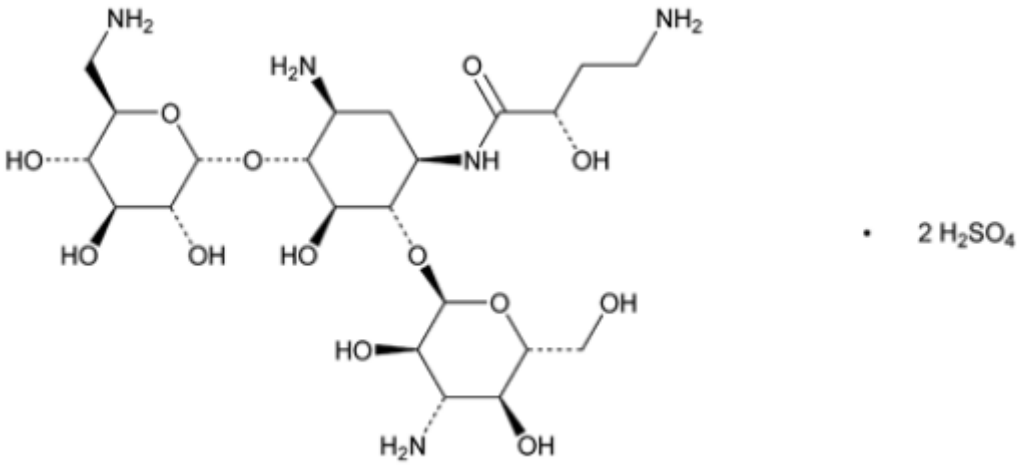


Figure 1: Active substance structure

The chemical structure of active substance was elucidated by a combination of IR, UV, and NMR spectroscopy. The solid state properties of the active substance were studied by XRD (X ray diffractometry).

The active substance is a non-hygroscopic, white or almost white powder freely soluble in water, practically insoluble in acetone and in ethanol (96 per cent).

Amikacin derives from kanamycin. As the molecule of kanamycin has four primary amino groups, it is possible during the synthesis to obtain isomers that differ only in the position of the acyl group. Two isomers are known, and their contents are routinely controlled in amikacin sulfate specifications.

Amikacin sulfate results to be a crystalline product. One polymorphic form is observed by XRD. No other polymorphic forms are known in literature. The active substance is in solution in the finished product, polymorphism is lost and therefore does not represent an issue.

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

The crude amikacin sulfate is synthesised in 5 main steps using three commercially available well-defined starting materials (kanamycin and α-hydroxy-γ-phthalimide butyric acid, and *N*-hydroxyphthalimide) with acceptable specifications. The main steps consist in esterification, silanization, acylation, hydrolysis, and hydrazinolysis. The synthesis of the crude active substance is followed by the synthesis of amikacin sulfate which consist in two steps: dissolution and discoloration, and crystallization.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.
The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

An adequate risk assessment has been undertaken in relation to the presence of nitrosamine-based impurities in the active substance according to EMA guidelines. The risk was deemed low, analysis of 19 batches of the active substance using an appropriately validated method indicate that the related impurities are at very low levels (or not present) and are at least below the current interim limits (as well as the technical limits) set for the relevant impurities.

Specification

The active substance specification, includes tests for appearance (visual), identification (IR, sulphates, HPLC, TLC), pH, crystallinity (physical), loss of drying (Ph. Eur.), , specific rotation (Ph. Eur.), residue on ignition (USP), sulfate (titrimetry), assay (HPLC), potency (USP), related substance (HPLC), residual solvents (GC), bacterial endotoxins (Ph. Eur.), microbial enumeration test (Ph.Eur.), total aerobic microbial count (Ph. Eur.), total yeasts and moulds count (Ph. Eur), and identification of amikacin sulfate (NIR).

The specification for amikacin sulfate is based on the Ph. Eur. monographs for amikacin sulfate and general requirements in this compendium.

The potential organic impurities that can originate from the synthesis process of the amikacin sulfate are those identified in the Ph. Eur. Monograph. Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set. Elemental impurities in the active substance were evaluated using the ICH Q3D "finished product based" approach, and the results comply with the ICH Q3D control threshold limits. This is considered satisfactory.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used has been presented.

Batch analysis data of 15 batches used in nonclinical, clinical, and stability studies were provided. The batches of the active substance are representative of the material used in the finished product intended for commercialization.

The active substance is packaged in two bags made of low-density polyethylene (LDPE) which complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Stability

Stability data from 10 batches of the active substance from the proposed manufacturer stored in the intended commercial package for up to 60 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested: appearance, identification, pH, crystallinity, water content, loss of drying, solubility, residue of ignition, transmittance, assay, related substances, residual solvents and

bacterial endotoxins. The analytical methods used were the same as for release and were stability indicating.

There are no obvious trends noted in the stability data under long term and accelerated conditions, it is apparent from the data provided that the active substance is very stable. The proposed retest period of 5 years when stored in LDPE bags is acceptable

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is a white, milky dispersion consisting of amikacin sulfate encapsulated in liposomes.

The finished product is delivered by the Lamira nebuliser system using eFlow technology. The device is a high efficiency electronic nebuliser that uses a vibrating perforated membrane to generate inhalable aerosol.

The goal of pharmaceutical development was to develop a liposomal dispersion to allow for the achievement of greater local concentrations of amikacin in the lung, while minimising systemic concentrations. To effectively treat pulmonary bacterial infections, amikacin was formulated into an inhalation dosage form to target the infected lung directly with a product with a pharmacokinetic profile that would permit once-a-day dosing. This effort resulted in the development of amikacin liposome inhalation dispersion (ALIS), which was designed to include DPPC as the primary lipid. Liposome technologies have been proven to alter pharmacokinetics (and liposome and lipid-complex formulations have been used successfully as drug delivery systems.

A Quality Target Product Profile (QTPP) was developed and includes considerations of clinical safety (including once daily administration), patient compliance and quality attributes. Relevant aspects of the QTPP that influenced product development are provided in Table 3. The safety, efficacy, and patient compliance requirements were used to guide decisions about the dosage form and packaging choices. These requirements were also used to establish critical quality attributes (CQAs) as shown in Table 4. The intention of this development strategy is to have a holistic understanding of the finished product formulation and manufacturing process parameters, and their impact on the finished product CQAs.

Table 1: Finished Product Quality Target Product Profile

Clinical/Safety Attributes	
Indication	Treatment of Mycobacterium avium complex (MAC) lung disease as part of a combination antibacterial drug regimen.
Route of Administration	Oral inhalation
Dose Frequency	Once a day/chronic
Impurity/Degradation Product	Controlled below ICH Q3 or qualified to the levels that do not impact product safety
Contamination	Aseptically manufactured and meet compendial sterility and bacterial endotoxins requirements
Patient Compliance Attributes	
Usage	Easy and convenient to use for adult patients, using advance nebulization technology
Dosing Duration	Less than 60 minutes
Quality Attributes	
Delivery	Aqueous formulation with suitable particle size distribution for pulmonary delivery
Performance	Dose accuracy with proper drug release profile from liposomes
Stability	At least 2 years shelf life

Table 2: Critical Quality Attributes Derived from QTPP

QTPP Attributes	CQA Attributes
Clinical/Safety Attributes	Concentration
	Content Uniformity
	Impurity and degradation product
	Sterility and Bacterial endotoxins
	In vitro release
	Liposome particle size distribution
	Aerodynamic particle size distribution
Patient Compliance Attributes	Appearance

The solid-state characteristics of the active substance have no impact on the performance of the finished product since amikacin sulfate is dissolved in water as part of the finished product manufacturing process. Its limited solubility in ethanol contributes to the high encapsulation efficiency achieved during manufacture of the finished product. Because it is multi-cationic it is relatively impermeable to the liposome membrane and can be effectively retained within the liposomes. Compatibility of amikacin sulfate with the excipients was confirmed in long-term and accelerated stability studies.

The excipients used were selected to ensure the compatibility with the lung fluids, efficient liposome formation, and stability of the product. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

Dipalmitoylphosphatidylcholine (DPPC) is the most abundant lipid in endogenous lung surfactant and studies are cited where added lipid is readily processed in the lung. It was therefore expected that formulations with this lipid would have a high degree of biocompatibility. Its primary degradation pathway is hydrolysis, which is relatively slow, especially when liposome preparations are maintained near neutral pH and at, or below room temperature.

Although DPPC is known to form stable liposome structures, the bilayer membrane undergoes changes in physical state at discrete temperatures (35 °C and 41 °C) which is accompanied by greater leakage of entrapped water-soluble compounds. The inclusion of cholesterol above 20 mole percent minimises this temperature sensitivity. Cholesterol is also known to stabilise liposome structures that are introduced into biological milieu by reducing leak of entrapped contents.

The following physicochemical properties of ALIS have been discussed during formulation development:

- **DPPC to Cholesterol Ratio**

DPPC to cholesterol ratio has not changed during development. The ratio was selected based on published literature to produce greater product stability, less rupture, and therefore less leakage. The DPPC to cholesterol ratio is controlled in ALIS by the manufacturing process.

- **Lipid to Drug (L/D) Ratio (w/w)**

L/D ratio is desired to be low to increase encapsulation efficiency, thereby increasing total amikacin and reducing the lipid to drug ratio.

Potency

The potency of ALIS (expressed as amikacin concentration) is controlled by the manufacturing process by in-process testing for amikacin concentration and is assured to be within specification at finished product release.

- **Mean Liposome Particle Size**

ALIS was developed to target a mean liposome particle size to allow for transport of the liposomes within the aerosol droplets. Liposome size is determined by the manufacturing process and is controlled at release and during stability.

- **pH**

The hydrolysis of DPPC to lyso-PC is affected by pH. Therefore, the pH of ALIS was controlled, monitored and maintained. It is controlled in the product specifications.

- **Osmolality**

The ability of the liposomes to retain drug depends on the osmotic gradient across liposomal membranes. Therefore, osmolality is controlled at the time of manufacture of ALIS using in-process control of the sodium chloride process solution. Additionally, the osmolality of ALIS is further controlled in the finished product specifications.

- **Percent Associated Amikacin Post-Nebulisation**

the percent associated amikacin (entrapped amikacin) is a critical attribute in assuring a consistent amount of liposomal amikacin delivered during nebulization. The nebuliser and finished product can both influence percent associated amikacin aerosols. The control of this attribute is achieved by controlling osmolality of the ALIS and the ratio of the lipids in the liposome membrane; it is also controlled in the finished product specification.

A suite of tests has been utilised to characterise the finished product across a number of batches and processes during the pharmaceutical development:

- **Density gradient:** The profile of amikacin and total lipid in the liposomes separated on a density gradient demonstrated co-localisation of lipid and active substance. This represents a function of the internal amikacin concentration as well as the liposome size distribution, shape variation and the range in lamellarity of the liposomes. The data indicate a uniform population.

- **Liposomal contents** are characterised by a number of inter-related measures: liposomal volume, captured volume, and internal amikacin concentration (IAC).
- ***In vitro* release:** The development of the method was based on the many considerations. The proposed method is based on an increase in permeability due to surfactant binding, with increasing concentrations over time. The *in vitro* release profiles of 79 batches manufactured by both the two proposed manufacturers along with an overall average release profile are provided. *In vitro* release is included as a release and stability test of the finished product.
- **Visual Observation of Lamellarity by Cryo-Electron Microscopy**: Ethanol infusion was used to make ALIS since it has been known historically that this process produces liposomes of a uniform size and relatively low lamellarity. The lamellarity of ALIS was assessed using cryo-electron microscopy (Cryo-EM) which visually shows the liposomes to be predominantly unilamellar and spherical. The manufacturing process was developed to achieve a robust manufacturing process with the consideration of the physiochemical and biological properties.
- **Liposome Net Charge:** It was confirmed by using zeta potential measurements that as expected the ALIS liposomes are neutral since they are comprised of neutral lipids.
- **Liposome Phase Transition**: it was shown that the incorporated cholesterol abolishes the DPPC phase transitions and ALIS shows no sharp phase transition and thus do not show greater leakage of entrapped water-soluble compounds under Differential Scanning Calorimetry from 5 °C to 60 °C ALIS is manufactured using a process in which an aqueous amikacin sulfate solution is combined with an ethanolic lipid solution to form liposomes. The resulting bulk suspension is then aseptically filled into 10 mL vials and crimp sealed. Because of the liposomal nature and heat lability of the product, terminal sterilization cannot be used. Therefore, the processes of liposome formation and filling of ALIS are all carried out aseptically.

There have been two different approaches used (and slight variations of those approaches) to manufacture clinical and non-clinical materials in the development of ALIS:

1. A single stream infusion process which was used in the early phases of ALIS nonclinical and clinical development referenced as Processes A, A1, and A2.
2. A multiple stream infusion process referenced as Processes B, B1, B2, C, D and E for non-clinical and later stage clinical development and commercial process development.

To increase potency and batch size of ALIS, a multiple stream infusion process with in-line mixing was developed. Compared to process A2, all "B" processes and Process C increased batch size. Further modifications to Process B, identified as B1 and B2, were made upon transferring the process to the two intended commercial manufacturing sites. All materials produced from the different B processes were aseptically filled with different volumes as needed for clinical and nonclinical studies. Process C differs from Process B2 only by the incorporation of pre-sterilised (gamma irradiation) filtration tubing assemblies and the addition of two filters placed in series, resulting in double sterile filtration of all starting process solutions. The proposed commercial manufacturing process (Process D) is approximately a two-fold batch size increase of Process C, with certain process parameters adjusted to accommodate the increase in process scale. When compared to Process D, the proposed commercial second manufacturing process (Process E) is approximately a fourfold batch size increase with certain process parameters adjusted to accommodate the increase in process scale.

The primary packaging is into a Type I borosilicate flint glass vial and closed with a Type I bromobutyl stopper which is sealed with an aluminium flip-tear off combination seal. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

The finished product is provided as drug/device combination together with the Lamira nebuliser system specific for the delivery of the finished product. The nebuliser system is a single patient use, reusable electronic nebuliser device for the inhalation delivery of medication. The Lamira nebuliser system consists of three major components, including aerosol head, handset and controller. The aerosol head is mounted into the handset and employs a technology that consists of a circular metal disk (membrane), perforated with thousands of laser-drilled holes. A ring-shaped piezoelectric actuator is used to vibrate the membrane at a high frequency to create an alternating pressure field. This alternating pressure forces ALIS through the holes producing a dense aerosol cloud on the distal side of the membrane which is then inhaled. The diameter of the membrane holes determines the aerosol droplet size. For inhalation, the drug is dispensed from an individual vial into the reservoir of the nebuliser handset by removing the Reservoir Cover (cap). ALIS is sealed into the reservoir when the cap is placed back onto the reservoir and locked in position. The reservoir design acts like a funnel to feed ALIS into contact with the perforated metal disk (the membrane) of the aerosol head. The bottom of the reservoir's funnel section also has a flexible sealing component that prevents the medication from leaking around the aerosol head. The controller provides the electrical signal to drive the aerosol head and provides the user interface for turning the nebuliser on and off. The controller has a display showing symbols indicating the actual mode of the device including charge of batteries and giving information of possible operation modes if necessary. The controller also features audible and LED light indicators next to the Controller On/Off button that provide audio-visual feedback to the user. This medical device has the EC declaration of conformity for medical devices. The applicant has provided satisfactory data on the characterisation of the aerodynamic particle size distribution and delivery dose via a breath simulator in line with Ph. Eur. 2.9.44 and EMEA/CHMP/QWP/49313/2005 Corr. Weekly ultrasonic cleaning is required according to the instructions for use (IFU). Performance was investigated for six nebulisers with or without this cleaning over 84 days. It was concluded than sonication cleaning is appropriate and that the nebuliser is robust enough for this regimen over three months. However, based on the burden on patients that cleaning presents it is now proposed to replace the nebuliser head every seven days. Two studies were conducted to provide a qualitative assessment of the extractable profiles and semi-quantitative estimates of the amounts of extractables of the ALIS handset. Organic extractables above the calculated analytical evaluation threshold of 42 µg/day were reported and subject to toxicological assessment. No extractables of concerns were identified and the health risk (taking the vial and stopper extractables into account as well) is considered negligible by the applicant. For leachables, the entire handset was exposed to ALIS. No organic leachables were reported i.e. below 42 µg/handset. The levels of elemental impurities were not of concern i.e. very low and/or below ICH Q3D control thresholds where applicable.

Manufacture of the product and process controls

The finished product is manufactured in two manufacturing sites. Each manufacturing site applies exclusively either manufacturing process D or E. Both manufacturing processes are the same, only differences related to size and within sterilization conditions due to equipment settings are noted.

The manufacturing process of the finished product using Process D and Process E consists in 6 main steps: compounding of process solutions, liposome formation and bulk processing, potency adjustment (if required), aseptic vial filling and stoppering, seal crimping of filled vials and inspection, and secondary packaging. The processes are considered to be a non-standard manufacturing process.

The critical parameters identified during development and process validation are described and the applied acceptance ranges have been justified. Holding time has been confirmed by validation data and is acceptable. The in-process controls used for both manufacturing process are adequate for this pharmaceutical form.

Major steps of the manufacturing process have been validated by a number of studies on production scale batches using process D, with one batch covering the new filter flush step. The process parameter data demonstrates that the manufacturer has tight control of the CPPs that influence sterile liposome formation and filling. The data indicated that a sufficient level of control is in place to consistently produce product meeting the quality requirements. The details provided of process validation for three production scale batches using process E are very similar to process D and acceptable.

The data provided on both process (D and E) on the sterilising filters is extensive and acceptable, extractable and leachable studies are detailed. Data is provided on several parameters not specific to this product, e.g. sterilisation of components, but provides additional sterility assurance

Product specification

The finished product release and shelf life specifications, include appropriate tests for this kind of dosage form: appearance (visual), identification of amikacin (HPLC, TLC), identification of sulfate (Ph. Eur.), pH, osmolality (Ph. Eur.), amikacin concentration (HPLC), percent associated amikacin (HPLC), amikacin degradation products (HPLC), content uniformity (Ph. Eur.), DPPC concentration (HPLC), cholesterol concentration (HPLC), lipid to drug ratio, lipid degradation product (HPLC), residual ethanol (GC), liposome particle size (photon correlation spectroscopy), aerodynamic particle size distribution (APSD) post nebulization using the Next Generation Impactor (NGI), percent associated amikacin post nebulization (HPLC), *In vitro* release (HPLC), fill weight (gravimetric), sterility (Ph. Eur.) and bacteria endotoxins (Ph. Eur.).

A discussion was provided on impurities, which are separated into different categories: amikacin-related, DPPC-related, cholesterol related, residual solvents and elemental impurities.

Process-related impurities of amikacin are monitored in the active substance but not in the finished product, in which only degradation products are monitored. The only process-related impurities that are also degradants are kanamycin (Ph. Eur. Imp D), and Ph. Eur. Imp I.

The sources of potential elemental impurities in batches of the finished product include the raw materials and water, the container closure system and the manufacturing equipment. The manufacturer of amikacin sulfate), DPPC, and cholesterol all have attested that they do not employ ICH Class 2B elements in their processes. Additionally, the raw materials DPPC and cholesterol are tested for heavy metals using the current colorimetric compendial test method. The other excipients meet Ph. Eur. requirements. It is considered unlikely that that elemental impurities are introduced into the finished product from the manufacturing equipment due to the materials used and the GMP procedures that are in place.

A risk assessment was conducted to assess the potential contamination of nitrosamine during the finished product manufacturing from excipients and raw materials, manufacturing process, and container closure system. Based on this risk assessment, it was concluded that there is neither a risk of introducing nitrosamines to the finished product by excipients, nor a risk of formation of nitrosamines during the manufacturing and storage of the finished product.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis results are provided for very large number of batches covering each iteration of the manufacturing process (A to E), including batches at non-commercial concentrations or in other container closures. For the proposed commercial processes (D and E) and sites, data from a combined number of 62 batches are presented. Of these batches, 24 (covering both sites) were used in phase 3 studies. The

results confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from twenty four different sizes batches of the finished product stored in the upright orientation included in these are batches from process B2, D and E for up to 36 months under long term conditions (5°C ± 3°C) and for up to 6 months under accelerated conditions (25°C ± 2°C) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, pH, liposome particle size distribution, amikacin content, percent associated amikacin, amikacin degradation products, DPPC content, cholesterol content, lipid degradation product, percent associated amikacin post nebulization, liposome particle size post nebulization, APSD, particulate matter, and sterility.

No significant changes have been observed under long term and accelerated stability conditions. It was demonstrated for tested stability batches that storage temperature and orientation have no impact.

In-use testing was performed for up to three months after long-term storage at 2-8°C for 24 months and up to two months after long term storage at 2-8°C for 36 months. Results demonstrate that the in-use period of the product is 4 weeks storage at 20-25°C with excursions permitted between 15-30°C.

Three separate studies were conducted to evaluate the effects of temperature changes. In one batch stored at 2-8°C for 15 months in the upright orientation testing was performed to provide baseline data for evaluating the effects of each condition. There is no other impact on the stability of the finished product.

The effects of short-term thermal exposure were studied. The data demonstrate that both short term and periodic temperature excursions up to 40°C affected nothing other than the rate of DPPC degradation to Lyso PC.

Freeze-thaw effect was assessed. Characterization tests were also performed and the in-vitro release, as well as the density gradient profile showed significant differences when compared to data for Cycle 0. These data demonstrate that the finished product cannot be frozen.

In addition, one batch was exposed to light as required by the ICH Guideline on Photostability Testing of New Drug Substances and Products. All reported results for all tests were within the acceptable limits of the current specification. Therefore, the finished product does not need to be protected from light.

Based on available stability data, the proposed shelf-life of 36 months and store in a refrigerator (2 °C – 8 °C), do not freeze, discard any vial that has been frozen, can be stored at room temperature below 25 °C for up to 4 weeks once at room temperature, any unused medicine must be discarded at the end of 4 weeks as stated in the SmPC (section 6.3) are acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

2.3.2. Pharmacology

Amikacin as an aminoglycoside antibiotic with known properties and for which there is extensive clinical experience with parenteral administration. Therefore, the applicant has submitted a limited primary pharmacology package for amikacin liposome inhalation solution (ALIS) and this is considered acceptable. *In-vitro* studies utilising adherent human macrophages infected with three *M*. *avium* strains (MAC 104, A5, and MAC 3388) demonstrate that ALIS is more bactericidal than non-liposomal amikacin referred to as free amikacin (FA) at equivalent amikacin concentrations (10 µg/mL).

ALIS was shown to exhibit increased uptake of fluorescent tetramethylrhodamine (TAMRA) tagged amikacin into THP-1 human peripheral blood monocytes in vitro relative to FA. Similar results were reported in cells isolated from bronchoalveolar lavage (BAL) fluid from rodents administered either ALIS or FA via inhalation with ALIS treated animals exhibiting higher BAL cell concentrations of amikacin relative to FA treated animals.

An *in-vivo* efficacy study undertaken in C57B6 mice infected with M. *avium* strain 104 demonstrated that inhaled ALIS administered via a number of different schedules exhibited at least similar efficacy in terms of reducing lung bacterial load relative to i.p. administered FA (100 mg/kg). Dosing every other day at 152 mg/kg was shown to be as effective as daily dosing at 76 mg/kg over 28 days with the higher dose every other day schedule resulting in a greater number of mice in which the infection was completely eradicated. In all ALIS treated groups the reduction in mean CFU/lung was numerically superior to 28 dosing with FA i.p., these differences were not however statistically significant.

A single *in-vitro* study examining the penetration of liposomes into sputum from a CF patient has been submitted in the secondary pharmacology section. This study is not a secondary pharmacology study. It was conducted to support the previously sought indication for CF patients and is not directly relevant for the current application. No dedicated secondary pharmacology studies have been conducted. Given the pharmacology of amikacin has previously been characterised and its clinical safety profile via other routes of administration is well established this is considered acceptable.

Primary pharmacodynamic studies

In the context of this application the primary pharmacodynamics concern measurements of the effects of inhaled ALIS on non-tuberculous mycobacteria (NTM) and, especially, MAC.

The applicant summarised 8 studies from the literature that report on the activity of amikacin against MAC.

For the discussion on the primary pharmacology of amikacin see section 2.4.3.

Secondary pharmacodynamic studies

The secondary pharmacodynamic effects centre on the effects of inhalation of liposomal amikacin on pulmonary function tests. In the NTM/MAC studies, these data are considered most important for the assessment of safety. However, they are described below, along with the microbiological and other clinical endpoints.

Safety pharmacology programme

No dedicated safety pharmacology studies were conducted. This is considered acceptable as the clinical safety profile of amikacin is well characterised and the systemic exposure to amikacin is significantly higher following parenteral administration of currently authorised products than following ALIS administration. ECG and respiratory measurements were taken as part of the 30-day repeat dose inhalation administration dog toxicity study utilising an early formulation of ALIS (Sustained release Lipid Inhalation Targeting, SLIT) (Study no. 667574). Treatment with SLIT was not associated with any dose dependent differences in respiratory or ECG measures. No statistical analysis of these data is presented. However, this is considered acceptable.

Pharmacodynamic drug interactions

In-vitro drug combination studies relevant to inhalation of ALIS have not been conducted. Numerous published studies have evaluated the combined antimycobacterial effect of amikacin and other agents used to treat Mycobacterial infections and have shown lack of antagonism.

2.3.3. Pharmacokinetics

The methods of analysis used in pivotal studies have been appropriately validated in terms of selectivity, accuracy, precision, stability, linearity and limits of quantification. Some minor deviations to what is normally considered acceptable were noted but these are unlikely to affect the interpretation of results generated via these methods. The methods of analysis are considered appropriately validated and acceptable.

The applicant has submitted a summary of several small-scale PK studies conducted in Sprague-Dawley rats. Oral bioavailability of amikacin is confirmed as very low ≈0.002% and 0.3% (of interest as up to 50% of amikacin administered as ALIS was recovered in the stomach). Absorption from the lungs following a single inhalation administration is rapid with Tmax reached at the first time point analysed. Elimination is biphasic with a rapid initial elimination following by a slower prolonged phase with amikacin concentrations shown to be significantly higher in lung tissue relative to serum up to 1 week following a single inhalation administration. ALIS was also shown to exhibit higher lung concentrations relative the same dose (60 mg/kg) of FA via inhalation administration. No dedicated PK data on absorption in dog has been provided but TK data have been acquired in pivotal repeat dose toxicity studies.

The applicant submitted a number of dedicated single dose studies in rat examining the distribution of ALIS within the lung in comparison to FA as well as studies comparing the distribution of fluorescently labelled amikacin (amikacin-TAMRA) in ALIS as well as fluorescently labelled liposomes. No dedicated studies examining systemic distribution have been submitted, though a summary of organ concentrations following single administration was submitted, indicating relatively low systemic distribution. No data on

melanin binding have been submitted. Bibliographic sources indicate that amikacin is not extensively protein bound (≈3.6%).

Lung amikacin concentrations following inhalation ALIS administration to rats are shown to exhibit biphasic elimination with a rapid initial alpha phase (lung $t_{1/2}$ ≈7 hours) followed by a more prolonged beta phase (lung $t_{1/2}$ ≈400 hours). The applicant has interpreted these data as the initial phase representing clearance of FA released during the nebulisation process (≈45%) with retention of liposomal amikacin at longer time points related to incorporation of the liposomes into macrophages. The interpretation of distribution to macrophages is based on the observation of punctate staining at later time points in the lungs of ALIS treated animals not present in FA treated animals. No co-staining with macrophage related markers has been conducted. This interpretation is endorsed (and supported based on in-vitro data discussed above reporting that liposomal formulation is associated with increased macrophage uptake).

Distribution was also assessed via fluorescence spectrophotometry and microscopy using DiIC18(5)DS-labelled ALIS liposomes. These analyses revealed that DiIC18(5)DS-labelled liposomes were equally distributed in the lungs with initial distribution to the large and small airways and then intracellularly in macrophages in tissues surrounding the airways or in alveoli. Clearance of DiIC18(5)DS from the lungs was slower than that of amikacin, free DiIC18(5)DS was cleared from the lungs more rapidly than DiIC18(5)DS administered in ALIS (i.e., with amikacin). DiIC18(5)DS was eliminated from the lung linearly in contrast to the previously defined biphasic elimination kinetics of amikacin. It should be noted that this lipid label is not a mimetic for DPPC or cholesterol to be used in the marketed product and so is only useful for demonstrating the initial distribution of the liposomes but not the fate of the constituent components. This is acceptable as the liposomal constituents are endogenous to the lung.

A single multiple dose PK study has been submitted in which rats were administered ALIS at daily doses of either 10 or 90 mg/kg for a period of 28 days. Again, this study focused on lung distribution and reported uniform distribution and clearance from the lung. Amikacin concentrations in the lung increased with dose (Cmax and AUC in high dose group ≈ 2-fold lower dose group). It should be noted that on the last day of dosing both groups received the same (high dose) which should which may partly explain this observation. In contrast, the concentration of conjugated amikacin-TAMRA did not increase with dose with the lower dose group exhibiting similar/higher concentrations relative the high dose group.

This issue was raised in the previous MAA and it is accepted that this isolated finding is likely specific to amikacin-TAMRA given the dose related exposures observed in all GLP-compliant repeat dose toxicity studies. The fraction of ALIS that remained in the lung appeared to be sequestered into pulmonary macrophages with deposition appearing uniform among the lobes/sections analysed.

Two single dose studies have been conducted examining the clearance of ALIS examining elimination 24 hours and 21-days post dose. These focus on clearance from the lungs but examination of urine concentrations following inhalation administration suggest that, following systemic absorption of amikacin from ALIS, it primarily undergoes renal excretion. Elimination time from the lung following ALIS administration is longer than following FA administration (≈2-fold increase in lung elimination $t_{1/2}$). Sub-regional lung analysis confirms that elimination proceeds uniformly across the whole lung. Both serum and urine concentrations of amikacin were reported as greater following single dose FA relative to ALIS administration 24 hours post dose. However, in contrast in the study examining the 21-day post dose period, the concentration of amikacin was comparable in serum in ALIS and FA treated groups and urine concentration was higher in the ALIS treated relative to the FA treated group. A clear cause for this contradictory finding is not evident. Data from the GLP-compliant 30-day repeat dose toxicity study in rats following SLIT administration reported similar urine levels following 30 days dosing.

A full discussion of the systemic elimination of amikacin has not been provided. However, it is accepted that elimination should not differ following ALIS administration relative to authorised IV administrations. Additional information related to elimination of aminoglycosides based on literature review was furnished

by the applicant in response to a query on this point raised as part of the initial MAA. Aminoglycosides are not significantly metabolised, undergo glomerular filtration and are actively resorbed in the proximal kidney tubules. It is considered unlikely that aminoglycosides are taken up by members of the organic ion transporters such as the organic anion transporter (OAT) and organic cation transporter (OCT) families which are expressed in the renal proximal tubule, with megalin, a multi-ligand endocytic receptor that is most abundantly expressed in the renal proximal tubules in segments 1 and 2, shown to mediate uptake of polybasic drugs such as aminoglycosides. The precise mechanism of resorption remains to be elucidated. In conjunction with the available clinical experience with amikacin administered parenterally, this is considered acceptable. No non-clinical PK DDI studies have been completed, this was acceptable to the CHMP.

2.3.4. Toxicology

Single dose toxicity

No single dose toxicity studies were conducted with ALIS, which was acceptable to the CHMP.

Repeat dose toxicity

Repeat-dose inhalation toxicity studies with ALIS included a 6-month study in rats (with a 3-month interim evaluation), a 3-month study in dogs, and a 9-month study in dogs (with a 6-month interim evaluation of in-life findings); each study also included a recovery period. These studies are considered pivotal regarding human safety.

A 13-week repeat dose toxicity study was conducted in mice. ALIS was well tolerated in this study. Primary findings included treatment related slight nasal turbinate degeneration at mid and high doses and increased foamy alveolar macrophages in the lungs. These findings were thought to be non-specific reactive changes to drug administration. Active foci of inflammation were evident in high dose animals in this study (90 mg/kg/day) which was interpreted as a response to macrophage degeneration following phagocytic overload.

A 30-day GLP compliant study conducted in rat utilising an early stage (SLIT) formulation of ALIS and inhaled FA reported that administration for this duration was relatively well tolerated. Primary findings related to increased foamy alveolar macrophages. Of note, focal alveolar macrophage accumulation was also evident in the empty liposomal control (ELC) treated group, demonstrating that the liposomes alone can induce this finding and supporting the applicants position that this finding is related to the non-specific clearance of the liposomes for the lungs. Lipid staining of lung sections did not provide any evidence of excessive accumulation of phospholipids. Plasma concentrations were only above the limits of quantification in high dose and FA groups (100 mg/kg/day) and were similar/higher in FA relative to SLIT high dose treated groups with the inverse shown in terms of lung concentrations. No NOAEL was defined in the study report though is listed as 100 mg/kg in the submitted toxicology summary.

In the 6-month repeat dose toxicity study conducted in rats (Study 07-6308) animals were administered ALIS at doses of 10, 30 or 90 mg/kg/day via nose-only inhalation. No FA or ELC groups were included in this study. Target organs identified were the lung, nasal turbinates, kidney and larynx. TK data acquired show non-linear and less than dose proportional increases in systemic exposure. Of note, low levels of amikacin were still present in lungs of recovery animals (i.e. following the 12-week recovery period). Primary findings were increased lung weight and macroscopic and microscopic findings associated with an increase in foamy alveolar macrophages which was dose-related. At mid and high dose multiple inflammatory foci were also observed. Degenerative changes in the nasal turbinates and laryngeal

changes including squamous/squamoid metaplasia/hyperplasia of the pseudostratified columnar epithelium in the larynx, and degenerative changes of the tracheal epithelium were attributed to a non-specific response to test-article administration. This is endorsed.

Nephropathy was evident in the high dose group at terminal sacrifice with higher prevalence in males relative to females. This is in line with the known systemic toxicity profile of aminoglycosides. The lung NOAEL was below the lowest dose tested in this study (i.e. < 10 mg/kg) due to the inflammatory and adaptive changes identified at all dose levels with the NOAEL for nephropathy set at 30 mg/kg/day.

Alveolar fibrosis was evident in several high dose animals at recovery which was not evident at treatment termination suggesting prolonged inflammation following treatment cessation. Further clarification on the cause of the continued inflammatory response was raised as a major objection in the assessment of the original MAA submission. The applicant provided additional argumentation that these findings were species-specific and are consistent with particle overload in the lungs following chronic inhalation administration to rats. Repeated deposition of particulates to the lungs can lead to chronic inflammation, particularly in rats due to anatomical and biological differences including smaller lung size volume and surface area and smaller macrophage size relative to larger animals. A characteristic of particle overload is impaired macrophage clearance function, associated with pulmonary inflammation, centroacinar and interstitial accumulation of particles and, eventually, epithelial cell proliferation possibly leading to chronic damage including fibrosis and neoplasia.

Similar changes have been observed following administration of other inhaled aminoglycosides to rodents. The relevance of these findings to humans is unknown.

A one-month repeat-dose toxicity study was carried out with an early ALIS formulation (SLIT) in dog. Findings were similar to those previously reported in rats with an increase in lung weight and lung foamy macrophage numbers reported. These showed a trend towards reversal in the one-month recovery group. On note the death of one high dose male in his study was associated with enterotoxaemia secondary to Gram-positive GI infection. This may indicate an effect of treatment on normal commensal bacteria in the GI tract. TK data from this study again show lower systemic and high lung amikacin concentrations in the high dose SLIT treated group relative to FA treated group. No treatment-related effects associated with ELC administration were evident in this study.

The 3-month repeat-dose toxicity study in dog reported similar findings with all treated animals exhibiting an increase in lung weight which was recoverable following cessation of treatment. Dose dependant increases in foamy macrophages in lung and mediastinal and tracheobronchial lymph nodes were reported. The findings in the lung were still present following in recovery animals following a 2-month treatment free period but were of lower severity than observed in terminal sacrifice animals suggesting reversibility. Of note, lung tissue concentrations were still 30% of those observed at terminal sacrifice in recovery animals demonstrating prolonged lung exposures. No other findings in this study were attributed to the test-article. The NOAEL for lung changes in this study was set at the highest dose observed as it was suggested that increases in lung macrophages and weight were a non-adverse adaptive response to administration related to clearance of ALIS.

In the pivotal 9-month repeat-dose toxicity study in dog primary findings again related to dose dependent increases in foamy alveolar foamy macrophages associated with increased lung weights. In the high dose groups in this study (30 mg/kg) this finding was still evident though at lower severity following the three-month recovery period. This was not associated with squamous metaplasia or proliferative/neoplastic changes in the lung. Increased numbers of foamy macrophages were also evident in mediastinal and tracheobronchial lymph nodes at all dose levels at treatment termination. Basophilic granules were evident in epithelial cells at the apex of the tracheal bifurcation indicative of deposition and epithelial uptake of the test article at doses in excess of 10 mg/kg. This finding was still evident but with lower frequency following the recovery period. The NOAEL for this study was set at 30 mg/kg/day, the

highest dose tested. This is not endorsed, at this does level following a 3-month recovery period, several findings were still evident including increased lung weight, foamy alveolar macrophages and foamy macrophages with intracytoplasmic basophilic granules in the mediastinal and tracheobronchial lymph nodes. Exposure margins based on systemic exposures from NOAELs identified in pivotal repeat dose toxicity studies to clinical exposures at the proposed dose are less than 1. Exposure margins when calculated on a delivered dose/g lung weight basis are greater ≈5 based on 9-month dog study (taking 10 mg/kg/day as the NOAEL) with no NOAEL defined in rat studies.

Genotoxicity

ALIS was not genotoxic in a standard battery of battery of tests as per ICH S2(R1).

Carcinogenicity

A single carcinogenicity study in rat following life-time inhalation exposure has been submitted. A study in a single species was considered appropriate to assess the effects of inhalation administration on carcinogenic risk as the clinical safety profile following IV exposure is well established, this is considered acceptable. Positive neoplastic findings were reported in this study. In the high dose female group (45 mg/kg/day) squamous cell carcinomas were observed in the lungs of 2 of 60 animals at study termination. As squamous cell carcinomas are rare in the rat lung these findings were considered treatment related. An increased incidence of non-neoplastic proliferative changes was also evident in this group with a keratinizing pulmonary cyst in one female and foci of squamous metaplasia of the alveolar epithelium evident in two females at 45 mg/kg/day. The keratinising pulmonary cyst had characteristics similar to a squamous cell carcinoma.

Bronchiolo/alveolar adenomas were found in 1 male and 1 female administered ALIS at 45mg/kg/day. The applicant contends that although this finding only occurred in the high dose group it was within the historical control range and therefore is of uncertain relationship to ALIS administration. This view is questionable given these findings only occurred in the high dose group.

One male and one female in the low dose group (5mg/kg/day) and one male in the high dose group (45 mg/kg/day) died from squamous cell carcinoma of the palate which was of uncertain relationship to ALIS administration. This tumour is known to occur in low incidence and these findings were not statistically significant relative to concurrent controls. Because these occurred sporadically without dose response they are considered of uncertain relationship to the test article.

Alveolar epithelium hyperplasia with dose dependent severity was evident in all treated groups. Non-proliferative lung changes included diffusely distributed foamy alveolar macrophages, focal/multifocal aggregates of alveolar foamy macrophages and interstitial/alveolar inflammation in line findings from repeat-dose toxicology studies. Similarly, minimal to slight aggregates of foamy macrophages were present in the mediastinal and bronchial lymph nodes. The incidence of these findings in the ELC group was similar to that in the mid dose ALIS group and the applicant attributes these findings to normal clearance of the liposomes from the lung. This is not fully endorsed as there is an increased total incidence and severity in the high dose group which received a similar lipid dose as the ELC group indicating these effects are (at least partially) amikacin related.

An increased incidence of pancreatic islet cell tumours (adenomas and carcinomas) was observed in the high dose male group. However, this was not considered test-article related as the increase was not statistically significant relative to controls and was still within historical control rates. These findings are represented in the proposed SmPC and should be taken into consideration in the benefit risk assessment of the product.

Reproduction and developmental toxicity

No dedicated developmental/reproductive toxicology studies with ALIS have been carried out. This approach is considered acceptable as there is significant clinical experience with the administration of amikacin via alternative routes resulting in significantly higher systemic exposures and aminoglycosides as a class. The applicant has made reference to a number of studies in publicly available literature which have assessed the potential reproductive toxicity of amikacin when administered via a different route of administration. These studies were not performed to GLP but are appropriately designed and considered of good quality and do not indicate a direct risk of teratogenicity or fetotoxicity associated with amikacin administration. Furthermore, ALIS administration was not associated with any adverse effects on reproductive organs in pivotal repeat-dose toxicity studies.

The non-standard nature of the submitted reproductive toxicity studies is outlined in the SmPC.

Juvenile toxicity

The applicant submitted two juvenile toxicity studies completed in rat. These are not directly relevant to the current submission as the proposed indication for ALIS is for administration to adults only and is therefore considered supportive data only. In the initial dose range-finding study, ALIS administration to rat pups from post-natal day (PND) 10 is reported as being well tolerated up to the maximum dose tested (60 mg/kg/day for 28 days). Therefore, the top dose for the pivotal juvenile toxicity study was set at 90 mg/kg/day. Following 28-days administration to rat pups from PND 10 findings were similar to those observed in adult animals. These related to dose dependent increases in foamy alveolar macrophages and laryngeal epithelial erosion/ulceration with minimal to slight epithelial hyperplasia in the respiratory epithelium. These were reversible/trending for reversing at the end of the recovery period. No additional toxicity on sexual maturity, bone development or motor activity was noted.

Other toxicity studies

Immunotoxicity
Two dedicated immunotoxicity studies were conducted, one following the administration of an early stage formulation to rats for 14 days and following administration of ALIS to rats for up to three 30-day cycles. In the 14-day study administration of 19.9 mg/mL of early stage formulation of ALIS (SLIT) was not associated with any significant difference in terms of BALF TNF-α, nitrite or cell numbers relative to FA or saline treated animals.

ALIS administration to rats at a dose of 90 mg/kg for up to three 30 day cycles with 30-day recovery periods was not associated with any significant effect on BALF TNF-α or nitrite content relative to saline treated controls. No effect on BALF derived macrophage opsonisation or yeast killing capacity was noted ex-vivo. Treatment was associated with a significant increase in BALF cell content which composed of alveolar macrophages and (presumed peripheral) polymorphonuclear (PMN) cells. BALF derived macrophages from treated animals were twice the size of those from saline treated controls, this was reversed following recovery. Macrophages isolated from treated animals were shown to produce nitric oxide and TNF-α in response to an LPS challenge. However, this response differed in magnitude from control animal isolates with lower levels of TNF-α and higher levels of nitrites relative evident. The applicant attributes this to the effects of PMN nitric oxide production resulting in decreased macrophage TNF-α. However, this is not convincing as the differences in expression of these markers remain significantly different from controls following recovery at which point BALF cell content has returned to control levels. Hence, these data indicate that ALIS administration may be associated with altered lung macrophage function. Of note, this study only assessed function following 30-days continuous exposure

and only examined two markers of inflammation. Data from longer term studies in rats indicate that prolonged exposure may result in impaired macrophage function as per the above discussion on the carcinogenicity findings.

Impurities/Leachables
Impurities' profile of ALIS could be considered as qualified and accepted from the toxicological point of view. The container closure system and valve components have a number of plastic and elastomeric components from which a range of compounds could potentially leach or be extracted into the formulation. Leachable studies were performed on both the primary container closure system (vials and stoppers) and the Lamira nebuliser system. Toxicology assessments of the identified leachables from the container closure, mouthpiece, and the Lamira nebuliser system and in-use simulation of amikacin liposome inhalation dispersion were conducted. Compounds were evaluated that were above the final analytical evaluation threshold which was derived from the Product Quality Research Institute (PQRI) recommended SCT of 0.15 µg/day. These evaluations concluded that there is a negligible health risk to humans under conditions of use. Margins of exposure (MOE) were determined for each compound by comparing the total daily intake (TDI) to the PDE (i.e., PDE/TDI). Toxicity information generated using inhalation routes of administration was used when possible. Based on the PDE value and the TDI of each organic compound, all 13 compounds present a negligible health risk because each MOE was well above the value of 1. In most cases, element MOEs were well above 1 for each element with the exception of nickel, chromium, and manganese. However, in the leachable study for elements with ALIS or saline, none of these three elements were identified, indicating a negligible health risk under conditions of use. All of the 7 elements found in the leachate had MOE substantially higher than the value of 1 supporting the absence of significant risk to human health under conditions of used of the ALIS drug product. Two elements, bromine and magnesium, were present in the handset leachates but not in the handset extracts. Magnesium is traceable to the ALIS stopper. Bromine was not identified in any extract but has an MOE value well above the PDE. It was presumed that the identified leachables are expected to pose a negligible health risk to humans under conditions of use.

2.3.5. Ecotoxicity/environmental risk assessment

Phase I PEC calculation showed that ALIS exceeded the action limit. Logkow was experimentally determined using the shake-flask method and was <-2 indicating this drug is unlikely to bioaccumulate in aquatic organisms.

Amikacin was shown not to be biodegradable in an OECD 301B compliant study and shown to be highly mobile in sludge and soil extracts in an OECD 106 compliant study indicating no need for an assessment of terrestrial toxicity assessment. An appropriately conducted OECD 308 study reported amikacin to exhibit long half lives in both water and sediment in two rive systems with little to no degradation or metabolism detected indicating persistence as well as significant partitioning (>10%) to sediment. Of note, the provided normalization of DT50 values from this study to 12 °C has been done using an outdated conversion factor (Q10 = 2.2) which is not considered acceptable. For the temperature correction to 12 °C in simulation studies, the Arrhenius equation with a specific activation energy Ea of 64.5 kJ/mol (current Q10 factor of 2.58) has to be used (see REACH R.7b, p. 222). Based on the data presented, amikacin was shown to be very persistent. Therefore, a phase IIB study on the effects of amikacin on sediment dwelling organisms was conducted (OECD 218, see below).

Amikacin was shown to dose dependently inhibit respiration in STP organisms in the activated sludge respiration test (OECD 209) with EC10 and EC50 values were 0.3 and 114 mg/L, respectively. No NOEC was defined in this study but is accepted that the EC10 for these effects is several orders of magnitude greater than the refined PECsurfacewater and therefore unlikely to pose a significant risk.

Toxicity was evaluated in several aquatic species in OECD 201, 210 and 211 compliant studies with Anabaena flos-aquae algae demonstrating the greatest sensitivity with a NOEC of 1.7 µg/L. The use of this species is acceptable for the assessment of an antimicrobial in line with the question 11 of the ERA Q&A document. This was based on the measured time weighted average concentration in the test system and is considered appropriate. The mean co-efficient of variation for section by section growth rates in the controls was significantly higher than the validity criteria of not more than 35% (158%). This was justified by the applicant as related to low cell density at early intervals and stated as not uncommon for historical control data for Anabaena flos-aquae at the laboratory. Similar findings were noted in treatment groups supporting the applicant's argument. The applicant provided historical control data from the test facility indicating that this was indeed a common finding. Given Anabaena flos-aquae was identified as the most sensitive species in the ERA and therefore used for pivotal PEC/PNEC calculations it is considered essential that this test is performed adequately. As such, in line with the answer to question 11 ii) of the EMAs Q&A document on the 'Guideline on the environmental risk assessment of medicinal products for human use (EMA/CHMP/SWP/44609/2010 Rev. 1)', due to the cited limitations in the completed study, the applicant committed to submit an appropriately conducted OECD 201 study**.**

Toxicity is reported as much lower as assessed in appropriately conducted studies as per OECD 210 and 211. PEC/PNEC comparisons do not indicate amikacin as posing a threat to the environment. However, due to the concern raised on the conduct of the OECD 201 study which was shown to be the most sensitive to the effects of amikacin, available data do not allow to conclude definitively on the potential risk of amikacin to the environment.

Table 3: Summary of main study results

Substance (INN/Invented Name): Amikacin			
CAS-number (if available): 37517-28-5			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	log K_{ow} < -2.00	Below 4.5 threshold, no PBT screening warranted
PBT-assessment			
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	< -2.00	Not Bioaccumulative
Persistence		Not readily biodegradable $DT_{50,\ whole\ system}$ = 1386 days % shifting to sediment = 22.6	Very Persistent
Toxicity	NOEC Algae	1.7 µg/L	
	NOEC Crustacea	1.7 mg/L	
	NOEC Fish	13 mg/L	
PBT-statement :	Amikacin is not PBT but is classified as vP		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, Default Refined (Prevalence)	 2.95 0.018	µg/L	> 0.01 threshold Action limit exceed, proceed to Phase II
Other concerns			Antimicrobial
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106 or …	Sludge K_{oc} = 14.5 ml/g 13.3 ml/g	2 sludge types, 3 soil types
		Soil K_{oc} = 0.467 ml/g	

		0.448 ml/g 0.673 ml/g			<10000 L/Kg Terrestrial studies not triggered
Ready Biodegradability Test	OECD 301B	Not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	Taunton river $DT_{50,\ water\ (12\ ^oC)}$ = 730 days $DT_{50,\ sediment\ (12\ ^oC)}$= 1460 days $DT_{50,\ whole\ system\ (12\ ^oC)}$= 2629 days % shifting to sediment = 22.6 Weweantic river $DT_{50,\ water\ (12\ ^oC)}$ = 1096 $DT_{50,\ sediment\ (12\ ^oC)}$ = 939 $DT_{50,\ whole\ system\ (12\ ^oC)}$= 2190 % shifting to sediment = 14.2			Amikacin can be considered very persistent. % partitioning to sediment >10%, hence Phase IIb sediment toxicity study triggered % orgC 3.4 and 0.64 for Taunton and Weweantic river systems respectively.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Anabaena flos-aquae, strain 67, class Cyanophyceae*	OECD 201	NOEC	1.7	µg/L	Growth rate
Daphnia sp. Reproduction Test	OECD 211	NOEC NOEC	1.7 16	mg/ L	Body length Reproduction
Fish, Early Life Stage Toxicity Test/ *Pimephales promelas*	OECD 210	NOEC	13	mg/ L	hatching success
Activated Sludge, Respiration Inhibition Test	OECD 209	EC10 EC50	0.3 114	mg/ L	No NOEC defined
Phase IIb Studies					
Sediment dwelling organism/ *Chironomus riparius*	OECD 218	NOEC	44.3	mg/ kg	Normalised for 10% organic carbon. Based on NOEC of 9.3 mg/kg for midge emergence and developmental rate

2.3.6. Discussion on non-clinical aspects

Toxicology

The applicant considers the lung carcinogenicity findings species specific. Additional discussion on these data and justification as to the species-specific nature of the findings was requested as part of a non-clinical major objection at day 120 of the initial procedure with additional justification submitted at that time and included in the non-clinical overview in this submission. The applicant states that the positive findings observed in this study occur via a non-genotoxic mechanism as ALIS was shown to be non-genotoxic in a standard battery. The applicant claimed that the findings are species-specific and related to a particulate overload, which is suggested to be threshold based (with tumorigenesis evident in animals dosed over 1 mg/g lung weight).

Additional argumentation has been provided based on species differences in relative pulmonary surface area and macrophage size to further support the contention this finding is species specific. The applicant also comments that no lung inflammatory or neoplastic changes were observed following up to 9-months inhalation administration to dog in the pivotal repeat dose toxicity study (Study 11-6400). Finally, the

applicant includes a comparison to reported non-clinical lung pathology findings from other inhalable aminoglycosides.

While these arguments are reasonable, they are not sufficient to conclude on the clinical relevance of the rat findings. It is accepted that amikacin is non-genotoxic and the proposed threshold effect on particulate clearance may in part explain these findings in rats. The applicant suggests that the neoplastic findings induced by particulate overload in rats are of questionable clinical relevance. This is not endorsed. The applicant suggests that these particulate overload- induced neoplastic lung changes in rat are secondary to chronic pulmonary inflammation. It is noted that amikacin is a bronchial irritant clinically with allergic alveolitis an identified risk in the proposed RMP, bronchospasm included as an AR in the proposed SmPC and cases of interstitial lung disease reported. These findings suggest that prolonged administration may result in human lung inflammation with unknown consequences.

Although the similarities in lung pathology findings are noted, in the absence of long-term administration studies for comparison, the reference to the development programmes of other inhaled aminoglycosides is not considered directly relevant to the question of carcinogenicity. Furthermore, as part of the responses, the applicant acknowledged the potential for a disease-drug interaction resulting in increased patient sensitivity to ALIS administration.

It is considered unlikely that additional non-clinical mechanistic studies or a request for further justification will alter the understanding of the clinical relevance of these findings at this time. As such, this potential risk should be taken into consideration when assessing the benefit risk of the product, information on this risk is included in the SmPC and this will be monitored in PSURs in the normal manner.

No dedicated reproductive and developmental toxicology studies with ALIS have been conducted. This is considered acceptable and the applicant has provided data from bibliographic sources to cover this requirement. The wording in the SmPC appropriately reflects this.

Environmental Risk Assessment
The applicant has completed an ERA in line with the EMAs 'Guideline on the environmental risk assessment of medicinal products for human use'. In general, the ERA was conducted appropriately but the applicant was requested to repeat the completed OECD 201 study as it did not meet its predefined validity criteria and has committed to do so in post-authorisation.

2.3.7. Conclusion on the non-clinical aspects

No non-clinical major objections are raised to the approval of Arikayce liposomal. However, it should be noted that the uncertain clinical relevance of the rat carcinogenicity findings should be taken into consideration when assessing the benefit risk of this product.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

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

Phase Study Identifier (Status)	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Route of Administration; Dosage Regimen	Healthy Subjects or Diagnosis Number of Subjects	Duration of Treatment
Single-Dose Studies (Not in Pooled Safety Population)					
Phase 1 Module 5.3.3.1 RD 201/23924 (completed)	Pulmonary deposition, clearance, and safety	Open-label, single dose	120 mg Amikacin-loaded radiolabeled liposomes, nebulizer inhalation	Healthy subjects N = 6 (6 treated)	Single dose
Phase 1a Module 5.3.3.2 TR02-101 (completed)	Safety/tolerability and PK	Double-blind, placebo-controlled, single ascending dose	Amikacin, or placebo; nebulizer inhalation ALIS 90, 270, and 500 mg	CF with chronic *P aeruginosa* infection N = 18 (12 ALIS; 6 Placebo)	Single dose (6 subjects had a second dose)
Target Indication: 3 Studies in Nontuberculous Mycobacteria (Primary Evidence of Efficacy and Pooled Safety)					
Phase 2 Module 5.3.5.1 TR02-112 (completed)	Efficacy, safety/tolerability, PK (substudy)	Randomized, double-blind, placebo-controlled phase, followed by open-label extension phase and safety addendum (follow-up for up to 1 year after last dose)	Amikacin 70 mg/mL, nebulizer inhalation Double-blind phase: ALIS 590 mg QD or placebo Open-label phase: ALIS 590 mg QD	Treatment-refractory NTM lung disease on a stable MDR Total N = 90 (89 treated) ALIS N = 45 (44 treated) Placebo N = 45 (45 treated)	84 days (double-blind phase), followed by an additional 84 days (extension phase)
Phase 3 Module 5.3.5.1 INS-212[a] (ongoing)	Efficacy, safety/tolerability, and PK (substudy)	Randomized, open-label phase, followed by off-treatment observational phase for 12 months	Amikacin 70 mg/mL, nebulizer inhalation ALIS 590 mg QD + MDR or MDR alone	Treatment-refractory NTM lung disease on a stable MDR Total: N = 336 (335 treated) ALIS + MDR: N = 224 (N = 223 treated) MDR alone: N = 112 (N = 112 treated)	Up to 8 months (non-converters) or 16 months (converters) in the randomized, open-label phase followed by an additional 12-month off-treatment observational period

Phase Study Identifier (Status)	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Route of Administration; Dosage Regimen	Healthy Subjects or Diagnosis Number of Subjects	Duration of Treatment
Phase 3 Module 5.3.5.2 INS-312[a] (completed)	Long-term safety/tolerability and efficacy	Open-label, extension study of INS-212	Amikacin 70 mg/mL, nebulizer inhalation ALIS 590 mg QD + MDR	Treatment-refractory NTM lung disease on a stable MDR Non-converters from Study INS-212 who continued Total: N = 163 Prior ALIS + MDR: N = 73 Prior MDR alone: N = 90	Up to 12 months
Other Indications (Contributing to Pooled Safety Data)					
Phase 1b/2a Module 5.3.5.4 TR02-103 (completed)	Safety/tolerability, PK, and efficacy	Open-label, multiple dose	Amikacin 50 mg/mL, nebulizer inhalation ALIS 500 mg QD	CF with chronic *P aeruginosa* infection N = 13 (13 treated)	14 days
Phase 1b/2a Module 5.3.5.4 TR02-104 (completed)	Safety/tolerability, PK, and efficacy	Open-label, multiple dose	Amikacin 50 mg/mL, nebulizer inhalation ALIS 500 mg QD	CF with chronic *P aeruginosa* infection N = 11 (11 treated)	14 days
Phase 2a Module 5.3.5.4 TR02-105 (completed)	Safety/tolerability, PK, and efficacy	Randomized, double-blind, placebo-controlled, dose-escalating	Amikacin 70 mg/mL, or placebo; nebulizer inhalation Cohort 1: ALIS 280 mg QD or placebo Cohort 2: ALIS 560 mg QD or placebo	CF with chronic *P aeruginosa* infection Total N = 66 (64 treated) ALIS N = 44 (42 treated) Placebo N = 22 (22 treated)	28 days
Phase 2a Module 5.3.5.4 TR02-105EXT (completed)	Safety/tolerability, and efficacy	Open-label extension phase of TR02-105	Amikacin 70 mg/mL, nebulizer inhalation ALIS 560 mg QD	CF with chronic *P aeruginosa* infection N = 49 (49 treated) (33 who received ALIS and 16 who received placebo in TR02-105)	18 months – up to 6 cycles (28 days on treatment and 56 days off treatment)

Phase Study Identifier (Status)	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Route of Administration; Dosage Regimen	Healthy Subjects or Diagnosis Number of Subjects	Duration of Treatment
Phase 1b/2a Module 5.3.5.4 TR02-106 (completed)	Safety/tolerability, PK, and efficacy	Randomized, double-blind, parallel group, placebo-controlled, stratified by FEV_1 % predicted	Amikacin 70 mg/mL, nebulizer inhalation Cohorts 1 and 2: ALIS 70 mg QD, ALIS 140 mg QD or placebo (1:1:1 ratio) Cohort 3: ALIS 560 mg QD or placebo (2:1 ratio)	CF with chronic *P aeruginosa* infection Total N = 46 (41 treated) ALIS N = 30 (27 treated) Placebo N = 16 (14 treated)	28 days
Phase 2 Module 5.3.5.4 TR02-107 (completed)	Safety/tolerability, PK, and efficacy	Randomized, double-blind, parallel group, placebo-controlled	Amikacin 70 mg/mL, nebulizer inhalation Cohort 1: ALIS 280 mg QD or placebo (2:1 ratio) Cohort 2: ALIS 560 mg QD or placebo (2:1 ratio)	Bronchiectasis with chronic *P aeruginosa* infection Total N = 64 (62 treated) ALIS N = 44 (43 treated) Placebo N = 22 (19 treated)	28 days
Phase 3 Module 5.3.5.4 TR02-108[a] (completed)	Efficacy, safety/tolerability, and PK (substudy)	Randomized, open-label, active-controlled, stratified by age and FEV_1 % predicted	Amikacin 70 mg/mL, nebulizer inhalation ALIS 590 mg QD or TOBI 300 mg BID	CF with chronic *P aeruginosa* infection Total N = 302 (294 treated) ALIS N = 152 (148 treated) TOBI N = 150 (146 treated)	3 cycles (28 days on treatment and 28 days off treatment)
Phase 3 Module 5.3.5.4 TR02-110[a] (completed)	Long-term safety/tolerability and efficacy	Open-label, extension study of TR02-108	Amikacin 70 mg/mL, nebulizer inhalation ALIS 590 mg QD	CF with chronic *P aeruginosa* infection N=206 (206 treated)	Up to 12 cycles (28 days on treatment and 28 days off treatment)

[a] Prior to Study TR02-108, two 4 mL vials of 280 mg were used to administer a dose of 560 mg. To improve patient convenience, in the first CF Phase 3 study (TR02-108), a single 10-mL vial was used. The average volume of ALIS delivered from the 10-mL vial to the nebulizer was 8.4 mL and a delivered dose of 590 mg more accurately reflects the drug product that was evaluated in the 2 Phase 3 CF Studies TR02-108 and TR02-110, and all NTM studies (TR02-112, INS-212, and INS-312).

ALIS = amikacin liposome inhalation suspension; BID = twice daily; CF = cystic fibrosis; FEV_1 = forced expiratory volume in 1 second; MDR = multidrug regimen; NTM = nontuberculous mycobacteria; PK = pharmacokinetic; *P aeruginosa* = *Pseudomonas aeruginosa*; QD = once daily; TOBI = tobramycin inhalation solution.

2.4.2. Pharmacokinetics

Absorption

The table below summarises serum concentrations of amikacin after inhalation of various formulations and using various nebulisers.

Table 4: Median (Range) of AUC_{0-24} or Concentration (µg/g) for Serum and Sputum Samples After Dosing With 3 Different Concentrations of Amikacin in ALIS

Study Dose (Highest in Study)	Serum AUC_{0-24} (µg•h/mL) or µg/g 1 Hour After Dose Day 1 Median (Range)	Serum AUC_{0-24} (µg•h/mL) or µg/g 1 Hour After Last Study Dose Median (Range)	Sputum µg/g 1 Hour After Dose Day 1 Median (Range)	Sputum µg/g 1 Hour After Last Study Dose Median (Range)
20-mg Formulation				
TR02-101 500 mg	0 (0-1.07) AUC_{24-48}	0 (0-2.21) AUC_{48-72}	206 (145-327) AUC_{24-48}	111 (85.4-419) AUC_{48-72}
50-mg Formulation				
TR02-103 500 mg	5.29 (3.37-12.0) AUC_{0-24}	10.9 (5.65-30.1) AUC_{0-24}	721.0 (78.73-17197) AUC_{0-24}	7770 (1735-2386) AUC_{0-24}
TR02-104 500 mg	9.95 (5.04-20.1) AUC_{0-24}	10.3 (7.75-17.4) AUC_{0-24}	6135 (655-9652) AUC_{0-24}	14934 (1930-49985) AUC_{0-24}
70-mg Formulation				
TR02-105 560 mg	NA	NA	1580 (250-7441)	1527 (11.6-15109)
TR02-105EXT[a] 560 mg	NA	NA	NA	NA
TR02-106 560 mg	NA	NA	4050 (11.6-11220)	2154 (8.28-5088)
TR02-107 560 mg	6.07 (3.32-15.1) AUC_{0-24}	9.49 (0.06-26.8) AUC_{0-24}	5620 (624-26100)	5050 (0.726-7200)
TR02-108 590[b] mg	6.72 (2.43-16.4) AUC_{0-24}	8.53 (1.64-15.4) AUC_{0-24}	982 (0-6120)	1530 (0-11000)
TR02-112 590[b] mg	15.2 (3.82-42.7) AUC_{0-24}	17.8 (4.47-54.3) AUC_{0-24} at steady state	NA	3185 (1.07-16799) Postdose for all samples
INS-212 590[b] mg	15.8 (4.16-53.5) AUC_{0-24}	16.7 (4.31-55.6) AUC_{0-24} at steady state	6.96 (2.33-2010) 8 hours postdose	414 (5.83-6660) Month 6, 1-4 hours postdose

Sources: Studies TR02-101, TR02-103, TR02-104, TR02-105, TR02-105EXT, TR02-106, TR02-107, TR02-108, and INS-212

[a] Pharmacokinetic/pharmacodynamic analysis only.

[b] Prior to TR02-008, two 4-mL vials of 280 mg were used to administer a dose of 560 mg. To improve subject convenience, in the first study in Phase 3 (TR02-108) a single 10-mL vial was used. A comprehensive review of all batches of 10-mL vials manufactured for use during Study TR02-108, Study TR02-110, and Study TR02-112 found that the average volume of ALIS delivered from the vials to the nebulizer was 8.4 mL and not 8.0 mL. Thus, a delivered dose of 590 mg more accurately reflects the drug product that was evaluated in Studies TR02-108, TR02-110, TR02-112, INS-212, INS-312.

- Six studies enrolled CF patients with chronic *P. aeruginosa* infection.
- TR02-107 enrolled patients with bronchiectasis
- TR02-112 enrolled patients with chronic non-tuberculous mycobacterial (NTM) lung infections
- INS-212/312 enrolled patients with chronic *Mycobacterium avium* complex (MAC) lung infections

Details of studies in NTM/MAC patients and the POPPK models are provided below. Additional details of PK data obtained during studies in patients with CF or bronchiectasis are provided in the Clinical Assessment Report.

The focus is on systemic exposures to amikacin after inhalation of ALIS once daily. Once amikacin reaches the systemic circulation, its PK properties are very well known. The mean serum half-life of amikacin after IV administration to adults is ~ 2 h with a mean Vd of 24 L (28% of the body weight). By the ultrafiltration technique, reports of serum protein binding range from 0 to 11%. Mean serum clearance rate is about 100 mL/min and the renal clearance rate is 94 mL/min in subjects with normal renal function. At low plasma concentrations, it is apparent that there is some tubular reabsorption that is saturated and thus not detectable at the exposures achieved with routine IV doses.

Distribution

The distribution of ALIS after inhalation was initially evaluated in RD 201/23924, in which 6 healthy male subjects received 120 mg ^{99m}Tc-radiolabelled amikacin loaded into liposomes using one of two versions of the nebuliser. A ventilation scan was performed using ^{81m}Kr radioactive gas to characterise the deposition of the amikacin-loaded liposomes by defining the ventilated area of the lungs. The margins of the lungs that were defined were used as a template to permit accurate determination of pulmonary deposition of radiolabelled drug.

Five subjects completed inhalation of the dose. The mean recovery of radioactivity was 102%. The mean fraction of the emitted dose impacting in the oropharyngeal region and swallowed was 12.3% whereas 47.8% of the emitted dose was deposited on the exhalation filter and mouthpiece. For all 6 subjects the mean emitted dose to lungs was 39.9% (with means of 32.3% and 47.5% in the nebuliser subgroups). Based on the measured fraction of the loaded dose retained within the nebuliser (mean 61.2%) and the fraction of the emitted dose delivered to lungs, it was calculated that 15.5% of the loaded dose was deposited in lungs and the mean dose reaching the lungs was 17.2 mg.

Table 4: Summary of radiolabel recovery and estimated dose (mg) to lung of amikacin

		% Recovered					
		Loaded Dose	*Emitted Dose				
Device	Subject Number	Nebuliser Retention	Exhalation Filter % MP	Oropharynx/ Stomach	Lung	Estimated Dose	sC/P
Pari LC Star	S101	62.71	58.25	13.08	28.67	12.83	1.60
	S102	58.79	55.66	8.94	35.41	17.51	2.12
	S103	51.84	53.01	14.07	32.92	19.03	1.17
	Mean	**57.78**	**55.64**	**12.03**	**32.33**	**16.46**	**1.63**
	SD	**5.51**	**2.62**	**2.72**	**3.41**	**3.23**	**0.48**
Pari LC Star/Akita	S104	67.51	12.69	24.68	62.63	24.42	1.04
	S105	84.97	37.54	11.14	51.32	9.26	1.38
	S106	41.16	69.81	1.71	28.47	20.10	1.48
	Mean	**64.55**	**40.01**	**12.51**	**47.47**	**17.93**	**1.30**
	SD	**22.05**	**28.64**	**11.54**	**17.40**	**7.81**	**0.23**
Overall Performance	**Mean**	**61.16**	**47.83**	**12.27**	**39.90**	**17.19**	**1.47**
	SD	**14.85**	**20.10**	**7.51**	**13.95**	**5.41**	**0.38**

* i.e. sum of recovery from mouthpiece (MP), exhalation filter and subject deposition

The calculations were very similar for the three subjects who were dosed in conjunction with the system vs. those dosed using a Pari Compressor (mean doses of amikacin reaching lungs were 17.9 mg and 16.5 mg, respectively).

The pattern of radiolabelled liposome deposition within the lung (based on the penetration index sC/P; the ratio of the counts in the central/peripheral lung regions corrected for regional lung volume) was described by a mean sC/P ratio of 1.47 (1.3 vs. 1.63 for the two subgroups described above). The data to calculate sC/P were derived from images acquired at about 20 min after the start of nebulisation. During this period redistribution of the radiolabelled liposomes may have occurred.

The time-dependent retention curve of radiolabelled liposomes was biphasic. There was an initial rapid reduction in counts over 3 h followed by a slower phase up to 48 h. Mean retention of radiolabelled liposomes within the lung at 48 h was 41.8% (45.3% vs. 38.3% for the two subgroups described above). Model-based simulations showed that peak (Cmax) and trough concentrations were not impacted markedly with changes in BMI or lung function.

Table 5: Summary of pulmonary retention of radiolabelled liposomes

Time Post-Dose (h)	% Deposited Dose Pari LC Star					% Deposited Dose Pari LC Star/Akita					Overall	
	S101	S102	S103	Mean	SD	S104	S105	S106	Mean	SD	Mean	SD
0	100.00	100.00	100.00	100.00	0.00	100.00	100.00	100.00	100.00	0.00	100.00	0.00
1	84.65	79.16	96.24	86.68	8.72	93.97	91.88	96.51	94.12	2.32	90.40	7.01
3	74.69	67.08	82.53	74.77	7.72	83.67	80.32	87.67	83.89	3.68	79.33	7.37
6	64.94	64.71	77.71	69.12	7.44	79.10	75.49	85.46	80.02	5.05	74.57	8.24
12	62.55	59.06	70.72	64.11	5.99	71.98	68.59	80.63	73.73	6.21	68.92	7.58
24	56.10	56.39	68.63	60.37	7.15	63.48	64.97	77.67	68.71	7.80	64.54	8.10
48	41.14	32.95	40.71	38.27	4.60	47.71	42.18	46.04	45.31	2.84	41.79	5.16

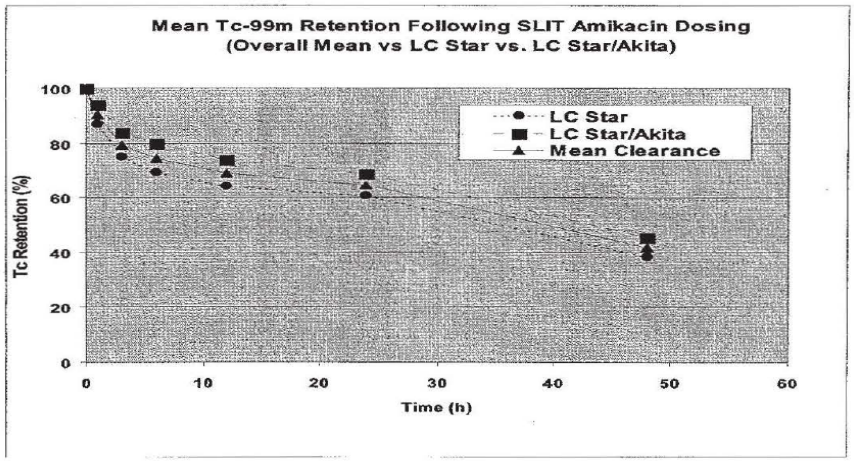


Figure 2: Plot to show the pulmonary clearance of radiolabelled liposomes

The Phase 2 study TR02-112 in NTM patients included a scintigraphy sub-study in 4 patients who completed the 3-month randomised phase. These patients received a single dose of ^{99}Tc-radiolabelled ALIS 590 mg via an eFlow® nebuliser on Day 1 at NIAID and then underwent gamma scintigraphy during the first 2 minutes of each 10-minute period over 2 h to determine initial drug deposition and clearance rates. An additional drug retention scan was performed 18-30 h following initial study drug inhalation on Day 2. On Study Day 3 they began administration of ALIS 590 mg for up to 84 days.

Almost half (42.8% ± 5.6%) of the loaded dose was deposited in the lungs immediately after dosing, corresponding to 252 mg of ^{99}Tc-ALIS. Only 12.8% ± 5.4% of the loaded dose was retained in the nebuliser. The C/P ratio of 2.05 indicated that twice as much radiolabelled ALIS was deposited in the lung centrally as compared to peripherally. Retention of the radiolabelled ALIS over time was 79% ± 7% at 1 h and 53% ± 3% at 24 h so more than half was retained in the lung at 24 h and the radiolabel was distributed to both central and peripheral compartments of the lung. Deposition of radiolabel in areas of cavitation and air trapping was not apparent.

Dipalmitoyl phosphatidylcholine (DPPC)

The ratio (w/w) of DPPC to amikacin in ALIS is 1.0. For the nominal 500 mg loaded dose, approximately 112.5 mg amikacin and 112.5 mg of DPPC are delivered to the lungs, taking into account the efficiency of the delivery by inhalation. For a 50 kg adult, this corresponds to a delivered dose of DPPC of 2.25 mg/kg and ~ 53 mg of DPPC per dose deposited in the alveoli. This is 1 to 2 orders of magnitude less than the 50-100 mg/kg doses of exogenous lung surfactants that have been instilled into neonate and adult lungs in the treatment of ARDS.

Liposomes deposited in the conducting airways are cleared by the mucociliary escalator, and are not expected to contribute to the endogenous phospholipid pool. Martini *et al*. have shown that DPPC is recycled into lamellar bodies of alveolar type II cells at a rate of 216 nmol/h/g tissue in ventilated pigs. For a 400 g human lung this corresponds to a basal absorption rate for DPPC of about 70 mg/h. Hence, the phospholipid dose delivered from ALIS can be easily cleared and recycled using existing metabolic pathways. Moreover, the rate of catabolism of DPPC accelerates at higher lipid loads. Surfactant treatments have been shown not to adversely affect endogenous synthetic and secretory phospholipids pathways by feedback inhibition.

Pharmacokinetics in target population

Cystic Fibrosis (CF) patients
Serum amikacin AUC_{0-24} during QD inhalation of ALIS by CF patients was much lower than reported after 30-35 mg/kg amikacin IV QD in CF patients. The mean steady-state serum AUC_{0-24} estimates (see below) were 13.7 to 23.3-fold lower for ALIS compared to IV amikacin.

In contrast, ALIS resulted in markedly higher concentrations of amikacin in sputum (several thousand-fold higher than those achievable on dosing with amikacin IV).

Bronchiectatic patients
Similar findings applied to the comparison between patients with bronchiectasis complicated with chronic *P. aeruginosa* infection treated with ALIS vs. published data after intravenous dosing.

Comparative Steady-State Serum and Sputum Exposures in CF Patients

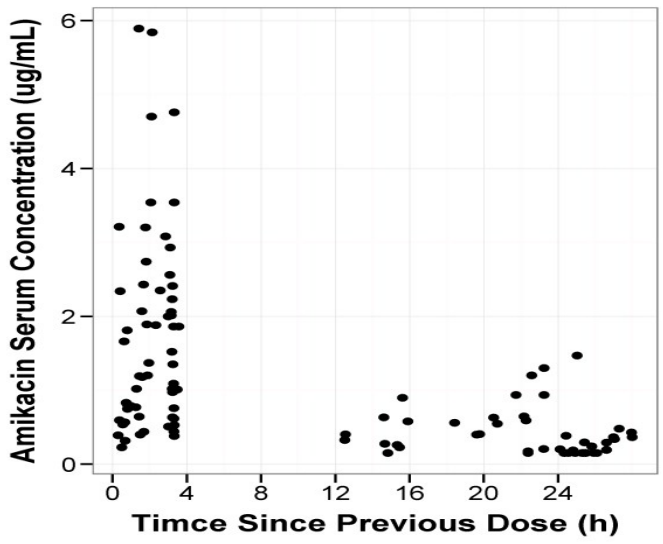
Exposure Measure	ALIS 560 mg QD			Amikacin 35 mg/kg IV QD[4]	Amikacin 30 mg/kg IV QD[5]
	TR02-105	TR02-106	TR02-108		
Serum	N = 20	N = 9	N = 27	N = 18	N = 12
AUC_{0-24} (mcg•h/mL)	14.6 ± 11.7[6]	17.1 ± 7.58[6]	8.17 ± 4.08[7]	~250	235 ± 110
C_{max} (mcg/mL)	2.27 ± 1.58[6]	2.71 ± 1.75[6]	1.15 ± 0.746[8]	121 ± 37.5	116 ± 37
Sputum	N = 20			N=13	N=12
AUC_{0-24} (mcg•h/mL)	22,445 ± 18,652	ND	ND	ND	83.7 ± 43.4
C_{max} (mcg/mL)	ND	ND	ND	10.9 (7.5)	5.9 ± 2.7

[4] Data from [Canis et al. 1997]
[5] Data from [Byl et al. 2001]
[6] Mean ± SD from Day 28 (highest value)
[7] Mean ± SD from Day 113 (highest value)
[8] Mean ± SD from Day 1 (highest value)
Data are expressed as means ± SD or means (CV%) or means only; AUC is AUC_{0-24} unless otherwise indicated

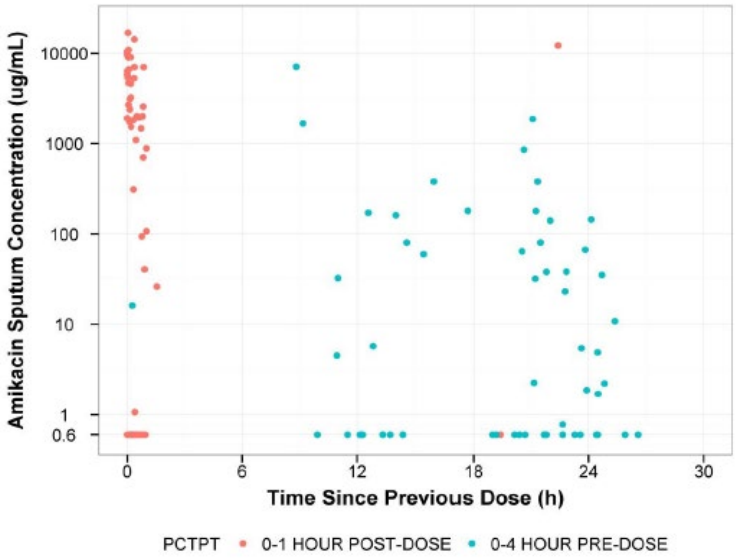
NTM (nontuberculosus mycobacterial) and Mycobacterium avium Complex (MAC) patients

Observed data

In TR02-112 blood was collected from a subset of 14 patients with frequent sampling in two time windows to capture pre- and post-dose serum levels on Days 1, 2, 28, 56, 84, 112 and 168. Sputum and urine were also obtained. Serum amikacin showed an early peak at up to 6 mg/L but levels by 12 h were generally < 1 mg/L.

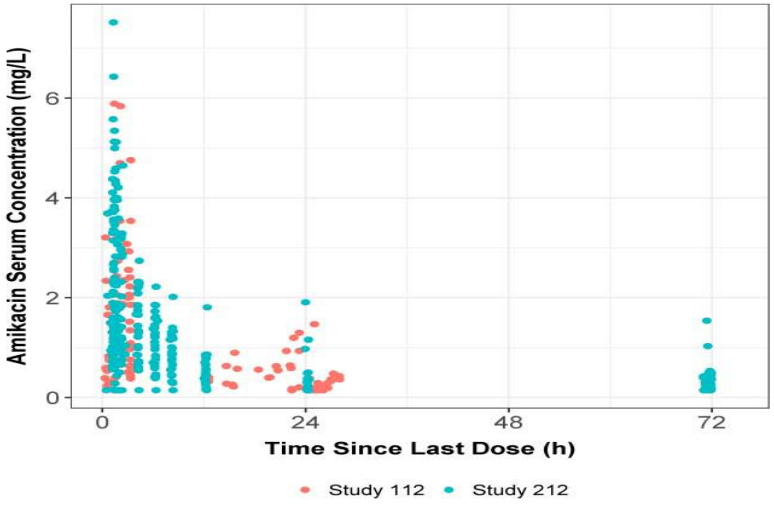


Sputum concentrations were much more variable and some subjects had very high concentrations during 12-24 h post-dose.



The Phase 3 study INS-212 included collection of blood and sputum samples from a subset of US and Japanese patients between 0 to 1 h pre-dose and 1 to 4 h post-dose at months 1, 3 and 6 on treatment. A sputum-only subset had samples collected to assess residual concentrations after interrupting/stopping ALIS at various time points, including 28 days and 3 months off-treatment.

Intensive blood sampling occurred in a subset of Japanese subjects. Of 39 patients providing PK data, 11 were from the US and 28 Japanese. The serum PK data are shown and compared below for TR02-112 and INS-212, the latter indicating that serum amikacin was still measurable after 72 h.



Population pharmacokinetics (POPPK) analysis of TR02-112 and INS-212

The PK data (collected as described above) from these studies in patients with NTM were used to conduct two POPPK analyses.
1- was performed on the data available from TR02-112 and data available from INS-212 when patients had completed the 6-month visit.
2 - was performed when patients had completed the follow-up visit at 6 months off-treatment. The serum PK data and thus the POPPK analyses of 1 and 2 are identical. A small amount of additional sputum data was added.

Candidate PK models were fit to serum concentration and urine amount data simultaneously using Monte Carlo Parametric Expectation Maximization, as implemented in the open-source software S-ADAPT Version 1.57. In general, the structural POPPK model was not planned to be modified from that which was applied to the data from TR02-112 alone due to the relative sparseness of the serum PK sampling scheme in INS-212. This model had been previously developed using data from CF studies. This was a three-compartment model absorptive lung compartment, serum compartment and urine compartment) with linear clearance. Random inter-occasion variability was not estimated on any of the PK parameters.

A formal covariate evaluation was not performed but screening plots were conducted using predicted amikacin exposures. No significant relationships were evident in these plots. However, the relationship between body weight and renal clearance, which had been previously identified, was included as a covariate in the model.

Individual estimates of amikacin AUC_{0-24} and Cmax on Day 1 and at steady state were generated for each patient using individual PK parameter estimates from the fit of the model. Additionally, non-compartmental estimation of AUC_{0-24} and Cmax was conducted for INS-212 patients in the PK sub-study. The non-compartmental estimates were then compared to those derived from the POPPK model to assess the robustness of the model.

The model used data from 14 and 39 patients in the two studies, providing 111 sera (16 were BLQ) and 23 urine samples from TR02-112 and 307 sera in INS-212. Sputum samples were available from 59 patients. The model that had been developed using data from CF studies and TR02-112 provided an adequate fit to the pooled data from NTM patients. The model parameter estimates are shown below.

Table 6: Population PK parameter estimates and the associated standard errors for amikacin from the pooled data from studies TR02-112 and INS-212 in subjects with nontuberculous mycobacterial lung disease administered 590 mg ALIS once daily (N=53)

	Population Mean		Inter-individual variability (%CV)	
Parameter	Final Estimate	%SEM	Final Estimate	%SEM
CL_r/F (L/h)	34.29	16.36	71.82	45.25
V_c/F (L)	272.6	11.41	65.09	31.2
ka (h^{-1})	1.866	24.86	40.30	122.1
CL_r (L/h)	1.990	-	30.24	142.3
CL_r coefficient (L/h)	1.931	14.29		
CL_r WTKG power	0.75	-		
Residual error for serum	0.615	3.941		
Residual error for urine	14.0	27.30		
Minimum value of the objective function = 225.3				

The final model described the observed data with acceptable precision.

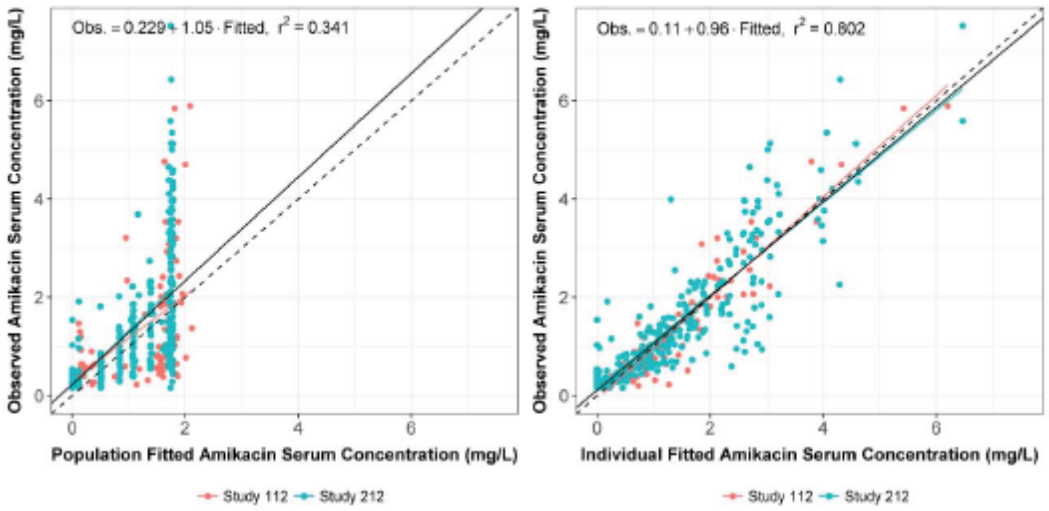


Figure 3: Goodness-of-fit plots serum concentrations pooled data from studies TR02-112 and INS-212 in subjects with nontuberculous mycobacterial lung disease administered 590 mg ALIS once daily

The comparison of the individual estimates for AUC_{0-24} and Cmax derived from the POPPK model vs. non-compartmental estimates are shown below. There was reasonable congruence in the AUC_{0-24} estimates by the two methods but those derived from the POPPK model were higher. The applicant ascribes this to the relatively sparse sampling scheme, which tends to result in AUC_{0-24} estimates that are biased low when calculated by non-compartmental methods.

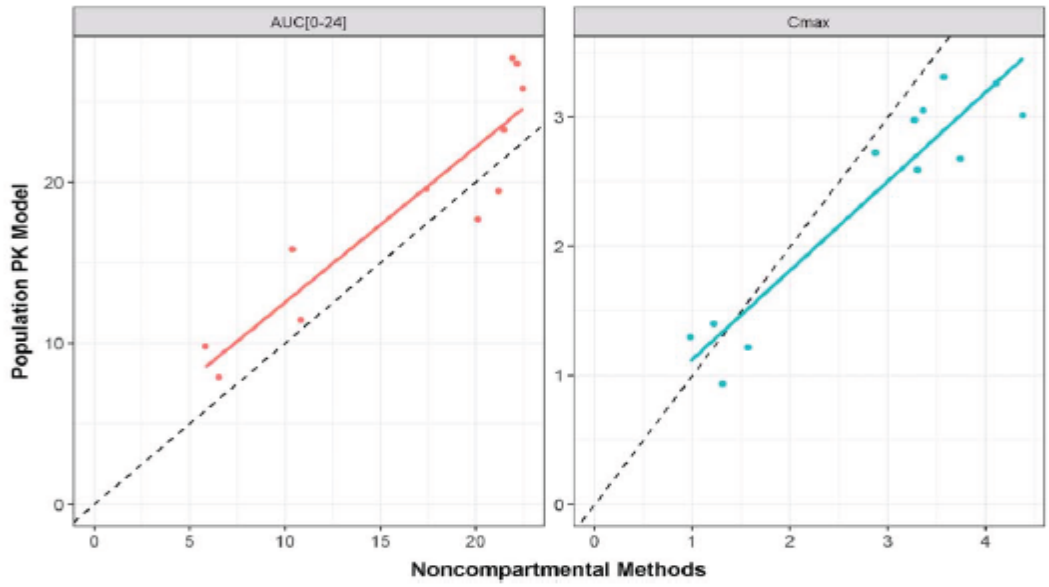


Figure 4: Comparison between AUC_{0-24} (µg•h/mL) and C_{max} (µg/mL) of the PPK model and a noncompartmental analysis of the pooled data from study INS-212 in subjects with nontuberculous mycobacterial lung disease (only those subjects enrolled in the comprehensive PK subset) administered 590 mg ALIS once daily

The exposure estimates determined using the POPPK model are shown below by study. The results indicate consistent serum exposures in the two studies. Systemic bioavailability could not be estimated in INS-212 due to lack of urine samples.

The applicant considered that the comparability in systemic exposures between the two studies indicates that the systemic bioavailability of amikacin after ALIS administration was also comparable. Thus, it was concluded that less than 10% of the inhaled dose reached the systemic circulation.

Table 7: Summary statistics of the amikacin serum half-life and exposure estimates on Day 1 and at steady-state

Parameter	Study 112 (n=14) Mean (CV%) Median (Min-Max)	Study 212 (n=39) Mean (CV%) Median (Min-Max)	PK Population (n=53) Mean (CV%) Median (Min-Max)
C_{max}, Day 1	1.91 (75.0%) 1.31 (0.621 – 5.48)	2.21 (60.4%) 1.75 (0.465 – 6.61)	2.13 (63.6%) 1.70 (0.465 – 6.61)
AUC_{0-24}, Day 1	19.0 (68.4%) 15.1 (4.99 – 44.3)	19.0 (55.7%) 15.8 (4.16 – 53.5)	19.0 (58.6%) 15.8 (4.16 – 53.5)
C_{max}, steady-state	2.12 (71.8%) 1.65 (0.636 – 5.65)	2.32 (59.7%) 1.85 (0.482 – 6.87)	2.27 (62.2%) 1.81 (0.482 – 6.87)
AUC_{0-24}, steady-state	21.6 (69.9%) 16.1 (5.11 – 51.7)	20.0 (55.2%) 16.7 (4.31 – 55.6)	20.4 (59.3%) 16.7 (4.31 – 55.6)
$T_{1/2}$[a]	6.71 (45.7%) 5.48 (4.32 – 14.0)	5.34 (14.8%) 5.48 (3.29 – 7.37)	5.70 (31.3%) 5.48 (3.29 – 14.0)

Initially, the applicant compared blood levels between NTM/MAC patients treated with ALIS and CF patients treated with IV amikacin at 30 or 35 mg/kg as shown below, which suggested ~10-fold lower AUCs. To further assess systemic bioavailability when treating MAC NTM patients with ALIS, a comparison was made from the ALIS POPPK estimates for NTM patients with serum AUCs when administering amikacin to non-CF and non-burns patients at IV doses from 15 to 30 mg/kg. As shown below, a >10-fold difference was observed.

Table 8: Mean (CV%) serum exposure after administration of ALIS compared to published data on systemic administration

Description	Dose/Route	N	AUC_{0-24} (mg•h/L)	C_{max} (mg/L)
Studies TR02-112 and INS-212[a]	590 mg QD via inhalation	53	20.4 (59.3)	2.27 (62.2)
MDR-TB Patients[b]	15–25 mg/kg QD, IM	28	~550	~45
CF Patients[c]	30–35 mg/kg QD, IV	12	235 (46.8)	116 (31.9)
Infected patients with CLcr > 30 mL/min[d]	15–40 mg/kg QD, IV	73	15 mg/kg: 370 (58.6) 30 mg/kg: 741 (58.4)	15 mg/kg: 65.0 (55.2) 30 mg/kg: 130 (55.3)
Infected patients with CLcr > 30 mL/min[e]	15 mg/kg QD, IV	14	351 (61.7)	45.1 (37.8)

[a]Estimates derived from the fit of the population PK model. Steady-state estimates shown.
[b]Modongo et al. 2015
[c]Byl et al. 2001
[d]White et al. 2015. Reported doses are based on total body weight
[e]Abdel-Bari et al. 2011
ALIS = amikacin liposome inhalation suspension;
AUC0-24 = Area under the serum concentration-time curve from time zero to 24 hours;
Cmax = Maximum serum concentration; CF = Cystic Fibrosis; CLcr = creatinine clearance;
CV% = Coefficient of variation; IM = intramuscular; IV = intravenous;
MDR-TB = multidrug resistant tuberculosis; N = number of subjects; QD = quaque die

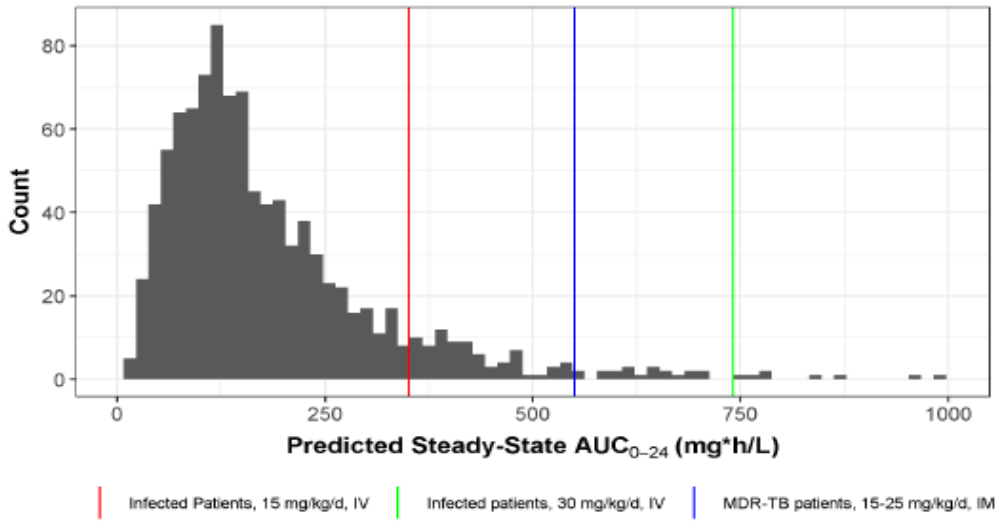
Further analyses investigated the possible worst-case scenarios for steady-state AUC0-24 and Cmax derived from the individual *post hoc* exposure estimates from subjects with NTM, all of whom had CrCL >50 mL/min. Even when using the maximum estimated AUC0-24 at steady-state from the NTM studies and the conservative AUC0-24 observed in CF patients from the literature as the worst-case exposure scenario, systemic amikacin exposure was predicted to be 4-fold lower after ALIS vs. IV amikacin.

Table 91: "Worst-case" exposures after ALIS administration by calculation method

Method	AUC_{0-24} (mg•h/L)	C_{max} (mg/L)	Fold-difference (CF, 30–35 mg/kg/d)	Fold-difference (infected, 15 mg/kg/d[a])
CV% from individual estimates (i)[b]	44.6	5.09	5.27/22.8	7.87/8.85
Maximum value (ii)[c]	55.6	6.87	4.23/16.9	6.31/6.56

[a] Values from Abdel-Bari et al. are used to be conservative.
[b] 97.5th percentile calculated using two standard deviations above the mean.
[c] Maximum individual estimates of steady-state AUC_{0-24} and C_{max} derived from the fit of the final population PK model to the pooled data from Studies TR02-112 and INS-212
Note: fold-difference expressed as AUC_{0-24}/C_{max} and is relative to the mean exposures from the CF or infected patients administered IV amikacin.
ALIS = amikacin liposome inhalation suspension;
AUC0-24 = Area under the serum concentration-time curve from time zero to 24 hours;
Cmax = Maximum serum concentration; CF = Cystic Fibrosis; CV% = Coefficient of variation

The proportion of subjects predicted to have steady-state AUC0-24 >40 mg•h/L after daily administration of ALIS is 7.5% based on individual estimates. Using Monte Carlo simulation and the population mean and inter-individual (IIV) variability estimates for apparent oral clearance (CL/F) from the population PK model, 12.2% of NTM subjects receiving ALIS 590 mg QD would be predicted to have a steady-state AUC0-24 above 40. Furthermore, the potential impact of severe renal impairment on exposure to ALIS was estimated and gave a distribution as shown in the figure.



Plot definition: vertical lines provided for reference and represent the mean AUC_{0-24} for the indicated population.

Figure 5: Distribution of predicted steady-state AUC_{0-24} estimates in hypothetical patients with severe renal impairment assuming a direct, linear relationship between amikacin CL/F and CL_{cr}

Since a relatively shallow relationship was found between CL/F and CrCL using the individual estimates from the population PK analysis, fewer subjects would be expected to experience exposures similar to that which have been reported for patients receiving systemic amikacin. Under the worst case scenarios detailed above, systemic amikacin exposure after ALIS administration is still expected to be well below that which is experienced by patients receiving amikacin via IV or IM administration.

Elimination

Aminoglycosides are not significantly metabolised, undergo glomerular filtration and are actively resorbed in the proximal kidney tubules.

Special populations

- **Impaired renal function**

In POPPK analyses conducted by the applicant creatinine clearance was evaluated as a covariate for a relationship with the inter-individual variability in amikacin PK and was not found to be significant. Arikayce was not studied in patients with renal impairment and dose adjustments were not employed in clinical studies due to the low systemic bioavailability. The median (range) creatinine clearance in patients with NTM was 86.3 (63.3 to 140) mL/min/1.73 m^2 in TR02-112 and 88.4 (57.4 to 124) mL/min/1.73 m^2 in INS-212. The median AUC_{0-24} (µg•h/mL) was 17.8 in TR02-112 and 15.8 in INS-212. See above regarding estimated worst-case exposures in severe renal impairment.

- **Impaired hepatic function**

Due to the fact that amikacin is not metabolised and has low protein binding the PK of amikacin after ALIS inhalation is not expected to be affected by hepatic impairment.

- **Other factors**

There were 45 female and 8 male patients with NTM/MAC that provided PK data. In the POPPK analyses there were no significant relationships between amikacin PK and gender and amikacin exposure was similar in Japanese and White patients.

The age range for CF patients was 6 to 68 years and that for NTM patients was 20 to 84. While the PK of ALIS has not been specifically studied in the elderly, there were 23 NTM patients 65 years of age or older studied in the PK analyses. Age was used and evaluated as a covariate in the POPPK analyses and was found to be not significant. Based on available data, there was no clear relationship between age and the systemic PK parameters of amikacin in each age subgroup and there was a nearly complete overlap seen in the distributions of the PK parameters.

Summary Statistics [Mean (CV%); Median (Min to Max)] of the Amikacin Serum Half-Life and Exposure Estimates on Day 1 and at Steady-State

Parameter	< 65 Years (n = 30)	65 – 70 Years (n = 9)	71-75 Years (n = 9)	76-84 Years[a] (n = 5)
C_{max}, Day 1 (mg/L)	2.43 (61.0%) 1.96 (0.621 - 6.61)	1.69 (55.6%) 1.60 (0.465 - 3.06)	2.01 (71.8%) 1.24 (0.693 - 4.74)	1.39 (37.4%) 1.27 (0.902 - 2.18)
AUC_{24}, Day 1 (mg•h/L)	20.9 (57.4%) 16.9 (4.99 - 53.5)	15.7 (57.1%) 14.3 (4.16 - 29.7)	18.7 (62.7%) 15.6 (6.95 - 40.5)	14.0 (51.2%) 9.61 (7.63 - 23.7)
C_{max}, Steady-State (mg/L)	2.56 (60.2%) 2.06 (0.636 - 6.87)	1.79 (56.4%) 1.65 (0.482 - 3.31)	2.17 (68.4%) 1.79 (0.740 - 4.97)	1.55 (41.5%) 1.29 (0.932 - 2.29)
AUC_{24}, Steady-State (mg•h/L)	22.2 (58.5%) 17.5 (5.11 - 55.6)	16.8 (58.0%) 15.1 (4.31 - 32.0)	20.5 (60.9%) 16.4 (7.42 - 42.4)	16.1 (64.0%) 10.1 (7.89 - 32.3)
$t_{1/2}$[b] (h)	5.39 (22.8%) 5.37 (3.29 - 9.75)	5.60 (10.7%) 5.68 (4.61 - 6.34)	6.43 (44.4%) 5.49 (5.29 - 14.0)	6.43 (51.0%) 5.43 (4.17 - 12.2)

[a] The oldest subject in the population PK analysis dataset was 84 years old and that subject is the only subject in the data older than 80 years.

[b] $t_{1/2}$ estimates are derived from the post-hoc CL_t/F and V_C/F and are independent of study day.

CL_t/F = apparent total serum clearance (L/h); CV% = percent coefficient of variation; Min = minimum; Max = maximum; $t_{1/2}$ = elimination half-life; V_C/F = apparent central volume of distribution (L).

Pharmacokinetic interaction studies

The applicant has not conducted any *in-vitro* or *in-vivo* studies based on the low systemic bioavailability after inhalation and lack of metabolism of amikacin.

2.4.3. Pharmacodynamics

Mechanism of action and resistance

The primary mechanism of action of amikacin is the same as that for all aminoglycosides, i.e. it binds to bacterial 30S ribosomal subunits and interferes with mRNA binding and tRNA acceptor sites. This leads to disruption of normal protein synthesis and production of non-functional or toxic peptides. Other actions have been postulated for drugs of this class.

In most types of bacteria, resistance to amikacin may reflect production of certain aminoglycoside-modifying enzymes (AMEs; although amikacin is less affected by some AMEs than other licensed agents in the class), the presence of ribosomal methyltransferases that block drug binding, efflux pumps and porin deficiencies. It is unknown whether any of these mechanisms of resistance has an impact on the efficacy of inhaled aminoglycosides. No scientifically sound susceptibility testing interpretive criteria that is applicable to inhalational administration of amikacin can be derived.

Mycobacterial resistance to aminoglycosides has been studied mostly in *M. tuberculosis* (MTB). The mycobacterial cell wall constitutes an intrinsic mechanism of resistance due to its low degree of permeability, in particular for large polycationic molecules such as aminoglycosides. In addition, the presence of chromosomally encoded AME among mycobacterial species plays a role in decreased

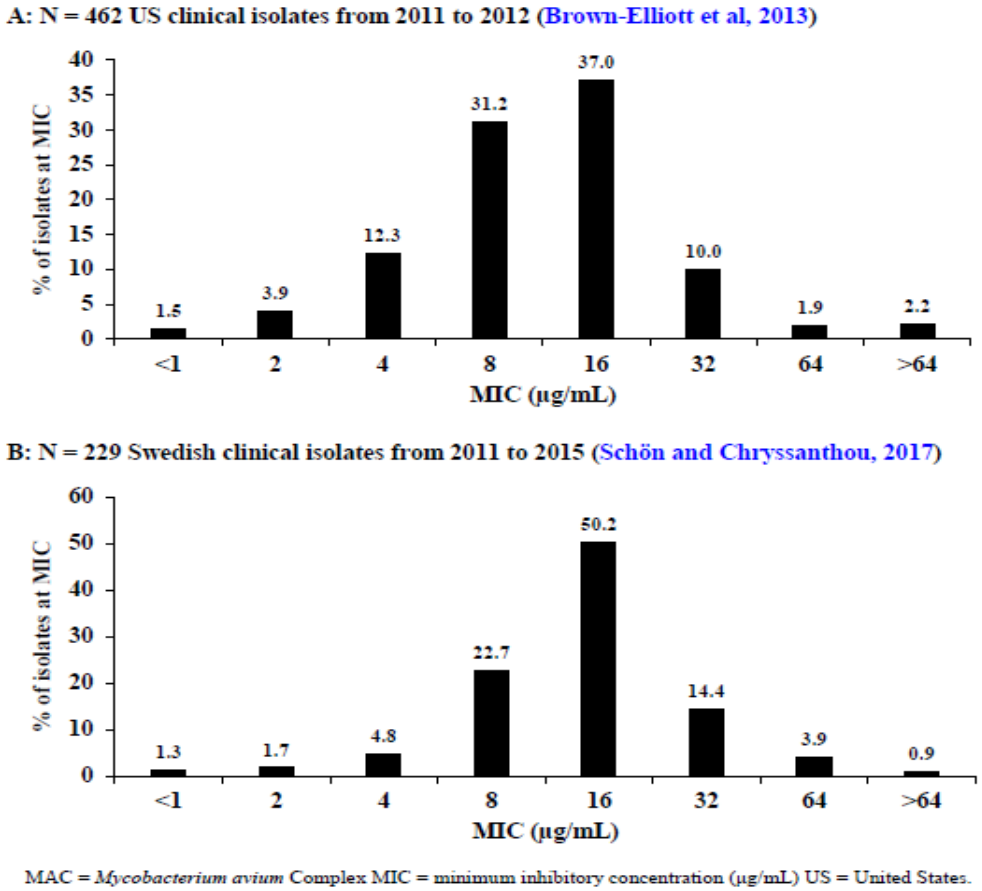
susceptibility and, along with the cell wall, the variation in susceptibility to aminoglycosides between mycobacterial species.

The primary mechanism of acquired resistance to aminoglycosides in mycobacteria is mutation of *rrn* at key binding sites of the 16S rRNA target. Due to the single copy of the *rrn* operon in MAC, *M. abscessus* and MTB, resistance to aminoglycosides via this mechanism is more common than in other Gram-positive and Gram-negative bacteria where there are typically multiple copies. The most common mutation is A1401G (MTB corresponds to the A1408 residue of *Escherichia coli*) or A1408G (MAC and *M. abscessus*), which is one of the primary contact points for aminoglycoside binding to the A site of 16S rRNA. Several other mechanisms of resistance have been found to impact on the susceptibility of MTB to streptomycin but not to amikacin.

Primary and Secondary pharmacology

Primary pharmacology

The applicant summarised 8 studies that report on the activity of amikacin against MAC. Two studies were conducted in accordance with the CLSI broth microdilution (BMD) method and tested MAC isolates from the US and Sweden. In both studies the amikacin MIC_{50} was 16 µg/mL and the MIC_{90} was 32 µg/mL. Isolates with amikacin MIC values > 64 µg/mL were rare (2.2% and 0.9%, respectively).



MAC = *Mycobacterium avium* Complex MIC = minimum inhibitory concentration (µg/mL) US = United States.

Figure 6: MIC distribution of amikacin against MAC

Other studies that used the CLSI BMD method reported similar MIC_{50} and MIC_{90} values against *M. intracellulare* and *M. avium* from China and against *M. intracellulare* from Taiwan. The activity of amikacin reported in the literature against NTM other than MAC generally gives MIC_{50} of 0.25 to 8 µg/mL and MIC_{90} of 2 to 32 µg/mL with the exception of *M. chelonae* (> 64 µg/mL).

In a study of 5 *M. avium* isolates and 4 MTB isolates, amikacin had MBCs of 16 to 128 µg/mL and 0.5 to 2 µg/mL, respectively. There was 99.9% kill with amikacin at high concentrations for *M. avium*. In a separate study, the killing observed with amikacin against single isolates of *M. avium* and *M. xenopi* was apparent at 4-fold to 32-fold the MIC and there was typically regrowth of *M. avium* observed between 120 and 240 h post-inoculation, suggesting the presence of persisters or the development of resistance (see below). Furthermore, in a time-kill study with *M avium* 101 (serovar 1), the killing observed with amikacin was rapid but there was some evidence of regrowth in the presence of amikacin at < 16 µg/mL between Days 10-21.

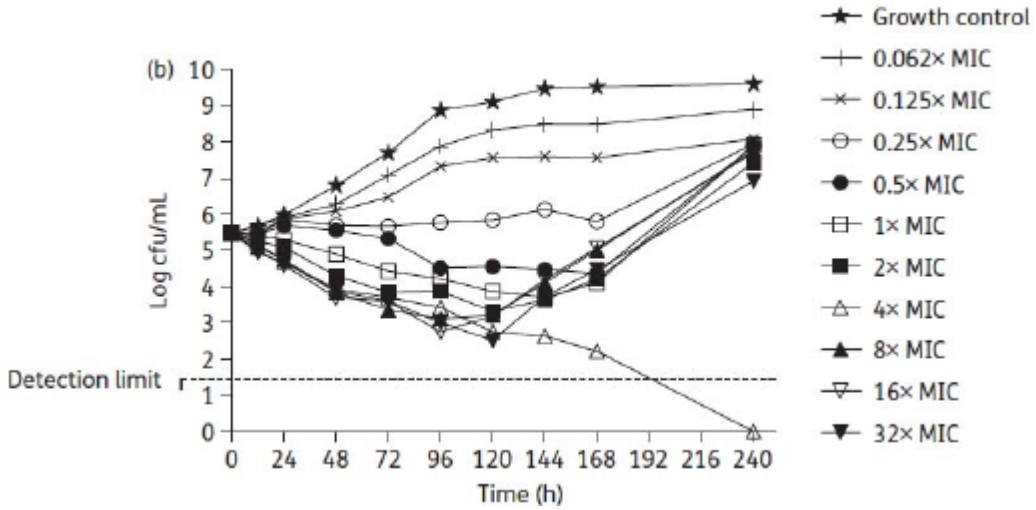


Figure 7: Time-kill of amikacin against *M avium* IWGMT49

In contrast, there have been reports of the lack of bactericidal activity for amikacin against *M. abscessus* linked to the chromosomal expression of AME.

In an *in-vitro* study conducted by Oregon State University ALIS (70 mg/mL amikacin in liposomes [2:1 molar ratio of DPPC to cholesterol at a total lipid concentration of 40 mg/mL] in 1.5% NaCl) and placebo liposomes were evaluated for bactericidal activity against 3 *M. avium* and 2 *M. abscessus* isolates internalised within THP-1 human macrophages. ALIS was diluted so that, over the 4-day test period, the daily concentration ranged from 1 to 10 µg/mL. Free amikacin at 10 µg/mL was administered as a control. A standardised dispersion of 3×10^8 CFU/mL of each mycobacterial isolate was made. On day 5 the cells were lysed and colony counts were performed. Empty liposomes gave counts very similar to those for untreated cells.

Significantly fewer mycobacteria were recovered at Day 4 for ALIS at 2, 4, 8 and 10 µg/mL and for free amikacin at 10 µg/mL for all evaluated isolates relative to controls and empty liposome controls. ALIS at 4-10 µg/mL amikacin killed or inhibited growth of the three *M. avium* strains and was more bactericidal against each strain (1.5-fold, 2.1-fold and 5.7-fold) than free amikacin at 10 µg/mL.

In an *in-vivo* study conducted by Oregon State University, six groups of 12 female mice were infected nasally with *M. avium* strain 104 (~$2x10^7$ CFU) on day 0. After 3 weeks the control mice lungs were

harvested, homogenised and plated on agar to determine the mean CFU (~0.7 x 10^5) after which dosing of remaining mice was as follows:

Group 1 - 28 QD doses over 1 h of 1.5% saline (no ALIS)
Group 2 - 28 QD doses over 1 h of ALIS 74 mg/kg (total 2128 mg/kg)
Group 3 - 14 QD doses over 2 h of ALIS 152 mg/kg; then 14 days off drug (total 2128 mg/kg)
Group 4 - 14 doses every other day over 2 h of ALIS 152 mg/kg (total 2128 mg/kg)
Group 5 - 28 QD doses of intraperitoneal amikacin 100 mg/kg (total 2800 mg/kg)

Aerosols of ALIS (Groups 2-4) and 1.5% Saline (Group 1) were administered using 12-port nose-only inhalation chambers. On Day 50 lungs were harvested from Groups 1-5.

ALIS 76 mg/kg QD for 28 days significantly (p = 0.0002) reduced the *M. avium* burden in the lungs vs. controls in Group 1. There were also significant reductions vs. controls in *M. avium*/lung (p < 0.0001) in mice treated with inhalation either every other day for 28 days or for 14 consecutive days. All ALIS groups had a numerically greater reduction in mean CFU/lung vs. Group 5 (intraperitoneal amikacin).

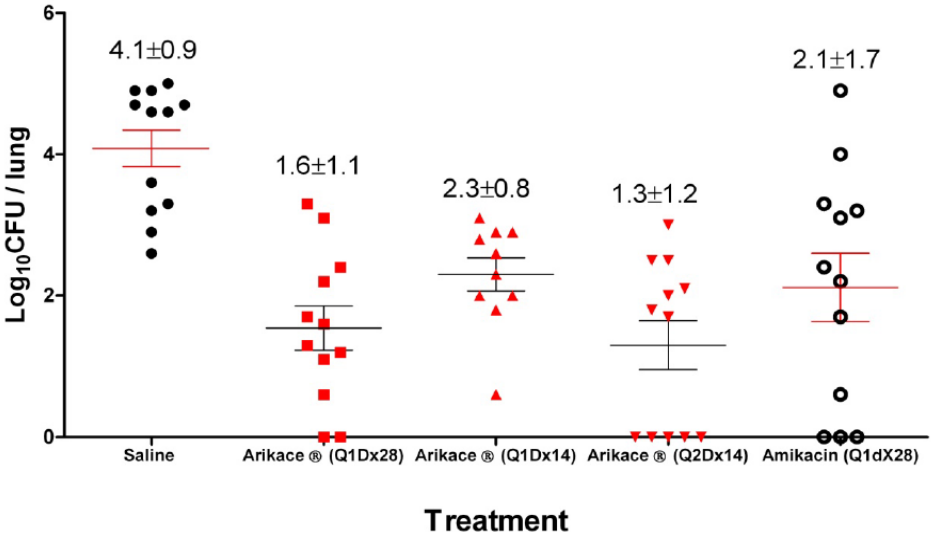


Figure 8: Significant reduction in the Log_{10}CFU of *M. avium* / lungs of mice after inhalation of Arikace and Intraperitoneal injections of amikacin. The symbols represent the Log_{10}CFU/lungs of each mouse 50 days after the instillation of *M. avium*. The horizontal lines and vertical lines represent the means and standard deviations that were calculated using Excel software by Microsoft. The numerical means and standard deviations are above each group's symbols.

From the time of initiation of treatment to the end of the study the ALIS regimens eliminated 99.5% of *M. avium* while parenteral amikacin eliminated 88% and 1.5 % saline eliminated 43%. The number of bacteria eliminated was significantly different between the saline group and Groups 2-5 but there was no statistically significant difference among active treatment groups. The rate of complete eradication of *M. avium* was the highest in Group 4 (42%) and lowest in Group 5 (25%).

Secondary pharmacology

The secondary pharmacodynamic effects centre on the effects of inhalation of liposomal amikacin on pulmonary function tests. In the NTM/MAC studies, these data are considered most important for the assessment of safety. However, they are described in section 2.5 (Clinical Efficacy) along with the microbiological and other clinical endpoints.

Pharmacodynamic interactions with other medicinal products or substances

In-vitro drug combination studies relevant to inhalation of ALIS have not been conducted. Numerous published studies, however, have evaluated the combined antimycobacterial effect of amikacin and other agents used to treat Mycobacterial infections and have shown lack of antagonism.

Relationship between plasma concentration and effect

The applicant did not attempt PK-PD analyses using the data from the NTM/MAC clinical studies.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Systemic bioavailability of amikacin after ALIS inhalation

Since the pharmacokinetics of amikacin after systemic administration are well known, the most important consideration for Arikayce is the estimated worst-case systemic exposure to amikacin after daily inhalations in comparison with that typically observed during IV dosing of non-CF patients.

Given the high degree to which amikacin is excreted by glomerular filtration, the percentage of a dose which is eliminated in the urine is expected to be a reliable surrogate for the bioavailability of amikacin after administration of ALIS. In the previous application, the amount of amikacin excreted in the urine over 24 h post-dose correlated with serum AUC_{0-24}. There were modest increases in serum Cmax and AUC values between days 1 and 14 of ALIS inhalations and measurable serum amikacin levels at 72 h post-dose that would not be expected based on the short half-life in blood after IV administration. This finding may reflect several factors, including slow release of amikacin from liposomes in the airways.

The POPPK analysis concluded that serum exposure to amikacin in patients with MAC in INS-212 was consistent with that seen in the patients with NTM in TR02-112. It was not possible to estimate systemic bioavailability in INS-212 as urine samples for determination of amikacin amount excreted were not collected. However, the comparable systemic exposures between the two studies suggest that systemic bioavailability of amikacin is also comparable between study populations.

The mean steady-state AUC_{0-24} in the NTM patients in TR02-112, with a similar value in INS-212 (about 20 mg.h/L), was ~10 times lower than the mean AUC_{0-24} reported in the literature for patients with CF given amikacin 30 mg/kg IV once daily (20.8 µg.h/mL compared with 235 µg.h/mL, respectively). An additional comparison was made with typical AUCs observed when dosing amikacin in non-CF patients at doses from 15-30 mg/kg. This indicated a >10-fold difference in mean AUCs for ALIS vs. systemic amikacin. However, worst-case scenario analyses that took into account the wide range of inter-individual variability is serum amikacin levels indicated that systemic exposures in patients with severe renal impairment who receive Arikayce could overlap with those observed with IV amikacin in patients with normal renal function. On this basis, and with no clinical data available, use of Arikayce should be contraindicated in NTM patients with severe renal failure. For all patients other than those with severe impairment, and whether or not they have pre-existing mild or moderate renal impairment, there is advice to conduct regular monitoring of renal function in section 4.4 of the SmPC.

Sputum concentrations (µg/mL or µg/g sputum) and residual antibacterial activity

There was very considerable variability in sputum concentrations of amikacin, even more so than was observed for serum levels. In TR02-112, sputum concentrations were measured in 16 patients and data from 4 were excluded, in 3 cases due to amikacin detected in pre-dose samples while receiving placebo. Prior investigations indicated that these patients had a history of treatment with nebulised amikacin (using the IV formulation) prior to study and/or were possibly still receiving such treatment on study in violation of the protocol. Previous questions and responses also examined likely mix-ups between samples. In the responses it became clear that of the remaining 12 retained in the analysis, 6 patients were randomised to placebo. Pre-dose samples (i.e. 24h post-dose) showed concentrations that ranged from 0.78 to 7080 µg/mL in the samples with quantifiable levels.

In INS-212, patients assigned to ALIS were to interrupt treatment 2 days before each visit so the sputum collected during the visit would have been obtained up to 72 h after the last dose. Amikacin concentration data were available from 59 patients and were highly variable. Overall, the sputum concentrations are considered not to provide a reliable estimation of amikacin concentrations in the airways. Their importance is with regard to understanding whether residual amikacin in samples that took up to 72 h to reach central laboratories could have impacted on the reported bacterial loads, including the risk of false negative cultures. To address this possibility, the applicant conducted an in-vitro study to assess whether on-treatment sputum culture results were significantly affected by carryover of residual amikacin.

This study employed incubation of sputa spiked with MAC at two similar load levels with non-liposomal amikacin at a maximum of 128 µg/mL. Therefore, although this study suggested no important effect of exposing MAC in sputa to amikacin for up to 72 h before processing for culture, the study does not mimic the application of liposomal amikacin nor does it cover the high concentrations observed in sputa even after 72 h in some individuals. Thus, whilst the majority of ALIS and non-ALIS patients failed to achieve SCC by month 6 in INS-212, it remains possible that not all patients considered to have achieved SCC on treatment really did so.

Loaded dose equivalent to amikacin

There was a difference in delivered volume on switching from 2x5-mL vials to 1x10-mL vial during the clinical programme. For the development of the 10-mL vial, a laboratory study was conducted to determine the fill required in order to deliver an 8 mL loaded dose of ALIS, equivalent to 560 mg of amikacin, to a nebuliser, taking into account residual drug. This study concluded that a target fill of 9.3 g (equivalent to 8.9 mL based on an average density of 1.05 mg/mL) would assure delivery of a loaded dose of 8 mL of ALIS. An interim analysis of the release data for 24 batches of ALIS manufactured and filled in 10-mL vials for Phase 2 and 3 clinical trials revealed that an average of 8.43 mL (equivalent to 590 mg of amikacin) was being delivered to the nebuliser instead of 8 mL. Therefore, the SmPC states that Arikayce 10-mL vials provide 590 mg ALIS for loading the nebuliser.

Lung distribution

The lung distribution study did not compare liposomal with non-liposomal amikacin, which would have been informative re the possible benefit of the liposomal formulation.

Based on the measured fraction of the loaded dose retained within the nebuliser (mean 61.2%) and the fraction of the emitted dose delivered to lungs, it was calculated that 15.5% of the loaded dose was deposited in lungs. If this estimate from healthy subjects can be applied to patients with NTM, and if the estimated serum bioavailability based on urinary excretion data is correct, then some patients must absorb a large proportion of the amikacin that finally reaches the lungs. If bioavailability were to be expressed relative to the amount deposited into the lungs, the estimate would be approximately 78% in

healthy adult volunteers using the PARI Nebuliser. This was calculated based on: 590 mg x 12% = 70.8 mg absorbed systemically; 590 mg x 15.5% = 91.5 mg deposited in lungs; bioavailability = 70.8 mg / 91.5 mg x 100% = 78% of deposited dose in healthy adults.

The data from the small scintigraphy sub-study of TR02-112 demonstrated that a higher proportion of the loaded dose is deposited in the lung of patients with NTM lung disease (approximately 43%) using the PARI eflow Electronic Nebuliser (using the electronic vibrating mesh). Applying the calculation method above, 27.9% of deposited drug in the lung is absorbed systemically in patients with NTM lung disease using the eflow device. This was calculated based on: 590 mg x 12% = 70.8 mg absorbed systemically; 590 mg x 43% = 253.7 mg deposited in lungs; bioavailability = 70.8 mg / 253.7 mg x 100% = 27.9% of deposited dose in patients with NTM lung disease. Whilst the estimate of 12% of a dose reaching serum was based solely on data from CF patients, the data from TR02-112 suggested that 10% or less of a dose is absorbed after inhalation by NTM patients. Taking the mean to be 8%, the revised calculation would give 47.2 mg absorbed, so bioavailability would be 47.2/253.7, which suggests that only ~19% of the dose deposited in the airways reaches the serum.

Fate of amikacin

In the lung distribution study, only the amikacin was radiolabelled. The report repeatedly refers to radiolabelled liposome deposition and clearance, but such statements assume that the radiolabelled amikacin remained associated with the liposomal material. This assumption conflicts with the proposed leakage of the active substance from the liposomes and it does not consider the proportion of the inhaled amikacin dose that is free drug.

The study showed that the radiolabel in lungs decreased rapidly initially (3 h) and then slowly over 48 h (beyond which accurate determinations are not possible due to the short half-life of the radioisotope) at which time 42% of the deposited dose was retained in the lung. Whilst it is not entirely clear how this fraction was calculated (the CSR being very unclear on several matters and with lack of clarity regarding exactly which fraction of what is referred to) the table and figure suggest that there is some initial rapid clearance by mechanical means and/or systemic absorption and then a slow clearance of amikacin. The pattern of decay described fits with the data on persistence of residual amikacin in pre-dose sputa. Unfortunately, this study did not assay radiolabel in blood, which would have assisted in confirming the estimates of systemic bioavailability based on urinary amikacin levels.

Once amikacin has been released from the liposomes there is no reason to expect that its fate differs in any way from that of amikacin after parenteral dosing. Due to the longstanding use of amikacin and the time of initial development it was never studied as would now be expected (e.g. in terms of full appraisal of interactions with transporters). However, it is freely filtered across the glomerulus and most is then excreted. However, ~5 to 10 % of the parenteral dose is taken up and sequestered by the proximal tubule cells (PTCs), where concentrations may greatly exceed concurrent serum concentrations.

Due to the cationic charge at physiologic pH, amikacin binds to anion phospholipids within the plasma membrane of the PTC in a saturable, electrostatic manner. It is then transferred to the transmembrane protein megalin, which mediates endocytosis. The endosomes containing amikacin are transported to the Golgi complex, endoplasmic reticulum and cytosol, where drug accumulates in subcellular organelles such as the mitochondria and the nucleus. Other than the above, which is widely recognised to apply to all aminoglycosides, there is a lack of data on interactions between amikacin and transporters.

Fate of the liposomal material

During the prior procedure, the applicant was requested to review relevant literature and to assess any possible problems with DPPC inhalation over several years. DPPC is an excipient in exogenous lung surfactants but it is an endogenous material that occurs as a monolayer at the air-water interface. The lung recycles exogenous DPPC in addition to its own endogenous production.

The applicant estimated that the amount of DPPC deposited in the lung after a dose of ALIS is ~43 mg based on the following calculation and assumptions:

- 15.5% Deposition
- 0.7:1 lipid to drug weight ratio

2:1 DPPC to cholesterol weight ratio
Leading to the calculation of 590 mg x 0.155 x 0.7 x 0.67 = 42.9 mg

As the turnover rate of DPPC in the lung is ~29 mg/hour (as reported by Martini, 1999), the DPPC is expected to be recycled within 60 - 90 minutes after dosing.

The applicant conducted a literature search for publications on inhalation of DPPC. Additional reviews on the toxicity of DPPC were identified from the lists of references in the publications found. Most of the reference papers found were not specific to the evaluation of DPPC toxicity (short- or long-term) in non-clinical or clinical studies. In summary, there was very limited information obtained from the review of the relevant literature to assess possible problems with DPPC inhalation over several years. However, there were no reports of serious adverse events associated with DPPC.

Pharmacodynamics

The microbiological data from the clinical studies in NTM/MAC patients are considered in the discussion of efficacy along with discussion of the microbiological methods applied during the efficacy trials.

The applicant has conducted very few studies to document the possible advantages of using liposomal ALIS rather than inhaling amikacin itself. Nevertheless, additional nonclinical studies are not likely to help and are not requested or encouraged at this stage of development. Furthermore, PK-PD analyses have not been conducted since no PDT can be established that is relevant to inhaled therapy and due to the small numbers of patients providing PK data. However, no relationship between serum or sputum amikacin and sustained SCC rates would be expected.

Very high MICs of amikacin have been documented for some NTM or, at least, for a subset of strains within specific species. For example, very high MICs have been linked to 16S RNA mutations in *M. abscessus* and *M. avium* complex and to cellular impermeability coupled with AME production in *M. abscessus*. TR02-112 enrolled a minority of patients infected with *M. abscessus* some of whom also had CF. The available data did suggest that any benefit of ALIS was likely confined to MAC but this finding does not inevitably lead to a conclusion that the MIC of amikacin is of relevance to the clinical response to inhaled therapy.

The applicant chose to impose a restriction on the amikacin MIC for baseline MAC in INS-212 (≤ 64 mg/L) based on the CLSI susceptibility test interpretive criteria relevant to parenteral amikacin usage when treating MAC. There was no relationship found between SCC and MIC (see the discussion of efficacy) in the Arikayce studies and there is no known rationale for recommending that ALIS is used to treat MAC only when the MIC is ≤ 64 mg/L simply because this restriction was applied in clinical studies. Nevertheless, it has to be acknowledged that it has not been established whether acquired resistance to amikacin (based on susceptibility criteria applicable to systemic use) in MAC can be overcome by very high local concentrations achievable after inhalation. There is, however, considerable evidence from CF patients colonised with *P. aeruginosa* to indicate that PFTs are maintained or even improved regardless of MIC of the agent(s) being inhaled.

Mutations in the *rrs* gene of the *rrn* operon resulting in changes to 16S rRNA that interfere with the binding of aminoglycosides to the A site of the ribosome are the most common aminoglycoside resistance mechanism in mycobacteria. Most mycobacteria have a single copy of the *rrn* operon

2.4.5. Conclusions on clinical pharmacology

There are no Major Objections regarding clinical pharmacology. It should be noted that several issues were addressed in the previous application that, if not wholly resolved, were considered not worth pursuing. The most important issue is the estimated worst-case serum amikacin levels that may occur taking into account the additional PK data obtained from INS-212 and the updated POPPK model. In some NTM patients, these can be expected to overlap with AUCs associated with IV dosing. The final SmPC has been modified to reflect the concerns, including contraindicating use in patients with severe renal impairment.

2.5. Clinical efficacy

There were 3 studies that enrolled patients with non-tuberculous mycobacterial lung disease.

TR02-112 enrolled patients with chronic NTM lung infections, including but not confined to MAC. This study was submitted and fully assessed in the prior MAA. The newly reported Phase 3 trial **INS-212** enrolled non-CF patients with chronic MAC lung infections. **INS-312** enrolled patients who failed to achieve SCC or relapsed in INS-212 and opted to receive open label Arikayce.

Protocol No. Study Start - Stop Date	Population	Total Enrollment	Study Objective	Primary Efficacy Endpoints	Study Design	Subject Sex (M:F)	Age Mean ± SD Range (Years)	Dose	Duration of Treatment
TR02-112 19 Apr 2012 to 18 Jun 2015	NTM lung disease in subjects 18 years old or older	89	Efficacy, safety, and tolerability	Change from Baseline (Day 1) to the end of the double-blind Phase (Day 84) measuring mycobacterial density on the SQS	Phase 2 R DB PC & OL phase	11:78	58.5 ± 15.83 (18, 85)	ALIS 590 mg QD Placebo	Up to 168 days
INS-212 27 May 2015 to ongoing	MAC lung disease in subjects 18 years old or older	336	Efficacy, safety, and tolerability	Proportion of subjects achieving culture conversion (3 consecutive monthly negative sputum cultures) by Month 6	Phase 3 R OL	103:233	64.7 ± 9.77 (32, 87)	ALIS 590 mg QD + M DR. MDR alone	Up to 16 months
INS-312 05 Feb 2016 to 15 Oct 2018	MAC lung disease in subjects 18 years old or older	163	Safety and tolerability	No primary efficacy endpoint all efficacy endpoints are secondary and exploratory	Phase 3 SA OL	58:105	64.8 ± 9.78 (33, 86)	ALIS 590 mg QD + M DR	12 months

Source: Study TR02-112 CSR, Study INS-212 CSR, Study INS-312 CSR
ALIS = amikacin liposome inhalation suspension DB = double-blind F = female M = male MAC = *Mycobacterium avium* Complex MDR = multidrug regimen NTM = nontuberculous mycobacteria OL = open-label PC = placebo-controlled QD = once daily R = randomized SA = single-arm SAP = statistical analysis plan SD = standard deviation SQS = semi-quantitative scale.

2.5.1. Dose response studies

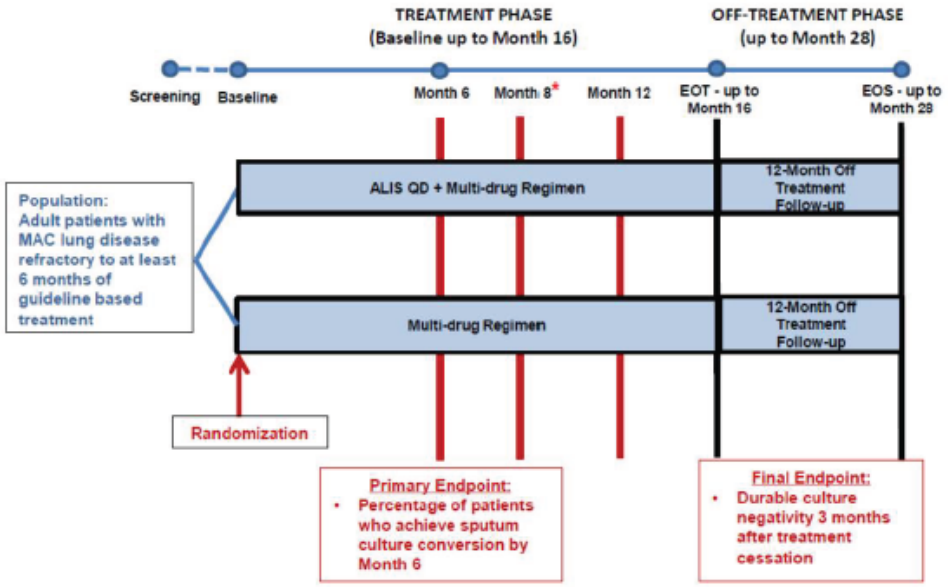
There were two dose-finding studies in CF patients colonised with *P. aeruginosa* that used the 70 mg/mL formulation. TR02-106, which compared doses of 70 mg, 140 mg or 560 mg QD, failed to show a significant difference for any ALIS dose group vs. placebo for mean relative change in pre-dose FEV_1 from baseline to day 28 or day 56. TR02-105 did provide some evidence of a dose-response. Taking into account the safety data in CF patients and in NTM patients in TR02-112, the applicant selected the highest dose (later found to be equivalent to 590 mg and not 560 mg) for the Phase 3 MAC study.

2.5.2. Main study

INS-212

- The final CSR dated 9 October 2019 was submitted on Day 121.
- INS-212 was initiated in May 2015 and all patients had reached the 12-month safety follow-up visit on 3 April 2019 or had previously discontinued.
- The initial CSR in the MAA included the 3-month off-treatment analysis (this is the EU-recommended primary endpoint as per the last CHMP scientific advice; these data were not available to the US FDA when they approved Arikayce).
- In the initial CSR, data were incomplete for the month 12 post-treatment visit. The applicant notified the CHMP that all data for this last visit could be supplied when responding to the D120 LoQ.

The overall study design is shown in the figure below.



Source: Appendix 16.1.1 Figure 3-1
* All converters (at least 3 consecutive monthly negative sputum cultures by Month 6) without relapse or recurrence remained in study for 12 months, starting from the first negative culture that defines culture conversion.
All non-converters and subjects who experienced a relapse or recurrence after culture conversion by Month 6 discontinued the study at Month 8 and may be eligible to enter a separate open-label study (INS-312).

Methods

- Study Participants

Inclusion Criteria

- Adult patients were to have been positive for MAC on culture (see below) while receiving a multi-drug regimen (MDR) consisting of at least two agents that had been administered for a minimum duration of 6 consecutive months and was either ongoing or had been stopped <12 months before screening. Exceptions to treatment for 6 consecutive months included doses or frequencies below those recommended by guidelines and/or short interruptions of therapy due to safety/tolerability.
- There was to be evidence of underlying lung disease such as nodular bronchiectasis and/or fibrocavitary disease by chest radiography or chest CT (preferably high-resolution CT scan).

- MAC lung infection had to be documented by at least 2 positive cultures (MAC or MAC as the dominant species) at least one month apart, one of which had to be obtained within 6 months prior to screening and one at screening (sputum samples or samples from bronchoscopy).

Exclusion Criteria

The most important of these included:

- MAC with amikacin MIC > 64 µg/mL
- Unable to perform the 6MWT
- Pregnant or breastfeeding
- Active pulmonary disease other than MAC
- Known hypersensitivity to aminoglycosides
- Use of inhaled or systemic aminoglycosides with activity against MAC in 28 days before baseline
- Acquired and primary immunodeficiency syndromes or HIV-positive

Treatments

Patients were to continue the same multidrug (MDR) regimen of at least 2 agents in accordance with the 2007 ATS/IDSA guidelines or local guidelines. Patients were not to change the MDR regimen during the treatment phase except for safety concerns or if rescue therapy was required, in which case they discontinued and were treated as non-converters in the primary analysis.

Patients with SCC by month 6 were to complete a treatment course of 12 months, starting from the first of 3 negative cultures that defined SCC. Patients who achieved SCC and completed treatment stopped all MAC treatment (not just ALIS) at the EOT visit. All non-converters and those with relapse or recurrence by the month 6 visit were discontinued at month 8 and offered ALIS in INS-312

ALIS 590 mg QD (70 mg/mL amikacin in 10mL water for injection) was administered via an eFlow nebuliser over ~ 14 minutes at home except for the 2 days prior to a scheduled study visit when sputum was collected. On the day of a study visit, treatment was given after sputum collection. ALIS could be interrupted in case of local respiratory events and reintroduced when symptoms subsided.

No other inhaled antibacterial agents or any aminoglycosides with activity against MAC were allowed from 28 days before baseline and throughout the study unless clinically indicated. If inhaled treatment was needed, ALIS was interrupted until the acute event had resolved. Inhaled tobramycin does not have activity against MAC and was permitted. Systemic antibacterial agents without activity against MAC could be used if necessary. Bronchodilator therapy was allowed and patients who developed bronchospasm were permitted to be pre-treated with a bronchodilator before ALIS dosing.

Objectives

In the protocol, the primary objective was to evaluate the SCC rate (3 consecutive monthly negative sputum cultures) by month 6 for ALIS + MDR vs. MDR alone. The date of conversion was the date of the first of 3 negative cultures. Following CHMP scientific advice, the primary endpoint for the EU submission was to be sustained SCC assessed at least 3 months after the end of all MAC treatment (i.e. negative sputum culture after 3 months off-treatment without intervening relapse or reinfection).

Outcomes/endpoints

Sputum specimens (with or without induction) were collected at screening, baseline, at months 1-6, months 8 and 12, at EOT and at the off-treatment safety follow-up visits at months 1, 3, 6 and 12. Sputum specimens were cultured in broth media in addition to agar media. If results were negative on

agar, the broth media was held for 6 weeks before being reported as culture negative. Standard sensitivity testing to determine MICs was performed in accordance with CLSI M48-A and NCCLS M24-A and isolates were stored for selective molecular typing. Isolates of MAC were identified to complex, using a commercial RNA probe and identified to sub-species (*M. avium*, *M. intracellulare*, MAC "X" group) using molecular methodology.

SCC by month 6

During the procedure, the applicant clarified that for a patient to be declared culture negative at any one visit, whether on-treatment or off-treatment, all cultures collected for that visit were required to be negative for MAC, regardless of agar or broth media. Thus, if 3 sputum samples were collected for a visit, all 3 agar media and all 3 broth media cultures must have been declared negative for MAC in order for that visit to be declared culture negative. A single broth positive sample would disqualify a visit from being declared culture negative. For a patient to meet the definition of culture conversion by month 6, there must have been 3 consecutive monthly MAC negative sputum cultures (i.e. up to 9 samples, all negative by culture on agar and in broth media).

To have achieved SCC by month 6, and thus stay on study after month 8 (when the month 6 culture results would be available), the latest visit at which SCC could have first occurred was month 4. If a patient was unable to produce sputum despite reasonable efforts, and had already met the definition of culture conversion, this was recorded as a negative culture result. All non-converters and those with relapse or recurrence as assessed by the month 6 visit (see below) were discontinued at month 8 and offered ALIS in INS-312.

Sustained SCC

Culture conversion was considered "sustained" if there were no positive agar media and no more than 2 consecutive positive monthly broth media for MAC from conversion through an additional 12 months of treatment, after which all treatment for MAC lung infection was stopped. Culture conversion was considered sustained at each follow-up visit if the conversion had been maintained up to and including that visit. Patients that had any positive agar media culture after conversion or had at least 3 consecutive positive monthly broth media cultures at any time after conversion while on treatment were considered to not have achieved sustained culture conversion. If a subject was unable to produce sputum despite reasonable efforts, and had already met the definition of culture conversion, this was recorded as a negative culture result at that time point.

Relapse/recurrence

Relapse or recurrence was defined as having MAC-positive sputum cultures in broth media (agar negative) for 3 or more consecutive months or having at least 1 MAC-positive sputum culture on agar media (agar positive) after SCC. Relapse was defined as a positive culture after SCC that was the same species and genotype (copy number and allele number) as that isolated at Screening/Baseline.

Recurrence was defined as a positive culture after SCC that was either a different species than that isolated at Screening/Baseline or the same species but different genotype (different copy number and/or allele number) than that isolated at Screening/Baseline.

Completers and non-completers

Completers were either 1) converters by month 6 who successfully completed their treatment regimen or 2) non-converters by month 6 who successfully completed all dosing and protocol requirements up to and including the month 6 study visit. All other patients were non-completers.

Other endpoints

A 6MWT of exertional capability was performed at baseline, at months 4, 6 and 8, at EOT and at the 3 months off-treatment safety follow-up visit. A standardised protocol based on the ATS guidelines was used. The 6MWT was conducted by a site member blinded to treatment assignment.

The SGRQ and the EQ-5D-3L were completed at baseline, at months 3, 6, 8 and 12, and EOT and the 3 months off-treatment safety follow-up visit.

Pulmonary function tests (PFTs) of FEV_1, FEF (25-75%) and FVC were performed at sites with access to spirometers and trained personnel at baseline, month 6 and at the 6 months off-treatment safety follow-up visit. Patients who underwent PFTs were optimally treated for their underlying lung disease before these assessments were performed and spirometry occurred before ALIS dosing.

Sample size

The sample size was based on the protocol-defined primary endpoint (SCC by month 6). Assuming a SCC rate by month 6 of ≥ 20% for the ALIS + MDR arm and a rate of 5% for the MDR alone arm and applying a 2:1 randomisation ratio, a sample size of 261 (174 ALIS + MDR and 87 MDR alone) was considered to provide at least 90% power for the continuity-corrected Chi-square test at the 2-sided significance level of 0.05. To ensure at least 261 evaluable patients (culture results every month from day 1 to month 6) it was anticipated that up to approximately 351 patients should be randomised.

Randomisation

Eligible patients were stratified at screening according to smoking status (current smoker or not) and prior MDR use (on treatment or off-treatment for at least 3 months) and then randomly assigned in a 2:1 ratio to ALIS + MDR or to MDR alone using an interactive web response system.

Blinding (masking)

The study was open-label.

Statistical methods

The Intent-to-Treat (ITT) population (all randomised) was the primary analysis population. The proportion with sustained SCC through 3-months off-treatment was analysed using a Cochran-Mantel-Haenszel (CMH) test (stratified by smoking status and prior MDR). The adjusted odds ratio (OR), the 95% CI for the OR and *P*-value are presented.

Results

Participant flow

The study enrolled 336 subjects at 127 sites in 18 countries. One ALIS patient was not treated.

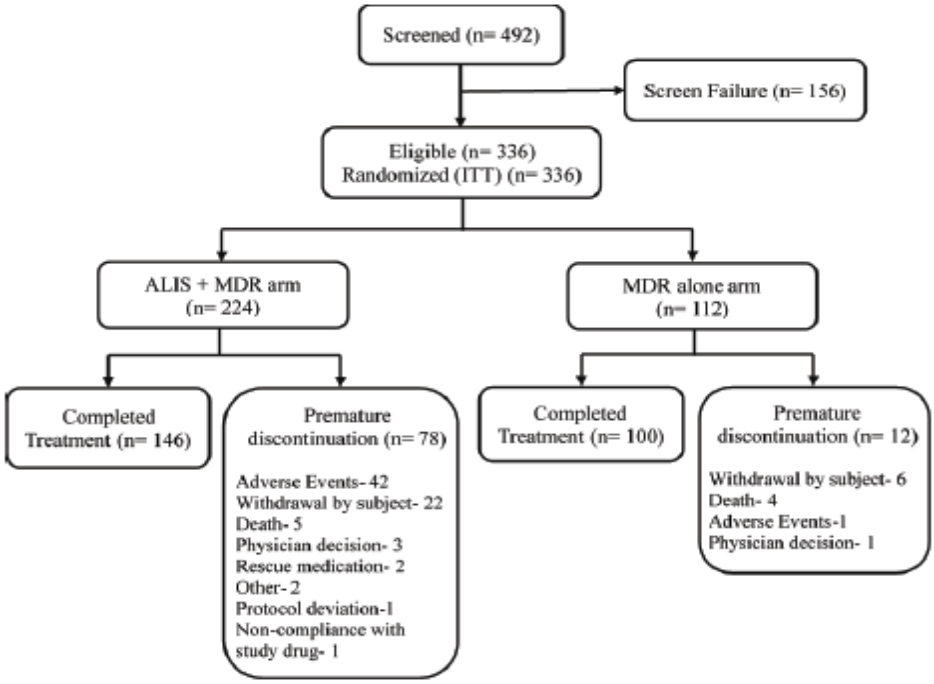


Figure 9: Disposition of subjects (end of treatment) – ITT population

While 246 (73.2%) were completers, the discontinuation rate was much higher in the ALIS group due to AEs or patient decision.

Protocol deviations were reported in 287 patients (85.4%) overall, including 195 (87.1%) in the ALIS + MDR arm and 92 (82.1%) in the MDR alone arm. Major protocol deviations (in 32.6% and 29.5%) concerned incorrect version of approved ICF signed (16.4%). In the ALIS + MDR arm, 122/224 (54.5%) reported deviations related to non-compliance with visit schedule, which included visits and/or assessments performed outside of schedule. In the MDR alone arm, 63/112 (56.3%) reported deviations related to non-compliance with visit schedule.

Baseline data

The mean age was 64.7 years with 69.3% being female (73.7% ALIS vs. 60.7% control). The highest number was enrolled in North America (47.3%) followed by Europe (22.6%) and most were White (69.9%). With the exception of gender, baseline characteristics were generally balanced across the two treatment arms. The majority was on a regimen including a macrolide (91.4%), a rifamycin (84.5%) or ethambutol (79.8%) and 68.5% were on triple therapy. Of 6 patients not on a MDR regimen at baseline, 4 restarted after Day 7, 1 withdrew consent and 1 was not dosed.

Table 10: Baseline characteristics – ITT population

	ALIS Plus Multidrug Regimen (N = 224)	Multidrug Regimen Alone (N = 112)	Total (N = 336)
Multidrug regimen prior to enrollment			
On treatment	201 (89.7%)	101 (90.2%)	302 (89.9%)
Off-treatment for at least 3 months	23 (10.3%)	11 (9.8%)	34 (10.1%)
Smoking status			
Current smoker	26 (11.6%)	10 (8.9%)	36 (10.7%)
Not a current smoker	198 (88.4%)	102 (91.1%)	300 (89.3%)
Prior nebulized IV amikacin			
No	200 (89.3%)	97 (86.6%)	297 (88.4%)
Yes	24 (10.7%)	15 (13.4%)	39 (11.6%)

The mean duration of MDR treatment prior to enrolment in the study was 3.94 years (SD = 3.863; median = 2.60; min, max = 0.2, 22), with means of 4.31 years in the ALIS + MDR arm compared to 3.20 years in the MDR alone arm.

During the study, concomitant medication use was reported by 99.4% of patients. These included azithromycin (56.3%), clarithromycin (39.0%), rifampicin (74.1%), rifabutin (14.0%) and ethambutol (72.0%). Other common medications used for the treatment of NTM lung disease included fluoroquinolones (29.8%), clofazimine (14.6%) and linezolid (1.8%). Selective beta-2-adrenoreceptor agonists were used by 47.3% (51.3% ALIS vs. 39.3% controls).

There were 336 patients in the ITT population (224 ALIS) and 243 in the PP population (145 ALIS). Treatment adherence within 80% to 120% from baseline to EOT was seen in 70.9% in the ALIS + MDR arm and 28.7% had adherence < 80%.

Primary analysis – sustained SCC at 3 months off-treatment

All non-converters (who could not therefore achieve sustained SCC) were counted in the denominators.

A patient was counted as positive at each visit after they died or if there was a missed visit or missed sputum sample.

Based on these criteria, 36/224 (16.1%) in the ALIS + MDR arm vs. 0/112 in the MDR alone arm achieved sustained SCC at month 3 post-treatment. Rates for sustained SCC at month 3 (all in the ALIS + MDR group) were 19/104 (18%) in N. America, 3/48 (6%) in Europe, 4/34 (12%) in Japan and 10/24 (42%) in Oceania. As shown below, 29/65 and 10/10 in respective groups with SCC at month 6 (hence 75 continued in the study beyond month 8) did not sustain SCC at 3 months off treatment.

Table 11: Analysis of durable conversion at 3-month follow-up based on subjects who achieved sustained culture conversion at 12 months of treatment since conversion – ITT population

Statistic	ALIS Plus Multidrug Regimen (N = 224)	Multidrug Regimen Alone (N = 112)
Number of Subjects Assessed	224	112
Durable Conversion[a]	36 (16.1%)	0
Non-Durable Conversion	188 (83.9%)	112 (100%)
Converters	29 (12.9%)	10 (8.9%)
Non-Converters	159 (71.0%)	102 (91.1%)
Odds Ratio (OR)[b]	NE	
95% Confidence Interval for OR	(NE, NE)	
P-Value (CMH)	< 0.0001	

All of the 36 ALIS + MDR patients with sustained SCC at month 3 off treatment had initially achieved SCC at or before month 3 of treatment (based on Figure 14 in CSR and the table below).

Based only on the 75 patients (65 ALIS + MDR and 10 MDR) who had achieved SCC by month 6, 36/65 (55.4%) vs. 0/10 had sustained SCC at the 3-month follow-up visit ($P = 0.0017$).

Based only on the 44 patients with sustained SCC at 12 months of treatment from start of SCC (41 ALIS + MDR and 3 MDR), 36/44 (81.8%) had sustained SCC at 3 months off-treatment. For the 8 patients (5 ALIS + MDR and 3 MDR alone) who did not sustain SCC off treatment:

- 3 ALIS + MDR and 2 MDR had missing visits or results (missing considered positive)
- 2 ALIS + MDR had at least 1 agar positive culture or at least 3 consecutive broth positive cultures after 12 months of treatment or at the 28-Day or 3-Month follow-up visit(s).
- 1 in the MDR alone arm withdrew from the study.

Sensitivity analyses of the EU primary endpoint were performed as follows:

- When missing data for converters with missing broth or agar sputum culture result after Month 6 up to and including 3 months off-treatment were imputed as negative if the visit with missing cultures was between two visits with negative cultures or if the patient was unable to produce sputum even after induction, 40/224 (17.9%) ALIS + MDR patients achieved sustained SCC at the 3-month follow-up visit vs. 0/112 for MDR alone ($P < 0.0001$). The same result applied when patients who converted with no more than 1 missing broth or agar culture result after month 6 were considered as converters with durability.
- When sustained SCC was defined as achieving SCC by month 6 and then having no broth or agar positive culture up to 3 months off-treatment and no visits missing broth or agar culture results 30/224 (13.4%) vs. 0/112 achieved sustained SCC at the 3-month follow-up visit ($P < 0.0001$).

Sustained SCC at 3 months off-treatment in those who achieved SCC by month 6 and continued to have negative agar cultures and no more than 2 consecutive positive broth cultures through EOT occurred in 41/224 (18.3%) in the ALIS + MDR arm vs. 0 in the MDR alone arm ($P < 0.0001$). All 41 had initially achieved SCC no later than month 4 on treatment.

Ancillary analyses

Sustained SCC at the 12-month follow-up visit

The final CSR provided during the procedure included an analysis of the secondary endpoint of durable conversion at 12-month follow-up. Similar to the approach taken for the analysis of the primary endpoint of durable culture conversion at 3-month follow-up, a visit was considered culture-positive due to death, no visit, or missing sputum samples (unless unable to produce despite induction).

At the 12-month follow-up visit, 30 subjects (13.4%) in the ALIS + MDR arm, and 0 subjects in the MDR alone arm ($p < 0.0001$) achieved durable conversion according to the rules applied by the applicant. The details of follow-up visits and whether there was a positive solid culture or broth culture result or no visit/no sample are provided in Figure 10 below. Note that Figure 10 shows the serial culture results for the 44 patients (41 ALIS and 3 MDR alone) who achieved SCC during the first 6 months on treatment and, based on the applicant's rules, were deemed to have sustained SCC at the month 12 on-treatment visit.

Rates of conversion, sustained conversion, and durable (at 3 and 12 months after stopping treatment for NTM) conversion showed a relatively consistent effect of the addition of ALIS and showed consistently that no subject in the control group had maintained conversion off treatment across species.

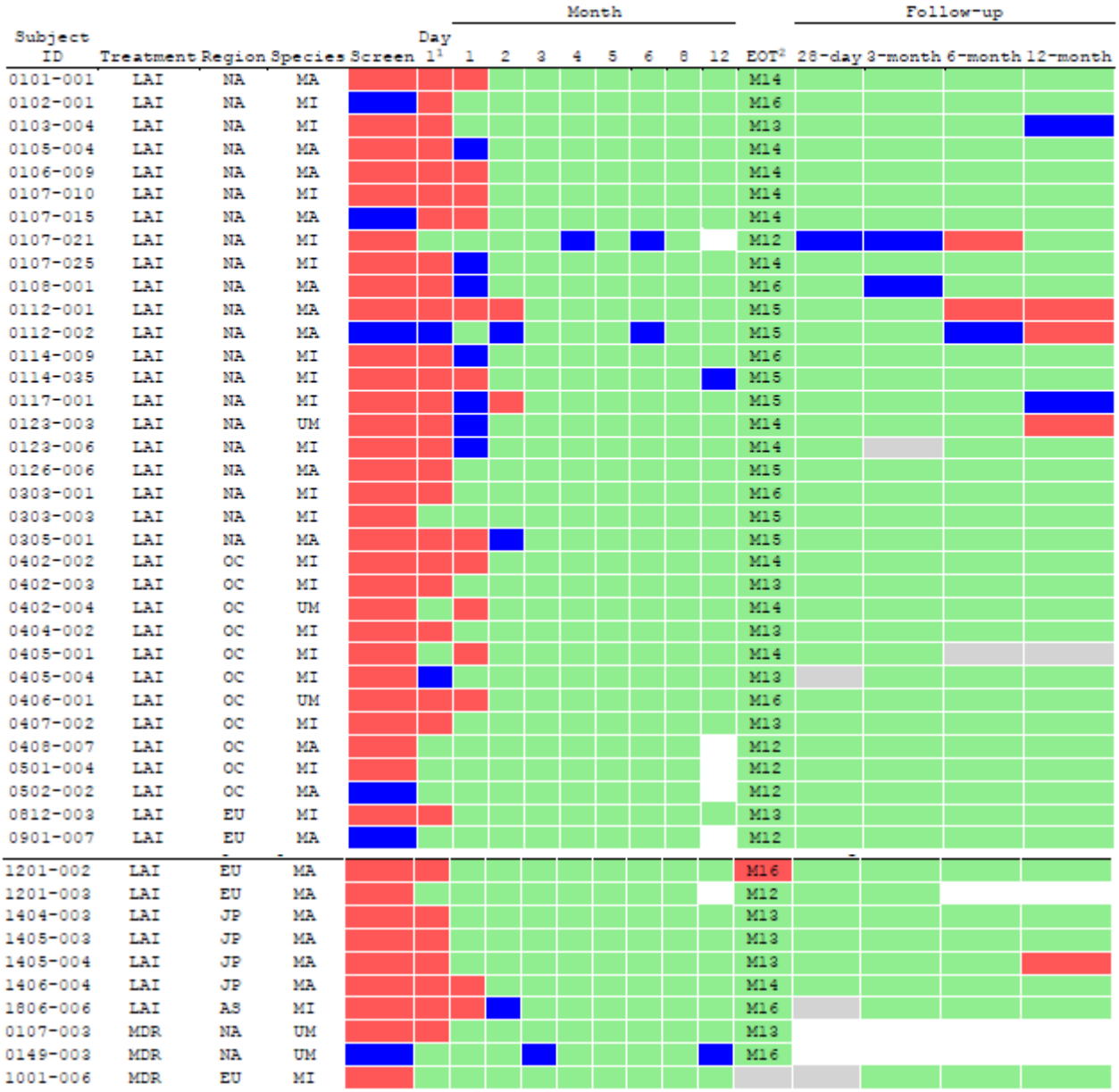
Rates of conversion, sustained conversion, and durable conversion are shown by region in the table below Figure 10. In Europe, more patients treated with ALIS + MDR achieved conversion, sustained conversion, and durable conversion compared to MDR alone, which is very consistent with observations made in North America, in Oceania, and in Japan.

Relapse or recurrence was defined as having MAC-positive sputum cultures in broth media (agar negative) for 3 or more consecutive months or having at least 1 MAC-positive sputum culture on agar media (agar positive) after SCC. Relapse was defined as a positive culture after SCC that was the same species and genotype (copy number and allele number) as that isolated at Screening/Baseline.

Recurrence was defined as a positive culture after SCC that was either a different species than that isolated at Screening/Baseline or the same species but different genotype (different copy number and/or allele number) than that isolated at Screening/Baseline.

In the ALIS arm, 13/65 (20.0%) who had SCC experienced relapse/recurrence, including 8 discovered during a planned on-treatment visit and 5 during the off-treatment follow-up visits. Of these 13, 7 had a MAC relapse, of which 5 occurred on or before Month 8, and 6 had a MAC recurrence, of which 3 occurred on treatment (after Month 8).

Of the 10 converters in the MDR alone arm, 4 (40.0%) experienced relapse (3) or recurrence (1), all of which occurred during the on-treatment study period.



Source: day120_Q44_Heatmap_sust12.

[1] Day 1 is Baseline.

[2] For EOT Visit, 'Mx' indicates the month the visit occurred.

Green highlight indicates negative sputum result

Red highlight indicates positive solid media culture

Blue highlight indicates positive broth media culture

White cells indicate that a visit did not happen, either because the visit was not scheduled, or the subject had discontinued the study

Grey cells indicate that the patient was still in the study but no culture result is available (for any reason, such as no sputum collection, or missing result)

Regions: NA – North America, EU – Europe, JP – Japan, AS - Asia (excluding Japan), OC – Oceana.

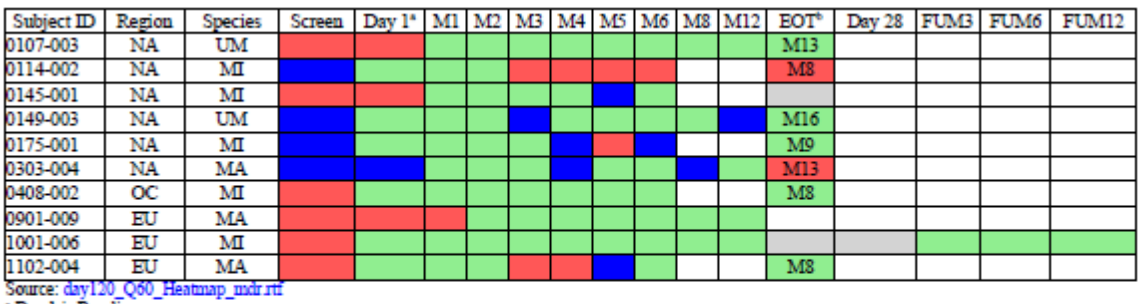
Species: MA - M. avium, MI - M. intracellulare, UM - Unspeciated MAC.

Figure 10: Serial Culture Results for all patients who sustained conversion through 12 months of treatment (Study INS-212, ITT population)

Table 12: conversion rates by region (Study INS-212)

	ALIS		MDR	
Species Conversion type	n	(%)	n	(%)
All regions	N = 224		N = 112	
Month 6 conversion	65	(29.0)	10	(8.9)
Sustained conversion	41	(18.3)	3	(2.7)
Durable at 3 months	36	(16.1)	0	–
Durable at 12 months	30	(13.5)	0	–
North America	N = 104		N = 55	
Month 6 conversion	32	(30.8)	6	(10.9)
Sustained conversion	21	(20.2)	2	(3.6)
Durable at 3 months	19	(18.3)	0	–
Durable at 12 months	16	(15.4)	0	–
Japan	N = 34		N = 14	
Month 6 conversion	9	(26.5)	0	–
Sustained conversion	4	(11.8)	0	–
Durable at 3 months	4	(11.8)	0	–
Durable at 12 months	3	(8.8)	0	–
Asia excluding Japan	N = 14		N = 6	
Month 6 conversion	1	(7.1)	0	–
Sustained conversion	1	(7.1)	0	–
Durable at 3 months	0	–	0	–
Durable at 12 months	0	–	0	–
Europe	N = 48		N = 28	
Month 6 conversion	9	(18.8)	3	(10.7)
Sustained conversion	4	(8.5)	1	(3.6)
Durable at 3 months	3	(6.3)	0	–
Durable at 12 months	2	(4.2)	0	–
Oceania	N = 24		N = 9	
Month 6 conversion	14	(58.3)	1	(11.1)
Sustained conversion	11	(45.8)	0	–
Durable at 3 months	10	(41.7)	0	–
Durable at 12 months	9	(37.5)	0	–

To complete the picture, the applicant also provided on request the serial culture results for the 10 control patients who had achieved SCC by month 6, 3 of whom are also shown in Figure 3 above.



Source: day120_Q60_Heatmap_mdr.rtf
[a] Day 1 is Baseline.
[b] EOT Visit 'M XX' indicates month visit occurred.
Note: Green indicates negative sputum test. Red: positive solid media culture. Blue indicates positive broth media culture. Grey indicates missing sputum collection or result. Empty cell indicates not applicable visit due to either subject's early termination of study or completion of visit at end of treatment.
EOT = end of treatment; EU = Europe; FUM = follow-up month; M = month; MA = *Mycobacterium avium*; *MI* = *Mycobacterium intracellulare*; NA = North America; OC = Oceania; UM = unspeciated *Mycobacterium avium complex*;

Figure 11: Converters from multi-regimen treatment alone group

6MWT change from baseline to month 6

There was no statistically significant difference between treatment groups in the change in 6MWT from baseline to month 6. For the entire ITT population, there was a numeric difference in favour of converters compared to non-converters (LS mean difference [SE]: 22.69 [9.404] meters; 95% CI: 4.17, 41.21; *P* = 0.0165).

Microbiological analyses

In the ITT population 335/336 patients (223 ALIS) had MAC isolated from sputum at baseline and/or screening. In the ALIS + MDR group, *M. avium* was isolated from 101/224 (45.1%), *M. intracellulare* from 88/224 (39.3%) and unspeciated MAC from 34/224 (15.2%). Similar proportions of MAC species were isolated from the patients in the MDR alone group. Most North American isolates from ALIS + MDR patients were *M. intracellulare* (55/104). Among European isolates the majority was *M. avium.* Nearly all Japanese isolates were *M. avium* (31/34) and 18/24 from Oceania were *M. intracellulare.*

For the 335 MAC isolates overall, an MIC_{50} of 32 µg/mL and MIC_{90} of 64 µg/mL were observed. European isolates were generally most susceptible (MIC_{50} of 8 µg/mL and MIC_{90} of 16 µg/mL). Amikacin MIC distributions were very similar for MAC isolated from the two treatment groups.

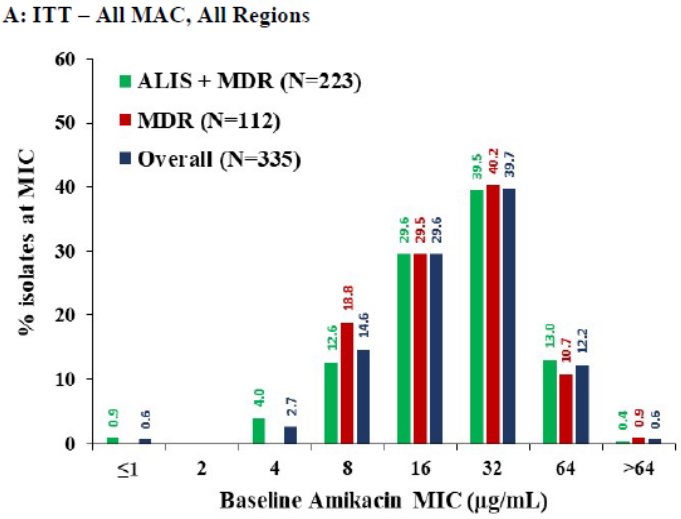


Figure 12: Amikacin MIC distribution – MAC at baseline/screening (Study INS-212)

Overall, 73/335 (21.8%) of baseline MAC isolates were resistant (based on criteria applicable to plasma levels) to clarithromycin (22.9% for ALIS + MDR and 19.6% for the MDR alone group). The highest degree of clarithromycin resistance was observed among *M. avium* (46/152 [30.3%]).

By geographic region, higher clarithromycin resistance rates occurred in Japan and rest of Asia.

The SCC rates by month 6 for ALIS + MDR patients with *M. avium* and *M. intracellulare* at baseline were similar (30/101 [29.7%] and 29/88 [33.0%], respectively). Corresponding rates for MDR alone patients were 3/51 (5.9%) and 5/45 (11.1%). For unspeciated MAC, month 6 SCC rates were 6/34 [17.6%] for ALIS + MDR vs. 2/16 [12.5%] for MDR alone. Rates by region are shown below.

Table 13: Culture conversion rates (Study INS-212, ITT)

Org.	Region	ALIS + MDR (N = 224)			MDR (N = 112)			Overall (N = 336)		
		n	Conv.	Non-Conv.	n	Conv.	Non-Conv.	n	Conv.	Non-Conv.
All MAC	All	223	65 (29.1)	158 (70.9)	112	10 (8.9)	102 (91.1)	335	75 (22.4)	260 (77.6)
	North America	104	32 (30.8)	72 (69.2)	55	6 (10.9)	49 (89.1)	159	38 (23.9)	121 (76.1)
	Europe	47	9 (19.1)	38 (80.9)	28	3 (10.7)	25 (89.3)	75	12 (16.0)	63 (84.0)
	Japan	34	9 (26.5)	25 (73.5)	14	0 (0.0)	14 (100)	48	9 (18.8)	39 (81.3)
	Asia excl. Japan	14	1 (7.1)	13 (92.9)	6	0 (0.0)	6 (100)	20	1 (5.0)	19 (95.0)
	Oceania	24	14 (58.3)	10 (41.7)	9	1 (11.1)	8 (88.9)	33	15 (45.5)	18 (54.5)
M avium	All	101	30 (29.7)	71 (70.3)	51	3 (5.9)	48 (94.1)	152	33 (21.7)	119 (78.3)
	North America	35	13 (37.1)	22 (62.9)	20	1 (5.0)	19 (95.0)	55	14 (25.5)	41 (74.5)
	Europe	27	6 (22.2)	21 (77.8)	16	2 (12.5)	14 (87.5)	43	8 (18.6)	35 (81.4)
	Japan	31	9 (29.0)	22 (71.0)	12	0 (0.0)	12 (100)	43	9 (20.9)	34 (79.1)
	Asia excl. Japan	5	0 (0.0)	5 (100)	1	0 (0.0)	1 (100)	6	0 (0.0)	6 (100)
	Oceania	3	2 (66.7)	1 (33.3)	2	0 (0.0)	2 (100)	5	2 (40.0)	3 (60.0)
M intracellulare	All	88	29 (33.0)	59 (67.0)	45	5 (11.1)	40 (88.9)	133	34 (25.6)	99 (74.4)
	North America	55	16 (29.1)	39 (70.9)	28	3 (10.7)	25 (89.3)	83	19 (22.9)	64 (77.1)
	Europe	9	2 (22.2)	7 (77.8)	9	1 (11.1)	8 (88.9)	18	3 (16.7)	15 (83.3)
	Japan	2	0 (0.0)	2 (100)	1	0 (0.0)	1 (100)	3	0 (0.0)	3 (100)
	Asia excl. Japan	4	1 (25.0)	3 (75.0)	1	0 (0.0)	1 (100)	5	1 (20.0)	4 (80.0)
	Oceania	18	10 (55.6)	8 (44.4)	6	1 (16.7)	5 (83.3)	24	11 (45.8)	13 (54.2)
Unspeciated MAC	All	34	6 (17.6)	28 (82.4)	16	2 (12.5)	14 (87.5)	50	8 (16.0)	42 (84.0)
	North America	14	3 (21.4)	11 (78.6)	7	2 (28.6)	5 (71.4)	21	5 (23.8)	16 (76.2)
	Europe	11	1 (9.1)	10 (90.9)	3	0 (0.0)	3 (100)	14	1 (7.1)	13 (92.9)
	Japan	1	0 (0.0)	1 (100)	1	0 (0.0)	1 (100)	2	0 (0.0)	2 (100)
	Asia excl. Japan	5	0 (0.0)	5 (100)	4	0 (0.0)	4 (100)	9	0 (0.0)	9 (100)
	Oceania	3	2 (66.7)	1 (33.3)	1	0 (0.0)	1 (100)	4	2 (50.0)	2 (50.0)

Based on susceptibility testing criteria applicable to plasma levels, the SCC rates by month 6 rates for patients with clarithromycin-susceptible MAC at baseline (MIC ≤ 8 µg/mL) were 55/165 (33.3%) in the ALIS + MDR group vs. 9/87 (10.3%) in the MDR alone group. Among the few with MAC showing intermediate resistance (MIC = 16 µg/mL) the rates were 3/7 and 0/3 while rates for those with clarithromycin-resistant MAC (MIC ≥ 32 µg/mL) were 7/51 (13.7%) and 1/22 (4.5%).

The figure below shows that there was no correlation between amikacin MIC value at baseline and SCC by month 6 in the ALIS group. The SCC rates varied from 28.6% to 34.5% for MAC with baseline amikacin MICs from 8 to 64 µg/mL. Lack of correlation was also confirmed when the data were examined by species and by region.

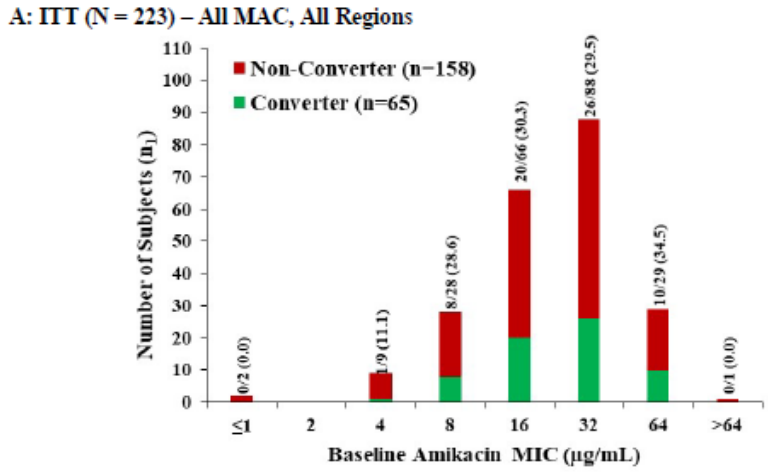


Figure 13: Correlation of amikacin MIC to Culture conversion of MAC for ALIS + MDR-Treated subjects (Study INS-212)

MAC isolates with an amikacin MIC of > 64 µg/mL were seen at one or more visits in 29 patients, of which 25 were randomised to ALIS + MDR and 4 to MDR alone. Of the 25 in the ALIS + MDR arm:

- 3 had an isolate with an amikacin MIC > 64 µg/mL at screening that at baseline and subsequent visits was ≤ 64 µg/mL. One achieved conversion but the conversion was not durable
- 1 had an isolate with an amikacin MIC > 64 µg/mL at baseline and did not achieve culture conversion
- 21 had isolates with an amikacin MIC > 64 µg/mL post-baseline

  In 13/21 the isolate was macrolide-susceptible
  - o 1 achieved culture conversion at Month 2
  - o 1 achieved culture conversion at Month 1 with amikacin MIC > 64 µg/mL for either a new or the same isolate cultured at Month 5 that subsequently reverted to amikacin MIC < 64 µg/mL at Months 6 and at EOT
  - o 3 had isolates that subsequently reverted to an amikacin MIC < 64 µg/mL at some point during treatment but did not achieve culture conversion
  - o 8 had isolates with either persistent MICs > 64 µg/mL or MIC > 64 µg/mL for the last cultured isolate and none achieved culture conversion

  The other 8 had macrolide-resistant isolates with either persistent amikacin MICs > 64 µg/mL or MIC > 64 µg/mL for the last cultured isolate and none achieved culture conversion.

None of the 4 in the MDR alone arm achieved sputum culture conversion
- o 3 had macrolide-susceptible isolates at baseline
- o 1 had a macrolide-resistant isolate at baseline

Of the 7 patients exposed to ALIS in the ALIS+MDR arm who did not achieve sustained culture conversion due to a microbiological reason for relapse/recurrence; 5 patients had changes in amikacin MIC that were acceptable within CLSI guidance (2 with a 2-fold increase, 2 with no change, and 1 with 2-fold decrease). Only 2 patients had an increase in amikacin MIC (4-fold increase).

In summary, treatment failure occurred in 24/25 ALIS patients who had isolates with an amikacin MIC > 64 µg/mL at baseline and/or post-baseline. Also, all patients with amikacin MIC > 64 µg/mL and baseline macrolide resistance failed treatment with ALIS.

Stepwise logistic regression (SLR)

Seven factors (age, baseline amikacin MIC, baseline clarithromycin MIC, geographic region, sex, SGRQ total score and randomisation stratum) were included in the initial list of predictors for the SLR.

The final model from the SLR analysis indicated that treatment (forced inclusion), region, SGRQ quartile and clarithromycin MIC were predictors of achieving SCC by month 6. Compared to North America, Asian patients were less likely to convert, Japanese and European patients had a similar chance of converting and patients from Oceania had an increased chance of conversion. Patients in the SGRQ first and second quartiles (better lung function) had higher chances of conversion than those in the fourth quartile. Patients with isolates that had baseline clarithromycin MICs ≤ 64 µg/mL had a better chance of conversion vs. those with MICs > 64 µg/mL.

For sustainable culture conversion through EOT, the selected effects were treatment, region and SGRQ quartile. Patients in Oceania had a better chance of achieving sustained SCC vs. North Americans but all other regions were no different to North America. Patients in the SGRQ first and second quartiles had better chances of sustaining SCC vs. those in the fourth quartile.

The effect of factors on sustained SCC at 3 months off treatment could not be assessed due to the lack of any patients in the MDR alone arm achieving this endpoint.

Table 14: Final model from stepwise logistic-regression analysis of sputum culture conversion status (Study INS-212 [ITT population])

		Conversion Status			Model Effects		
					Coefficient		
Effect	Level	No n (%)	Yes n (%)	Odds Ratio (95% CI)	Estimate (SE)	*P* Value[a]	Effect *P* Value[b]
Treatment Arm	ALIS + MDR	157 (47.3)	65 (19.6)	5.093 (2.388, 10.863)	0.8139 (0.1932)	< 0.0001	< 0.0001
	MDR Alone	100 (30.1)	10 (3.0)	-	-	-	-
Region	Asia	19 (5.7)	1 (0.3)	0.158 (0.020, 1.272)	-1.5753 (0.8462)	0.0627	0.0089
	Japan	39 (11.7)	9 (2.7)	0.688 (0.289, 1.640)	-0.1053 (0.3943)	0.7895	-
	Europe	62 (18.7)	12 (3.6)	0.747 (0.345, 1.615)	-0.0235 (0.3622)	0.9483	-
	Oceania	17 (5.1)	15 (4.5)	3.213 (1.354, 7.627)	1.4356 (0.3942)	0.0003	-
	North America	120 (36.1)	38 (11.4)	-	-	-	-
SGRQ Quartile	First Quartile	56 (16.9)	27 (8.1)	5.188 (2.036, 13.219)	0.6745 (0.2427)	0.0055	0.0054
	Second Quartile	60 (18.1)	23 (6.9)	3.659 (1.439, 9.300)	0.3252 (0.2419)	0.1788	-
	Third Quartile	66 (19.9)	17 (5.1)	2.570 (0.983, 6.717)	-0.0279 (0.2564)	0.9133	-
	Fourth Quartile	75 (22.6)	8 (2.4)	-	-	-	-
Clarithromycin MIC	≤ 64 µg/mL	196 (59.0)	68 (20.5)	2.794 (1.136, 6.870)	0.5137 (0.2296)	0.0252	0.0252
	> 64 µg/mL	61 (18.4)	7 (2.1)	-	-	-	

Source: Module 5.3.5.3 SLR Analysis, Study INS-212 Table 1.1

[a] *P* value testing if coefficient differed from zero.

[b] Type 3 ANOVA *P*-value testing if effect differed from zero.

Note: Odds ratio was based on final analysis model with adjustments for all effects.

Note: Only subjects with non-missing data for all effects in the initial model are included in the analysis.

ALIS = amikacin liposome inhalation suspension (590 mg); ANOVA = analysis of variance; CI = confidence interval; ITT = intent-to-treat; MDR = multidrug regimen; MIC = minimum inhibitory concentration; SGRQ = St George's Respiratory Questionnaire; SE = standard error.

During the procedure it was clarified that about 30% of patients enrolled into INS-212 had been exposed to prior aminoglycoside treatment (systemic and/or inhaled) aimed at MAC. About 12-14% of all patients had received an inhaled aminoglycoside off-label (even if they received an approved inhaled formulation it would not have been indicated for treating MAC NTM).

Those patients who had not already tried aminoglycoside treatment were more likely to respond to Arikayce but this was not accounted for by baseline amikacin MIC.

Post-hoc analysis of persistence of SCC in patients with SCC by month 6

In this *post hoc* analysis patients were assumed to have lost persistence of culture negativity at the first instance of any of the following situations:

- First agar positive culture or first of 3 consecutive monthly broth positive cultures
- First instance of a missing visit or culture result
- First use of rescue medication
- Discontinuation of the study or of treatment

Loss of response included new as well as recurring infections.

At Month 2 since conversion all of the 75 patients in either arm with SCC by month 6 had persistent culture negativity. Subsequently, all 10 patients in the MDR alone arm lost SCC status, of which 4 had a positive culture, 4 had missing visit/result and 2 discontinued the study prior to receiving 12 months of treatment since conversion.

In the ALIS + MDR and MDR alone arms 29/65 patients lost culture negativity for the reasons shown in the table below. As shown, 9 had positive cultures and another 6 were known to have withdrawn due to AEs. This accounts for ~half of the 29 cases.

Table 15: Summary of culture negativity over time in the ALIS + MDR Arm in subjects who converted by month 6 in Study INS-212 (ITT population)

		Reason for Loss of Culture Negativity, n (%)			
Month Since Conversion[a]	Persistent Culture Negativity, n (%)	Culture Positive	Missing Visit/Missing Result	Rescue Medication	Early Discontinuation of Treatment/Study
0	65 (100)	0	0	0	0
1	65 (100)	0	0	0	0
2	65 (100)	0	0	0	0
3	63 (96.9)	1 (1.5)	0	0	1 (1.5)
4	60 (92.3)	3 (4.6)	0	0	0
5	58 (89.2)	1 (1.5)	0	1 (1.5)	0
6	58 (89.2)	0	0	0	0
7	56 (86.2)	0	2 (3.1)	0	0
8	51 (78.5)	0	2 (3.1)	0	3 (4.6)
9	50 (76.9)	0	0	0	1 (1.5)
10	48 (73.8)	1 (1.5)	0	0	1 (1.5)
11	48 (73.8)	0	0	0	0
12	41 (63.1)	1 (1.5)	0	0	6 (9.2)
13 (28DFU)	37 (56.9)	2 (3.1)	2 (3.1)	0	0
15 (3MFU)	36 (55.4)	0	1 (1.5)	0	0
Total	-	**9 (13.8)**	**7 (10.8)**	**1 (1.5)**	**12 (18.5)[b]**

Source: Module 5.3.5.3 Table AdHoc.2 (Study INS-212)

[a] Months 0, 1, and 2 represent the 3 consecutive negative cultures required for establishing conversion. Months 0 to 12 are on-treatment and Months 13 and 15 are off-treatment.

[b] 6 subjects discontinued treatment due to an adverse event, 4 subject discontinued treatment prior to completing 12 months of treatment, and 2 subjects withdrew from the study.

Note: Percentages are based on the number of converters.

3MFU = 3-month off treatment follow-up visit; 28DFU = 28-day off treatment follow-up visit; ALIS = amikacin liposome inhalation suspension; ITT = intent-to-treat; MDR = multidrug regimen.

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 (see later sections).

Table 16: Summary of Efficacy for trial INS-212

A RANDOMIZED, OPEN-LABEL, MULTICENTER STUDY OF LIPOSOMAL AMIKACIN FOR INHALATION (ALIS) IN ADULT SUBJECTS WITH NONTUBERCULOUS MYCOBACTERIAL (NTM) LUNG INIONS CAUSED BY MYCOBACTERIUM AVIUM COMPLEX (MAC) THAT ARE REFRACTORY TO TREATMENT			
Study identifier	INS-212		
Design	Randomised, open label, parallel group		
	Duration of main phase: Duration of follow-up:		6 months to primary endpoint Up to 16 months to end of therapy 12 months off all treatment
Hypothesis	Superiority		
Treatment groups	Amikacin Liposome Inhalation Dispersion (ALIS)		Inhalation of ALIS 590 mg QD in addition to standard of care multidrug systemic regimen (MDR) for a minimum of 8 months and up to 16 months Converters by month 6 were to receive 12 months counted from the time of the first of 3 negative samples indicating SCC Non-converters and any patient with recurrence or relapse before month 6 were discontinued at month 8 and offered participation in INS-312
	Control		Standard of care MDR for a minimum of 8 months and up to 16 months Converters and non-converters were managed as above
Endpoints and definitions	Primary endpoint in protocol	SCC at month 6	Percentage of patients who achieve sputum culture conversion (negative for MAC) by month 6 on treatment EU Secondary endpoint
	EU Primary endpoint	SCC at 3 months off all treatment	Sustained SCC at 3 months off ALIS and SOC [complete results for 12 months off treatment not yet available]
	SCC at month 12 Time to culture conversion Six minute walk test at month 6	On treatment 6MWT	 Change from baseline compared between treatments; repeated at months 4, 6, 8, EOT and follow-up
Database lock			

Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Sustained SCC at 3 months follow-up (assessable only in the subset of the ITT population that remained on study after month 8)			
Descriptive statistics and estimate variability	Treatment group	ALIS +SOC ITT =224	SOC ITT =112	Notes
	Number with confirmed SCC by month 6 (continued in study after month 8)	65 (29%)	10 (8.9%)	159 ALIS and 102 SOC were non-converters so discontinued at month 8 (if not already discontinued)
	Sustained SCC at 3 months FU Based on ITT	36/65 (55.4%) 36/224 (16.1%)	0/10 0/112	29/65 ALIS and 10/10 SOC did not sustain SCC
	p-value CMH			P-value for ITT = <0.0001
Analysis description	**Pre-specified secondary analyses**			
Effect estimate per comparison	SCC at month 12	ALIS	SOC	
		41/65 (63.1%) 18.3% of ITT	3/10 (30%) 2.7% of ITT	
			P-value for ITT = <0.0001	
Notes	The 6MWT showed no significant differences between ALIS and SOC in change from baseline to months 6, 8 or 3 months after end of treatment Median time to SCC could not be estimated The HR of 3.92 (95% CI: 2.078, 8.570) indicated the greater likelihood of achieving SCC by month 6 in the ALIS group			
Analysis description	**Exploratory analyses at day 28, month 6 and month 12 off treatment**			
Effect estimate per comparison	SCC Day 28 Month 6 Month 12	ALIS	SOC	
		37/224 (16.5%)	0	
		33/224 (14.7%) 30/224 (13.4%)	0 0	
Notes	The applicant's counting method applied to on-treatment and post-treatment sustained/durable SCC is not agreed. Please see the discussion of efficacy for an explanation of the discrepancies.			

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

The applicant provided a table of SCC rates on treatment in Phase 2 and 3 as shown below. These data cannot be directly compared due to differences in study populations and designs.

Clinical studies in special populations

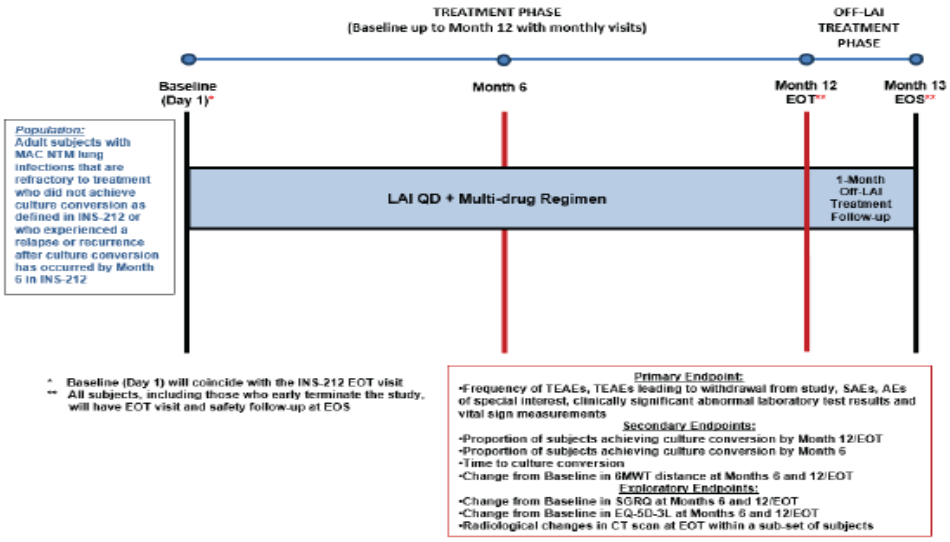
There were no studies confined to special populations. The numbers of patients aged > 65 years in INS-212 and their outcomes was provided during the procedure. Patients < 65 years of age were the largest age subgroup. The overall trend of outcomes between the ALIS + MDR arm and MDR alone was similar regardless of age subgroups.

Table 17: Conversion study INS-212 age group (ITT population)

	< 65 Years		65 to 74 Years		75 to 84 Years		≥ 85 Years	
	n	(%)	n	(%)	n	(%)	n	(%)
ALIS + MDR	**N = 105**		**N = 86**		**N = 29**		**N = 4**	
Month 6 Conversion	31	(29.5)	29	(33.7)	4	(13.8)	1	(25.0)
Sustainable Conversion	25	(23.8)	13	(15.1)	3	(10.3)	0	–
Durable Conversion at 3 Months Follow-Up	23	(21.9)	11	(12.8)	2	(6.9)	0	–
MDR	**N = 52**		**N = 40**		**N = 19**		**N = 1**	
Month 6 Conversion	5	(9.6)	2	(5.0)	2	(10.5)	1	(100.0)
Sustainable Conversion	0	–	1	(2.5)	2	(10.5)	0	–
Durable Conversion at 3 Months Follow-Up	0	–	0	–	0	–	0	–

Supportive studies

This extension study was conducted at 77 sites in 16 countries. The primary objective was to assess the safety of ALIS 590 mg QD in conjunction with systemic SOC in patients who had been enrolled in INS-212 and had completed the month 6 and 8 visits but failed to achieve confirmed SCC (i.e. did not have 3 consecutive monthly negative sputum cultures or had experienced a relapse or recurrence (defined as in INS-212) after culture conversion had occurred.



All patients who elected to enrol into INS-312 were to continue the multidrug anti-mycobacterial regimen that they were receiving during study INS-212 and were to also receive ALIS 590 mg QD for up to 12 months. There was a final visit at 13 months (1 month off ALIS treatment) for safety follow-up. No statistical hypotheses were pre-specified and all endpoints were reported descriptively.

Results as reported in the final CSR dated 3 May 2019

There were 163 patients who opted to enrol in INS-312 (73 prior ALIS+MDR and 90 MDR alone in INS-212). Since 75 continued in INS-212 (=238), that leaves 98 patients (336-238) unaccounted for after the month 8 visit in INS-212. Overall, 104/163 (63.8%) completed treatment and 107/163 (65.6%) completed the study while 31 (19.0%) achieved SCC by Month 6 and 40 (24.5%) by Month 12.

Table 182: Analysis of culture conversion by month 6 and month 12 – safety population

Statistic	Prior ALIS Plus Multidrug Regimen (N = 73)	Prior Multidrug Regimen Alone (N = 90)	Total (N = 163)
Culture Conversion by Month 6			
Converter[a]	7 (9.6%)	24 (26.7%)	31 (19.0%)
Non-Converter	66 (90.4%)	66 (73.3%)	132 (81.0%)
Culture Conversion by Month 12			
Converter[b]	10 (13.7%)	30 (33.3%)	40 (24.5%)
Non-Converter	63 (86.3%)	60 (66.7%)	123 (75.5%)

Source: Table 14.2.2.1.1 and Table 14.2.2.1.1.1

[a] Converters are defined as subjects who had 3 consecutive monthly MAC-negative sputum cultures by Month 6 (last opportunity to convert was at Month 4). A subject with monthly missing culture data was considered positive for MAC, unless the subject was unable to produce sputum after induction.

[b] Converters are defined as subjects who had 3 consecutive monthly MAC-negative sputum cultures by Month 12 (last opportunity to convert was at Month 10). A subject with monthly missing culture data was considered positive for MAC, unless the subject was unable to produce sputum after induction.

In both subgroups defined by prior exposure to ALIS most of those that did achieve SCC did so by month 6 and most by month 4.

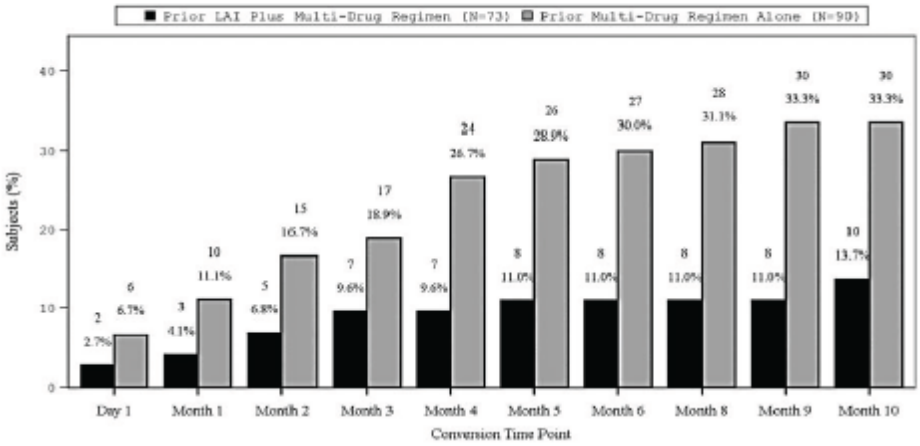


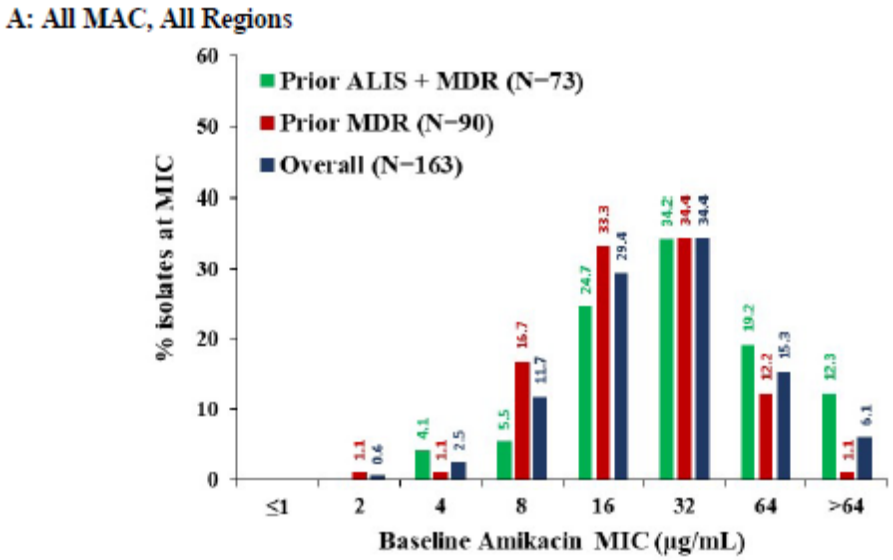
Figure 14: Bar chart for culture conversion by month 12 – safety population

Although INS-312 involved 12 months of treatment and a last visit at month 13 it seems from the table below that very few patients who achieved SCC at some point maintained SCC despite continuing treatment. At EOS, based on the ITT population, 24/163 (14.7%) had achieved and still sustained SCC but there were no further visits so sustainability beyond month 13 is not known.

Summary of Sustained Conversion by Time Point Since Conversion
Safety Population

Site	Time Since Conversion		Prior LAI Plus Multi -Drug Regimen [N=73] n(%)	Prior Multi-Drug Regimen Alone [N=90] n(%)	Total [N=163] n(%)
All	3 MONTHS	Number of Subjects Assessed	70 (95.9)	89 (98.9)	159 (97.5)
		Sustained Conversion	6 (8.2)	27 (30.0)	33 (20.2)
		Non-Sustained Conversion	64 (87.7)	62 (68.9)	126 (77.3)
		Converters	1 (1.4)	2 (2.2)	3 (1.8)
		Non-converters	63 (86.3)	60 (66.7)	123 (75.5)
	4 MONTHS	Number of Subjects Assessed	70 (95.9)	87 (96.7)	157 (96.3)
		Sustained Conversion	5 (6.8)	24 (26.7)	29 (17.8)
		Non-Sustained Conversion	65 (89.0)	63 (70.0)	128 (78.5)
		Converters	2 (2.7)	3 (3.3)	5 (3.1)
		Non-converters	63 (86.3)	60 (66.7)	123 (75.5)
	5 MONTHS	Number of Subjects Assessed	70 (95.9)	85 (94.4)	155 (95.1)
		Sustained Conversion	5 (6.8)	17 (18.9)	22 (13.5)
		Non-Sustained Conversion	65 (89.0)	68 (75.6)	133 (81.6)
		Converters	2 (2.7)	8 (8.9)	10 (6.1)
		Non-converters	63 (86.3)	60 (66.7)	123 (75.5)
	6 MONTHS	Number of Subjects Assessed	70 (95.9)	85 (94.4)	155 (95.1)
		Sustained Conversion	4 (5.5)	16 (17.8)	20 (12.3)
		Non-Sustained Conversion	66 (90.4)	69 (76.7)	135 (82.8)
		Converters	3 (4.1)	9 (10.0)	12 (7.4)
		Non-converters	63 (86.3)	60 (66.7)	123 (75.5)
All	7 MONTHS	Number of Subjects Assessed	70 (95.9)	83 (92.2)	153 (93.9)
		Sustained Conversion	4 (5.5)	14 (15.6)	18 (11.0)
		Non-Sustained Conversion	66 (90.4)	69 (76.7)	135 (82.8)
		Converters	3 (4.1)	9 (10.0)	12 (7.4)
		Non-converters	63 (86.3)	60 (66.7)	123 (75.5)
	8 MONTHS	Number of Subjects Assessed	69 (94.5)	81 (90.0)	150 (92.0)
		Sustained Conversion	2 (2.7)	13 (14.4)	15 (9.2)
		Non-Sustained Conversion	67 (91.8)	68 (75.6)	135 (82.8)
		Converters	4 (5.5)	8 (8.9)	12 (7.4)
		Non-converters	63 (86.3)	60 (66.7)	123 (75.5)
	9 MONTHS	Number of Subjects Assessed	69 (94.5)	75 (83.3)	144 (88.3)
		Sustained Conversion	2 (2.7)	10 (11.1)	12 (7.4)
		Non-Sustained Conversion	67 (91.8)	65 (72.2)	132 (81.0)
		Converters	4 (5.5)	5 (5.6)	9 (5.5)
		Non-converters	63 (86.3)	60 (66.7)	123 (75.5)
	10 MONTHS	Number of Subjects Assessed	68 (93.2)	73 (81.1)	141 (86.5)
		Sustained Conversion	2 (2.7)	8 (8.9)	10 (6.1)
		Non-Sustained Conversion	66 (90.4)	65 (72.2)	131 (80.4)
		Converters	3 (4.1)	5 (5.6)	8 (4.9)
		Non-converters	63 (86.3)	60 (66.7)	123 (75.5)
All	11 MONTHS	Number of Subjects Assessed	66 (90.4)	70 (77.8)	136 (83.4)
		Sustained Conversion	1 (1.4)	5 (5.6)	6 (3.7)
		Non-Sustained Conversion	65 (89.0)	65 (72.2)	130 (79.8)
		Converters	2 (2.7)	5 (5.6)	7 (4.3)
		Non-converters	63 (86.3)	60 (66.7)	123 (75.5)
	12 MONTHS	Number of Subjects Assessed	65 (89.0)	65 (72.2)	130 (79.8)
		Sustained Conversion	1 (1.4)	1 (1.1)	2 (1.2)
		Non-Sustained Conversion	64 (87.7)	64 (71.1)	128 (78.5)
		Converters	1 (1.4)	4 (4.4)	5 (3.1)
		Non-converters	63 (86.3)	60 (66.7)	123 (75.5)
	END OF TREATMENT	Number of Subjects Assessed	73 (100.0)	90 (100.0)	163 (100.0)
		Sustained Conversion	6 (8.2)	18 (20.0)	24 (14.7)
		Non-Sustained Conversion	67 (91.8)	72 (80.0)	139 (85.3)
		Converters	4 (5.5)	12 (13.3)	16 (9.8)
		Non-converters	63 (86.3)	60 (66.7)	123 (75.5)

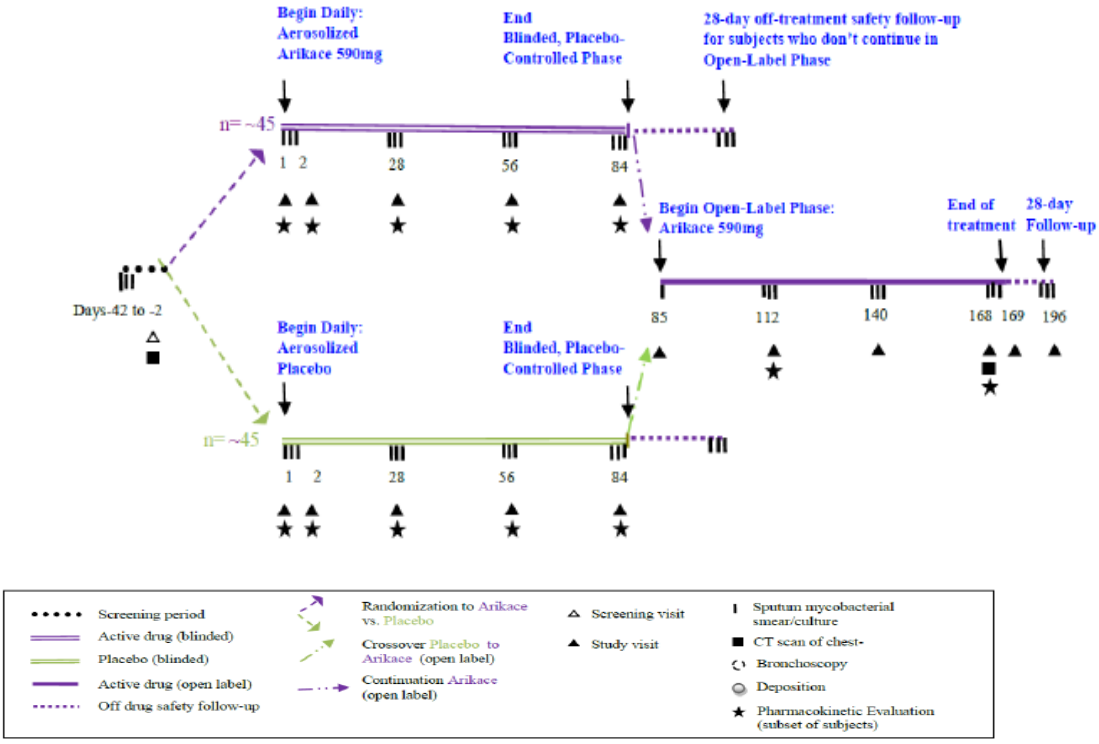
For the 163 MAC isolates overall, the amikacin MIC_{50} was 32 µg/mL and the MIC_{90} was 64 µg/mL. There was a suggestion that prior exposure to ALIS influenced the MIC distribution.



Among patients previously treated with MDR alone, 13/42 (31.0%) with *M. avium*, 13/38 (34.2%) with *M. intracellulare* and 4/10 (40.0%) with unspeciated MAC achieved conversion when treated with ALIS + MDR. Patients with clarithromycin-susceptible isolates converted at a rate of 37.1% (26/70) vs. 33.3% (1/3) for intermediate susceptibility and 17.6% (3/17) for resistant isolates. Overall there was no detectable correlation between amikacin MIC value at baseline and SCC by month 6. Regardless of prior exposure to ALIS, patients with strains having amikacin MICs > 64 µg/mL did not convert. Similar results were observed for *M. avium* and *M. intracellulare*.

TR02-112

This Phase 2 randomised, double-blind, placebo-controlled study evaluated the use of ALIS in patients in N. America with recalcitrant NTM lung disease. It commenced in 2012 and completed July 2015. The CSR is dated 4 August 2017. The general design is shown below.



- The double-blind phase compared ALIS 590 mg QD vs. placebo for 84 days in patients with treatment-refractory NTM lung infection on a stable multi-drug regimen.
- All patients who consented to continue in the open-label phase received ALIS 590 mg QD for 84 days and had a safety follow-up visit 4 weeks after the end of treatment visit.
- Patients who completed either phase of the study were invited to attend further safety follow-up at 12 and 24 months (window ± 2 months) after the last dose.

The primary efficacy endpoint was the change from baseline on the SQS for mycobacterial culture for the ALIS vs. placebo group at Day 84. The endpoint used the semi-quantitative mycobacterial culture reporting method, expressed on a 7-step scale.

With a 2-sided significance level of 0.05, 50 patients per arm were believed to provide 80% power to detect a difference between the treatment arms of at least 0.94 steps on the semi-quantitative scale (SQS) in the change from baseline in mycobacterial culture, assuming a pooled standard deviation of 1.6 (based on simulated information), based on a Wilcoxon rank sum test. Additionally, 50 patients per arm were considered to provide 80% power to detect a difference between treatments of at least 17% in the proportion with NTM culture conversion to negative, assuming rates of 3% for placebo and 20% for ALIS, based on a CMH test with a 2-sided significance level of 0.05.

As shown below, the study failed in the pre-defined primary analysis.

Table 19: Change from baseline of the full SQS scale for mycobacterial culture at Day 84 (mITT population)

Categorical Result	Number (%) of Subjects		
	LAI 590 mg QD (N = 44) n (%)	Placebo (N = 45) n (%)	Total (N = 89) n (%)
Baseline[a]			
Culture negative (confirmed with no growth in liquid medium)	5 (11.4)	5 (11.1)	10 (11.2)
Growth in liquid medium only (liquid positive)	1 (2.3)	1 (2.2)	2 (2.2)
Agar positive (1-49 colonies, manual count on agar)	17 (38.6)	10 (22.2)	27 (30.3)
1+ (50-100 colonies)	2 (4.5)	4 (8.9)	6 (6.7)
2+ (> 100-200 colonies)	2 (4.5)	2 (4.4)	4 (4.5)
3+ (> 200-500 colonies)	3 (6.8)	4 (8.9)	7 (7.9)
4+ (> 500 colonies)	14 (31.8)	19 (42.2)	33 (37.1)
Day 84			
-6	1 (2.3)	0	1 (1.1)
-5	0	0	0
-4	1 (2.3)	0	1 (1.1)
-3	3 (6.8)	0	3 (3.4)
-2	6 (13.6)	6 (13.3)	12 (13.5)
-1	5 (11.4)	5 (11.1)	10 (11.2)
0	23 (52.3)	23 (51.1)	46 (51.7)
+1	2 (4.5)	5 (11.1)	7 (7.9)
+2	0	3 (6.7)	3 (3.4)
+3	1 (2.3)	0	1 (1.1)
+4	1 (2.3)	2 (4.4)	3 (3.4)
+5	0	1 (2.2)	1 (1.1)
+6	0	0	0
+7 (Death)	1 (2.3)	0	1 (1.1)
P-value for stratified Wilcoxon rank sum test of treatment arm adjusting for the randomization strata			0.072
P-value for unstratified Wilcoxon rank sum test of treatment arm			0.065

LAI = liposomal amikacin for inhalation; mITT = modified intent-to-treat; QD = once daily; SQS = semi-quantitative scale.
Note: All reasons for missing data were handled as missing equals failure, except due to death. Missing data due to death was handled as missing equals failure *and* assigned a 'unique' change of +7.
a Baseline is defined as the measurement prior and closest to the administration of the first dose of study drug (LAI or placebo).

In patients with *M. abscessus* and/or with CF there was no difference in mycobacterial loads between ALIS and placebo at Day 84. In contrast, the change in load at day 84 for patients without CF or with MAC gave p-values of 0.036 and 0.045, respectively. A similar pattern of findings applied to proportions with a negative culture at day 84.

Post hoc analysis of SCC and sustained SCC

In the *post hoc* analyses SCC was defined as 3 consecutive negative cultures. This analysis (using the revised SQS assignment of samples and including those with negative cultures at baseline) showed that 23 patients demonstrated SCC at some time point by the 28-day follow up visit. Of the 23, 20 patients achieved SCC while receiving ALIS in the double-blind phase or in the open-label phase of the study. Of these 23 patients, 19 had non-CF underlying disease and were infected with MAC.

When focussing on the non-CF MAC population that is the subject of this MAA:

- 54 patients with non-CF MAC lung disease were randomised and treated in TR02-112
- In the double-blind phase 27 received ALIS and 27 received placebo

- The open-label phase enrolled 22/27 from the ALIS group and all 27 from the placebo group; thus 54 non-CF MAC patients had the opportunity to receive between 84 and 168 days of ALIS.

Of the 23 patients the CSR states had SCC at some time on treatment:

- 19/23 were non-CF MAC patients, 12 from the initial ALIS group and 7 from the initial placebo group.
- 5/12 from the initial ALIS group had negative cultures on day 1. One of these never had a positive culture at any visit. The other four each had a single visit with a positive culture (all were step 2 or 3). Two were positive at day 28, one at day 168 and one at the day 28 follow-up. There were negative cultures at all other visits. With negative cultures at day 1 and single positives on therapy it is not possible to conclude that these patients really had SCC on study.
- 7/12 from the initial ALIS group were positive on day 1 and at some time had 3 consecutive visits with negative cultures (i.e. met the *post hoc* definition of SCC). Of these 7:
  - 1 was positive at the day 28 follow-up and had no M12 follow-up visit
  - 1 was positive at M12 follow-up
  - 1 was negative up to the day 28 follow-up but had no M12 visit
  - 1 was negative from day 112 to the day 28 follow-up but had no sputum at the M12 visit
  - 3 were negative from first SCC time point to M12 follow-up

- 3/7 from the initial placebo group had negative cultures on day 1. One never had a positive culture and one had a single positive result (step 2 on day 112). These two patients cannot be included in the analysis of SCC on ALIS (see also above). The third was positive from day 28-112 and is counted below in the SCC rates.

- 5/7 from the initial placebo group (4 who were positive on day 1 and the patient described above who was negative on day 1 but positive from day 28-112) could be assessed for possible SCC:
  - 1 had SCC on placebo and remained negative at the day 28 follow-up but had no M12 visit
  - 4 had SCC at some time after switching to ALIS. Of these 4:
    - 1 was negative at M12
    - 1 was positive at M12
    - 2 have no result at M12 (one had no day 28 or M12 follow-up and one had no sputum)

- Of the 47/54 non-CF MAC patients treated with ALIS who had positive baseline cultures there were 4 with a confirmed SCC plus a negative culture at the M12 follow-up visit, which gives a SCC rate of 4/47 (= 8.5%).

- If the two patients who attended M12 but had no sputum are assumed to be negative, then the SCC rate is 6/47 (= 12.8%).

If the other two patients who were negative at the day 28 follow-up but did not attend the M12 visit are assumed to be negative, then the most optimistic SCC rate is 8/47 (= 17%).

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Dose of Arikayce and duration of treatment

There is no good rationale for the daily dose or for once daily dosing. Since PK-PD analyses cannot be applied to dose-finding in this situation, the only way to select a dose would be from dose-finding studies. Dose-finding studies of a size sufficient to draw clear conclusions would likely be difficult in this indication

and, for feasibility and timing, would probably have to rely on an on-treatment SCC rate. Once daily dosing has been pursued throughout the ALIS programme. The sputum concentration data up to 72 h post-dose in NTM/MAC patients generally support a conclusion that amikacin is released slowly from liposomes deposited in airways.

In INS-212, the duration of treatment after confirmed SCC was to be 12 months, which followed recommendations from the American Lung Association. In line with INS-212, the SmPC recommends that Arikayce is continued for 12 months after SCC. It is also recommended that treatment should not be continued of SCC has not occurred by month 6, with a maximum duration of 18 months.

INS-212

This is the single pivotal study. It was conducted in the target population of non-CF patients with chronic MAC lung disease and it prospectively followed-up patients eligible to stop all MAC treatment for a total of 12 months off therapy. Following CHMP advice and development of a separate SAP for the EU, INS-212 set out to evaluate post-treatment sustained SCC rates with a primary endpoint at 3 months off all treatment. The final CSR submitted during the procedure also provided complete data for the month 12 post-treatment visit.

There are some design issues that merit mention as follows:

INS-212 was open-label. The possibility that the open-label design influenced the discontinuation rates and/or AE reporting rates cannot be dismissed.

Patients were discontinued at month 8 if they had not had SCC confirmed by month 6. Whilst the primary analysis is based on the entire ITT population, the interpretation of this analysis rests on the assumption that the post-treatment sustained SCC rate in the patients initially assigned to MDR alone would have been zero if they had been continued on MDR alone in the study. Overall, in a population that had mostly received prior unsuccessful treatment for MAC for several years, and given the actual results for the 10 control group patients retained in the study after month 8, it is reasonable to assume that the post-treatment sustained SCC rate on MDR alone would have been zero or, at least, negligible.

According to protocol rules, a patient was considered to have sustained SCC up to end of 12 months post-SCC treatment provided there were no positive agar cultures and no more than 2 consecutive positive monthly broth cultures. Also, a patient was considered to have sustained SCC at the 3-month follow-up visit provided that there had been no positive agar cultures and no more than 3 consecutive positive monthly broth cultures at any time after conversion. Reflecting his definition, patients were determined to have experienced relapse/recurrence if they had positive sputum culture in broth media for 3 or more consecutive months, or 1 positive sputum culture in agar media, after achieving SCC. Furthermore, if the patient was unable to produce sputum despite reasonable efforts, and had already met the definition of SCC, this was recorded as a negative culture result.

These definitions are not considered appropriate. Any positive culture (agar or broth) post SCC should be counted as a positive for the visit at which the sample was obtained since this result is evidence of residual MAC in the airways. However, patients with intermittent positives who were negative at EOT and negative at each post-treatment follow-up visit could be counted as successes in the primary analysis. Due to these concerns, the applicant was requested to provide a tabulation of serial culture results for the ALIS and MDR alone patients who were deemed to have sustained SCC at least up to the time that they completed month of post-SCC treatment.

Although patients were to have received at least 6 months of treatment for MAC, this could have consisted of only two agents and it could have been stopped < 12 months before screening. Overall, the study

population was not confined to patients who had failed to respond to what could be considered an adequate treatment regimen for MAC and could be regarded as a mixture of inadequately treated (some of whom may have been non-adherent) and recalcitrant patients.

The study required that MAC isolates should have amikacin MIC ≤ 64 mg/L at baseline for the patient to be eligible for enrolment. This threshold MIC was based on the CLSI Guideline M62, which set the breakpoint for amikacin for testing MAC, noting that MAC with amikacin MICs > 64 mg/L may be resistant. However, this criterion is based on systemic administration of amikacin and cannot be regarded as relevant to inhalation. There was no attempt to "optimise" the background MDR at baseline. Other than amikacin, only susceptibility to clarithromycin of baseline MAC isolates was determined and this was conducted retrospectively.

This single pivotal study was powered to meet the FDA-recommended primary endpoint of on-treatment SCC rate at month 6 with a 2-sided significance level of 0.05.

INS-312

This was an uncontrolled study in which patients enrolled into INS-212 who had failed to achieve SCC by month 6 or had relapsed within that period could elect to receive open-label ALIS for up to 12 months. The aim was to analyse safety and there was follow-up for only one month off-treatment.

TR02-112

The study employed a double-blind design vs. placebo (empty liposomes) over the first 84 days (12 weeks), after which patients (including CF patients and NTM not confined to MAC) could elect to receive open-label ALIS for up to 84 days. The study was not planned *ab initio* to support MAA. It was primarily designed to detect a difference between the treatment arms of at least 0.94 steps on the semi-quantitative scale. The assessment of SCC based on consecutive negatives was conducted in a post hoc fashion. Patients often continued background MAC treatment after stopping ALIS and the follow-up visits were planned for safety so that there was incomplete sputum sampling. This was regarded as a hypothesis-generating study that was not designed to detect and quantify the clinical benefit of ALIS. It provided useful safety data vs. empty liposomes (placebo) and the results pointed to confining Phase 3 to non-CF patients with MAC.

Efficacy data and additional analyses

INS-212

The study met the pre-defined enrolment target to address the FDA-recommended primary endpoint. The age and gender distribution were in line with published data on disease epidemiology. The duration of prior treatment ranged from 0.2-22 years and only one patient had been treated for <6 months.

Treatment effect

In the prior MAA, the applicant reported a post-treatment sustained SCC rate of 36/224 (16%) at month 3 for ALIS vs. 0/112 for MDR alone. During the procedure, the final CSR for INS-212 was submitted, including data to month 12 post-treatment. The applicant reported a continued SCC in 30/224 (13.4%) vs. 0/112 at this final visit. This is based on the applicant's counting schema as described previously, which is not entirely agreed.

Serial culture data were provided for 44 patients – 41 initially assigned to ALIS and 3 initially assigned to MDR alone – who had SCC (as defined in the protocol) by month 6 on treatment so continued in the study on their assigned treatment after month 8 and were solid culture negative at month 12. Of these 44, two

were broth culture positive at month 12 and 6 did not have a result. Also, at end of treatment, one ALIS patient was solid culture positive and one MDR alone patient had no result.

Importantly, not all of these 44 patients had MAC cultured from their baseline (as opposed to screening visit) sputum specimen. There were 9 ALIS and 2 MDR patients with completely negative cultures on Day 1. Of these subjects, 6/9 ALIS and one of the 2 MDR patients had no post-baseline positive solid or broth cultures. It cannot be ruled out that on-study treatment with ALIS+MDR or MDR alone made no difference to these 7 patients, leaving 35 and 1 that can be assessed.

Focussing on the 35 ALIS patients for whom an on-treatment SCC was demonstrated, and counting any solid or broth culture positive after SCC occurred as failure, there were 30/224 (13.4%) with SCC through to month 3 post-treatment and 25/224 (11%) with SCC through to Month 12 post-treatment.

It was agreed with the applicant that there were no MDR alone patients who achieved SCC on study and had a documented post-treatment response.

In summary, whilst the applicant reports a post-treatment sustained SCC rate of 36/224 (16%) at month 3 and 30/224 (13.4%) at month 12, the assessment indicated rates of 30/224 (13.4%) and 25/224 (11%) at respective visits.

Success rates were comparable for *M. avium* and *M. intracellulare* and, perhaps, may be lower for the unspeciated NTMs that were considered to fall within the MAC complex. Also, success rates were comparable for the US and Japan, where the majority was enrolled. In Europe, <10% of 48 patients had a sustained conversion compared to ~40% of the 24 enrolled in Oceania. However, these differences may have arisen by chance.

TR02-112 and INS-312

TR02-112 did not provide clear evidence of clinical benefit for adding ALIS for 84 or 168 days and was considered to be of low relevance to the overall conclusion on efficacy. However, the lack of a microbiological response in patients with *M. abscessus* and patients with CF were important findings and led to exclusion of such patients from INS-212.

INS-312 was uncontrolled. The on-treatment SCC rates by month 6 in the patients carried over from INS-212 who had been initially randomised to the MDR alone group gave similar rates to those in the patients randomised to ALIS in INS-212.

Additional expert consultation

A SAG was held on 10 July.

The questions to the SAG and their answers are as follows:

1. Approximately 1/8 patients who ever start on Arikayce might have a sustained SCC on treatment that is maintained after stopping all NTM treatment. In light of the target patient population for Arikayce [*Arikayce is indicated for the treatment of non-tuberculous mycobacterial (NTM) lung infections caused by Mycobacterium avium Complex (MAC) in adults with very limited treatment options*] the SAG is requested to comment on whether the magnitude of efficacy observed is of clinical relevance.

The experts agreed that the magnitude of effect is limited. However, this might still be counted as clinically relevant in a selected population (e.g. with intractable disease, for whom very limited treatment options remain. Ideally, '*very limited treatment options*' would be clarified).

Adequately selected patients may particularly benefit, e.g. those for whom conventional therapy cannot be used and inhalational amikacin could offer an alternative.

It is however difficult to identify the best target population, as inclusion of a heterogeneous population with lack of stratification is one of the shortcomings of the study design. Another shortcoming is absence of clinical endpoints (e.g. survival, quality of life measures).

However, for the small number of patients affected, it is recognised that it would be difficult to have additional studies performed to collect these additional data. The company said 275 European patients were treated in a compassionate use programme. The outcomes should be known. Is a registry something that could be explored to complement the submitted clinical data?

Sustained sputum culture conversion is one outcome goal to be achieved, amongst others.

2. Does the SAG consider that there could be a clinical benefit of Arikayce in patients who achieve on-treatment SCC that is not sustained post-therapy?

No evidence-based data exist. However, the consensus amongst the experts was that indeed for patients achieving on-treatment SCC without sustained post-therapy, a clinical benefit exists for those with very limited treatment options remaining. The reduction in bacterial load could provide a short-term amelioration of symptoms, which is considered clinically meaningful. This would need to be weighed against the potential increase of drug-resistance caused by inappropriate use.

3. Does the SAG consider the documented safety profile of Arikayce, including the considerable discontinuation rates due to AEs that include airways intolerance and side effects typical of aminoglycosides, to be manageable in the target patient population?

The experts agreed that the listed adverse events would be mostly manageable. Patients should however be treated in experienced, specialised centres and be well informed on the risks. For the longer-term side effects, ototoxicity might be most problematic and irreversible. Tinnitus could seriously hamper quality of life. To limit that risk, the approximate cumulative doses with increased probability for ototoxicity should be determined.

2.5.4. Conclusions on the clinical efficacy

Overall, it was concluded that Arikayce could result in a sustained post-treatment SCC, which is of undeniable clinical benefit, in approximately 1/8 patients. The fact that the month 6 on-treatment SCC rate was significantly higher in the ALIS group (65/224 vs. 10/112) was also taken into consideration but it was not possible to discern the clinical benefit that might be associated with such an event from the data provided.

Taking into account the difficulty in managing such patients, it was finally concluded that this modest benefit might suffice to support a very restricted approval for use that also reflected the concerns over the safety profile. Thus, the final indication statement is confined to: *Arikayce is indicated for the treatment of non-tuberculous mycobacterial (NTM) lung infections caused by Mycobacterium avium Complex (MAC) in adults with limited treatment options who do not have cystic fibrosis. See sections 4.2, 4.4 and 5.1.*

This wording reflects the fact that patients entering INS-212 had MAC, did not have CF and had received variable prior treatments without achieving or sustaining SCC. The data from INS-212 did not allow

conclusions on efficacy in subgroups such that a more specific wording directing patient selection was deemed to be possible.

The need to use Arikayce as part of a combination regimen, along with information on stopping treatment and maximum duration of treatment, has been reflected in section 4.2.

2.6. Clinical safety

- In the prior application the focus of the safety assessment was on the comparison between ALIS and placebo (empty liposomes) in the NTM patients enrolled into TR02-112, which clearly showed that amikacin *per se* is a bronchial irritant.
- In the current application the safety data from NTM/MAC patients who received ALIS in any of TR02-112, INS-212 and INS-312 were pooled and compared with those who received placebo (empty liposomes) in TR02-112 or MDR alone in INS-212.
- A second pooled analysis population included data from all studies in which patients with any of NTM/MAC, CF or bronchiectasis received multiple doses of ALIS.

Patient exposure

In the ALIS group of the NTM population, all 404 subjects (100%) received ALIS dosing at 590 mg. Note that the applicant denotes all controls as "placebo" in the tables that follow but there was no placebo used in INS-212 (controls had MDR alone).

Table 20: Exposure to study drug

	NTM Lung Infection		Safety Population	
	ALIS	Placebo	ALIS	Placebo
Variable	N = 404	N = 157	N = 818	N = 212
Mean (SD), days	267 (183)	197 (97)	229 (177)	153 (112)
Median (maximum[a]), days	237 (626)	239 (744)	191 (786)	174 (744)
Total exposure (subject years)	295.0	84.5	513.1	88.6
Subject years on-study	326.7	86.5	770.5	94.8

[a] Minimum duration of exposure in all groups was 1 day.

Adverse events

Table 21: Summary of treatment emergent adverse event (NTM studies)

Study:	TR02-112				INS-212				INS-312		INS-212 + INS-312	
	ALIS N = 91		Placebo N = 45		ALIS N = 223		Placebo N = 112		ALIS N = 163		ALIS N = 313	
Type of TEAE	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Any	**89**	**(97.8)**	**39**	**(86.7)**	**219**	**(98.2)**	**102**	**(91.1)**	**158**	**(96.9)**	**311**	**(99.4)**
Serious	17	(18.7)	4	(8.9)	45	(20.2)	23	(20.5)	52	(31.9)	92	(29.4)
Leading to discontinuation	26	(28.6)	–	–	42	(18.8)	–	–	28	(17.2)	70	(22.4)
Leading to drug interruption	31	(34.1)	4	(8.9)	106	(47.5)	–	–	61	(37.4)	160	(51.1)
Pulmonary exacerbation	49	(53.8)	10	(22.2)	43	(19.3)	15	(13.4)	30	(18.4)	69	(22.0)
Related	64	(70.3)	16	(35.6)	185	(83.0)	–	–	105	(64.4)	266	(85.0)
Maximum CTCAE grade:												
1 (mild)	21	(23.1)	24	(53.3)	72	(32.3)	45	(40.2)	43	(26.4)	77	(24.6)
2 (moderate)	50	(54.9)	10	(22.2)	101	(45.3)	40	(35.7)	63	(38.7)	141	(45.0)
3 (severe)	17	(18.7)	5	(11.1)	29	(13.0)	9	(8.0)	42	(25.8)	67	(21.4)
4 (life-threatening)	–	–	–	–	11	(4.9)	–	–	4	(2.5)	14	(4.5)
5 (death)	1	(1.1)	–	–	6	(2.7)	8	(7.1)	6	(3.7)	12	(3.8)

In the NTM population, AEs and AEs considered related to study treatment were reported more often in patients who received ALIS. AEs leading to discontinuation or interruption were also more likely to occur in ALIS-treated patients and greater proportions in the ALIS group had SAEs and/or experienced AEs of highest maximum CTCAE Grade ≥ 3. AEs in NTM patients with a difference in incidence of ≥ 10 percentage points between treatment groups within any individual study are shown below.

Table 223: Treatment-emergent adverse events by MdeDRA preferred term with difference ≥ 10 percentage points between groups (NTM studies)

Study:	TR02-112				INS-212				INS-312		INS-212 + INS-312	
	ALIS N = 91		Placebo N = 45		ALIS N = 223		Placebo N = 112		ALIS N = 163		ALIS N = 313	
MedDRA PT	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Infective exacerbation of bronchiectasis	37	(40.7)	9	(20.0)	19	(8.5)	8	(7.1)	18	(11.0)	35	(11.2)
Infective pulmonary exacerbation of cystic fibrosis	12	(13.2)	1	(2.2)	–	–	–	–	–	–	–	–
Nasopharyngitis	4	(4.4)	–	–	12	(5.4)	8	(7.1)	17	(10.4)	28	(8.9)
Cough	23	(25.3)	6	(13.3)	85	(38.1)	17	(15.2)	41	(25.2)	123	(39.3)
Dysphonia	36	(39.6)	3	(6.7)	104	(46.6)	2	(1.8)	44	(27.0)	145	(46.3)
Dyspnoea	7	(7.7)	1	(2.2)	48	(21.5)	10	(8.9)	25	(15.3)	72	(23.0)
Oropharyngeal pain	15	(16.5)	1	(2.2)	24	(10.8)	2	(1.8)	9	(5.5)	32	(10.2)

AEs in the total safety population with a difference between treatment groups within either population of ≥ 5 percentage points are shown below.

Table 43: Treatment-emergent adverse event by MedDRA PT (≥ 5% of subjects in any group)

	NTM Lung Infection				Safety Population			
	ALIS N = 404		Placebo N = 157		ALIS N = 818		Placebo N = 212	
Preferred term	n	(%)	n	(%)	n	(%)	n	(%)
Tinnitus	28	(6.9)	3	(1.9)	31	(3.8)	5	(2.4)
Diarrhoea	45	(11.1)	7	(4.5)	70	(8.6)	8	(3.8)
Nausea	49	(12.1)	9	(5.7)	65	(7.9)	10	(4.7)
Fatigue	59	(14.6)	12	(7.6)	71	(8.7)	14	(6.6)
Infective exacerbation of bronchiectasis	72	(17.8)	17	(10.8)	72	(8.8)	17	(8.0)
Infective pulmonary exacerbation of cystic fibrosis	12	(3.0)	1	(0.6)	207	(25.3)	1	(0.5)
Nasopharyngitis	32	(7.9)	8	(5.1)	121	(14.8)	11	(5.2)
Rhinitis	8	(2.0)	–	–	41	(5.0)	–	–
Cough	146	(36.1)	23	(14.6)	217	(26.5)	29	(13.7)
Dysphonia	181	(44.8)	5	(3.2)	233	(28.5)	5	(2.4)
Dyspnoea	79	(19.6)	11	(7.0)	103	(12.6)	16	(7.5)
Haemoptysis	76	(18.8)	21	(13.4)	141	(17.2)	24	(11.3)
Oropharyngeal pain	47	(11.6)	3	(1.9)	77	(9.4)	3	(1.4)

Among AEs shown above, those that were clearly more common in ALIS patients included cough, dysphonia, dyspnoea, haemoptysis and oropharyngeal pain. In the NTM population, additional AEs that were more common in the ALIS patients included tinnitus, diarrhoea, nausea, fatigue and infective exacerbation of bronchiectasis.

In INS-212, most AEs were Grade 1 and Grade 2. Much of the difference between treatments was due to AEs affecting the respiratory tract.

In TR02-112 72.7% ALIS vs. 37.8% placebo patients reported treatment-related AEs. The difference mainly reflected dysphonia, cough, oropharyngeal pain and infective exacerbation of bronchiectasis.

Table 24: Treatment-related TEAEs (≥ 2 patients) in the double-blind phase of TR02-112 (Safety Population)

	ALIS 590 mg QD (N=44)				Placebo (N=45)		
System Organ Class MedDRA Preferred Term Version 15.0	**n**	**%**	**events**		**n**	**%**	**events**
Number (%) of patients with at least 1 treatment-emergent adverse event related to study drug	32	(72.7)	95		17	(37.8)	27
Respiratory, thoracic and mediastinal disorders	25	(56.8)	52		11	24.4)	13
Dysphonia	16	(36.4)	22		4	(8.9)	4
Cough	12	(27.3)	12		3	(6.7)	3
Oropharyngeal pain	7	(15.9)	7		0		0
Dyspnoea	2	(4.5)	2		1	(2.2)	1
Bronchospasm	0		0		2	(4.4)	2
Haemoptysis	2	(4.5)	2		0		0
Infections and infestations	8	(18.2)	10		1	(2.2)	1
Infective exacerbation of bronchiectasis	5	(11.4)	6		0		0
Laryngitis	3	(6.8)	3		0		0
Ear and labyrinth disorders	5	(11.4)	7		2	(4.4)	2
Ear pain	2	(4.5)	2		0		0
General disorders and administration site conditions	6	(13.6)	7		1	(2.2)	2
Fatigue	4	(9.1)	4		1	(2.2)	1
Chest discomfort	3	(6.8)	3		0		0
Gastrointestinal disorders	3	(6.8)	5		2	(4.4)	2
Dry mouth	2	(4.5)	2		0		0
Nervous system disorders	4	(9.1)	6		1	(2.2)	1
Aphonia	2	(4.5)	2		0		0

In INS-212 the investigator assessment of relatedness was confined to ALIS. The vast majority of ALIS patients had TEAEs deemed to be related to ALIS (185/224; 83.0%). The most common TEAEs considered related to ALIS were in the Respiratory, Thoracic and Mediastinal Disorders SOC (163; [73.1%]), including dysphonia (99 [44.4%]), cough (74 [33.2%]), dyspnoea (38 [17.0%]), haemoptysis (25 [11.2%]) and oropharyngeal pain (19 [8.5%]).

In NTM studies 404 patients treated with ALIS were observed (on study) for a cumulative 326.7 patient-years. This compares with 157 controls observed for a cumulative 86.5 patient-years. When analysed by numbers experiencing TEAEs per 100 patient-years of exposure, the rates of discontinuations, interruptions, pulmonary exacerbations and severe AEs were still higher with ALIS.

In the NTM population, some notable differences between the treatment groups (higher rate with ALIS) were observed as summarised below.

Table 25: Adverse events by MedDRA SMQ in pooled populations

	NTM Lung Infection				Safety Population			
	ALIS N = 404		Placebo N = 157		ALIS N = 818		Placebo N = 212	
SMQ	n	(%)	n	(%)	n	(%)	n	(%)
Acute renal	15	(3.7)	4	(2.5)	16	(2.0)	4	(1.9)
Hearing impairment	51	(12.6)	12	(7.6)	58	(7.1)	14	(6.6)
Hypersensitivity	115	(28.5)	28	(17.8)	178	(21.8)	38	(17.9)
Interstitial lung disease	15	(3.7)	4	(2.5)	16	(2.0)	4	(1.9)
Respiratory failure	20	(5.0)	5	(3.2)	23	(2.8)	5	(2.4)
Vestibular disorders	34	(8.4)	5	(3.2)	45	(5.5)	8	(3.8)

An exposure-adjusted analysis of these events indicated that there was still an excess of vestibular disorders (including vertigo, dizziness and balance disorder).

AESIs

Within the NTM population, the proportions with AESIs were higher in the ALIS group for all categories.

Table 56: Adverse events of special interest

	NTM Lung Infection				Safety Population			
	ALIS N = 404		Placebo N = 157		ALIS N = 818		Placebo N = 212	
AESI Group	n	(%)	n	(%)	n	(%)	n	(%)
Other respiratory	295	(73.0)	58	(36.9)	466	(57.0)	79	(37.3)
Bronchospasm	110	(27.2)	17	(10.8)	177	(21.6)	24	(11.3)
Infective exacerbation of underlying disease	109	(27.0)	23	(14.6)	305	(37.3)	23	(10.8)
Hemoptysis	76	(18.8)	21	(13.4)	141	(17.2)	24	(11.3)
Ototoxicity	72	(17.8)	16	(10.2)	84	(10.3)	20	(9.4)
Exacerbation of COPD	29	(7.2)	6	(3.8)	30	(3.7)	6	(2.8)
Nephrotoxicity	17	(4.2)	4	(2.5)	19	(2.3)	5	(2.4)
Allergic alveolitis	13	(3.2)	2	(1.3)	13	(1.6)	2	(0.9)
Neuromuscular	12	(3.0)	1	(0.6)	12	(1.5)	1	(0.5)

When AESI rates in NTM patients were adjusted for duration of exposure, rates were still higher with ALIS except for haemoptysis. The risk of allergic alveolitis in NTM patients is summarised in more detail in the table below.

Table 27: Characterisation of risk of treatment-emergent adverse events of special interest category – Alveolitis allergic – multiple dose studies – safety population - frequency

	Indication: NTM Lung Infection	
	Amikacin liposome inhalation suspension* (N=404) [SYE=327] n (%) [IR] {95% CI}	Placebo (N=157) [SYE=87] n (%) [IR] {95% CI}
Frequency		
Any TEAE	13 (3.2%) [4.0] { 2.1, 6.8}	2 (1.3%) [2.3] { 0.3, 8.4}
Any Serious TEAE	9 (2.2%) [2.8] { 1.3, 5.2}	2 (1.3%) [2.3] { 0.3, 8.4}

Data presented through the cutoff date (25 OCT 2018) for ongoing study INS-212.

Most cases (9/13 in the ALIS group) were known to have resolved after stopping treatment and administration of steroids. Most were Grade 2 or 3 in severity and none was fatal in ALIS patients.

In the NTM population with AEs in the SOC of ear and labyrinth disorders, the higher AE incidence in the ALIS group (16.6% vs. 9.6%) was driven mainly by tinnitus (see first table below).

During the procedure, it was clarified that the majority of patients who had any AESI had only one such event. Nine (2.2%) ALIS patients had more than one AESI and one patient had 3 but the timing of these events generally did not suggest onset at similar times during treatment (see second table below).

Table 28: Treatment-emergent adverse events in MedDRA SOC of ear and labyrinth disorders (≥ 1.5 percentage points difference between groups within either population)

	NTM Lung Infection				Safety Population			
	ALIS N = 404		Placebo N = 157		ALIS N = 818		Placebo N = 212	
Preferred term within SOC	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Any within SOC	**67**	**(16.6)**	**15**	**(9.6)**	**80**	**(9.8)**	**17**	**(8.0)**
Tinnitus	28	(6.9)	3	(1.9)	31	(3.8)	5	(2.4)
Deafness	8	(2.0)	–	–	8	(1.0)	–	–
Ear discomfort	7	(1.7)	–	–	8	(1.0)	–	–

Table 29: Patients with at least 1 type of selected treatment-emergent adverse events of special interest (NTM lung infection population)

Category or Preferred Term of Special Interest	ALIS N = 404		Placebo N = 157	
	n	(%)	n	(%)
Overall:				
None of the Selected AESIs	301	(74.5)	138	(87.9)
Any 1 of the Selected AESIs	93	(23.0)	15	(9.6)
Ototoxicity	72	(17.8)	16	(10.2)
Nephrotoxicity	17	(4.2)	4	(2.5)
Allergic Alveolitis	13	(3.2)	2	(1.3)
Neuromuscular Toxicity	12	(3.0)	1	(0.6)
Any 2 of the Selected AESIs	9[a]	(2.2)	4	(2.5)
Any 3 of the Selected AESIs	1	(0.2)	0	(0)
All 4 of the Selected AESIs	0	(0)	0	(0)
AESI Combinations:				
Ototoxicity and Nephrotoxicity	2	(0.5)	3	(1.9)

Serious adverse event/deaths/other significant events

Deaths

The overall incidence of AEs with an outcome of death was not higher in the ALIS group.

In the NTM population, the exposure-adjusted death rate was lower in the ALIS group (3.96 deaths per 100 patient-years) than in the placebo group (9.25 deaths per 100 patient-years). Corresponding rates in the overall safety population were 1.81 vs. 8.44 deaths per 100 patient-years. None of the TEAEs with an outcome of death were considered related to the study medication.

Table 30: Treatment-emergent adverse events with outcome of death

	NTM Lung Infection				Safety Population			
	ALIS		Placebo		ALIS		Placebo	
	N = 404		N = 157		N = 818		N = 212	
Preferred term	n	(%)	n	(%)	n	(%)	n	(%)
Any	13	(3.2)	8	(5.1)	14	(1.7)	8	(3.8)
COPD	3	(0.7)	–	–	3	(0.4)	–	–
Respiratory failure	2	(0.5)	2	(1.3)	2	(0.2)	2	(0.9)
Cachexia	1	(0.2)	1	(0.6)	1	(0.1)	1	(0.5)
Pneumonia	1	(0.2)	1	(0.6)	1	(0.1)	1	(0.5)
Lower respiratory tract infection	1	(0.2)	–	–	1	(0.1)	–	–
Lung infection	1	(0.2)	–	–	1	(0.1)	–	–
Acute respiratory distress syndrome	1	(0.2)	–	–	1	(0.1)	–	–
Acute respiratory failure	1	(0.2)	–	–	1	(0.1)	–	–
Mycobacterium avium complex infection	–	–	1	(0.6)	–	–	1	(0.5)
Pneumothorax	1	(0.2)	–	–	1	(0.1)	–	–
Pulmonary embolism	1	(0.2)	–	–	1	(0.1)	–	–
Pulmonary fibrosis	1	(0.2)	–	–	1	(0.1)	–	–
Cardiac failure	–	–	–	–	1	(0.1)	–	–
Infective pulmonary exacerbation of cystic fibrosis	–	–	–	–	1	(0.1)	–	–
Cardiogenic shock	–	–	1	(0.6)	–	–	1	(0.5)
Hypercapnic coma	–	–	1	(0.6)	–	–	1	(0.5)
Interstitial lung disease	–	–	1	(0.6)	–	–	1	(0.5)

SAEs

In the NTM population, SAEs were more commonly reported in the ALIS group (109; 27.0%) than in the placebo group (27; 17.2%). This pattern was also observed in the safety population.

In the NTM population, in the SOC of respiratory, thoracic and mediastinal disorders, SAEs were reported for 47 (11.6%) ALIS vs. 14 (8.9%) control group patients. In the NTM population, in the SOC of infections and infestations, SAEs were reported for 51 (12.6%) ALIS vs. 9 (5.7%) controls.

Table 31: Treatment-emergent SAEs by MedDRA PT (≥ 2% in any group)

	NTM Lung Infection				Safety Population			
	ALIS		Placebo		ALIS		Placebo	
	N = 404		N = 157		N = 818		N = 212	
MedDRA PT	n	(%)	n	(%)	n	(%)	n	(%)
Any	**109**	**(27.0)**	**27**	**(17.2)**	**233**	**(28.5)**	**33**	**(15.6)**
Infective exacerbation of bronchiectasis	11	(2.7)	4	(2.5)	11	(1.3)	4	(1.9)
Infective pulmonary exacerbation of cystic fibrosis	7	(1.7)	–	–	100	(12.2)	–	–
Pneumonia	16	(4.0)	4	(2.5)	17	(2.1)	5	(2.4)
Chronic obstructive pulmonary disease	13	(3.2)	3	(1.9)	14	(1.7)	3	(1.4)
Haemoptysis	10	(2.5)	5	(3.2)	13	(1.6)	5	(2.4)

Laboratory findings

Individual clinically significant changes

The incidence of potentially clinically meaningful hepatobiliary laboratory values after baseline was low (<3.5% in any group of either population). In the safety population, there were higher rates for the ALIS group, which the applicant ascribes to the effect of data from CF patients.

Table 32: Potentially clinically meaningful hepatobiliary laboratory values (any after baseline)

		NTM Lung Infection				Safety Population			
		ALIS		Placebo		ALIS		Placebo	
	Meaningfulness	N = 404		N = 157		N = 818		N = 212	
Variable	Criterion	n	(%)	n	(%)	n	(%)	n	(%)
ALT	> 3× ULN	3	(0.7)	1	(0.6)	28	(3.4)	2	(0.9)
AST	> 3× ULN	1	(0.2)	1	(0.6)	15	(1.8)	2	(0.9)
ALP	> 2× ULN	6	(1.5)	3	(1.9)	29	(3.5)	5	(2.4)
Albumin	< 3 g/dL	8	(2.0)	1	(0.6)	12	(1.5)	3	(1.4)
Bilirubin	≥ 2× ULN	–	–	–	–	9	(1.1)	–	–

The table below shows potentially clinically meaningful renal laboratory values after baseline. Increases in serum creatinine from baseline to worst on treatment by either > 0.3 mg/dL or 50% were more commonly observed in the ALIS group but there were no noteworthy differences in proportions with a worst on-treatment eGFR of < 60 mL/min in either pooled population.

Table 33: Potentially clinically meaningful renal function values (any after baseline)

		NTM Lung Infection				Safety Population			
		ALIS		Placebo		ALIS		Placebo	
	Meaningfulness	N = 404		N = 157		N = 818		N = 212	
Variable	Criterion	n	(%)	n	(%)	n	(%)	n	(%)
Serum creatinine increase (from baseline)	50% or > 0.3 mg/dL	17	(4.2)	3	(1.9)	63	(7.7)	12	(5.7)
Serum creatinine	> 2× ULN	–	–	–	–	2	(0.2)	–	–
eGFR (Cockroft-Gault)	< 60 mL/min	2	(0.5)	3	(1.9)	2	(0.2)	3	(1.4)
eGFR (Schwartz)	< 60 mL/min/1.73 m²	–	–	–	–	4	(0.5)	–	–
eGFR (IBW)	< 60 mL/min	26	(6.4)	10	(6.4)	28	(3.4)	10	(4.7)
eGFR	< 60 mL/min	124	(30.7)	42	(26.8)	124	(15.2)	42	(19.8)

The overall incidence of shifts in hepatobiliary or chemistry parameters was low and there were no noteworthy differences between treatment groups. The incidence of shifts from normal at baseline to levels potentially of concern at 6 months for renal variables did not suggest an effect of ALIS on renal function. For haematology variables low leukocyte counts occurred more often in NTM patients treated with ALIS (17; 4.2%) vs. controls (4; 2.5%). Similarly, low neutrophil counts were reported for 9 (2.2%) vs. 1 (0.6%).

Safety in special populations

In the NTM population, SAEs overall were more commonly reported in men (36.8% in the ALIS group) than in women (23.5% in the ALIS group).

Incidence of Serious Treatment-Emergent Adverse Events
By Sex
NTM Studies
Safety Population

System Organ Class Preferred Term	Subgroup	TR02-112 ALIS# (N=91)	TR02-112 Placebo* (N=45)	INS-212 ALIS# (N=223)	INS-212 Placebo** (N=112)	INS-312 ALIS# (N=163)	INS-212 + INS-312 ALIS# (N=313)	Total NTM ALIS# (N=404)	Total NTM Placebo$ (N=157)
Male (Total)		12 (13.2%)	5 (11.1%)	58 (26.0%)	44 (39.3%)	58 (35.6%)	94 (30.0%)	106 (26.2%)	49 (31.2%)
Female (Total)		79 (86.8%)	40 (88.9%)	165 (74.0%)	68 (60.7%)	105 (64.4%)	219 (70.0%)	298 (73.8%)	108 (68.8%)
At Least One	Male	5 (41.7%)	0	18 (31.0%)	11 (25.0%)	16 (27.6%)	34 (36.2%)	39 (36.8%)	11 (22.4%)
	Female	12 (15.2%)	4 (10.0%)	27 (16.4%)	12 (17.6%)	36 (34.3%)	58 (26.5%)	70 (23.5%)	16 (14.8%)

However, as shown in the ISS table above, the overall difference was driven by the two comparative studies since the SAE rate was lower in males during INS-312. Also, the SAE rate was higher in males in the MDR alone group in INS-212 (in which males accounted for 26% of ALIS and 39% of the control group) but this was not seen in the placebo group in TR02-112 (where only 11-13% of the total enrolled was male). Review of the distribution of SAEs by SOC/PT did not reveal any single explanation for the overall differences.

Deaths were also more commonly reported in men than women in NTM studies (5.7% vs. 2.3% in the ALIS-treated patients) but the difference was greater in the placebo group (12.2% vs. 1.9%). The overall differences were driven by INS-212 but review of the fatal AEs by gender did not identify any individual differences by SOC/PT that resulted in the overall difference.

Immunological events

See above re total rates of "hypersensitivity" AEs, at least some of which may have been instances of bronchospasm. However, the rates for rashes were higher with ALIS in both safety populations.

Table 34: Treatment-emergent adverse events in MedDRA SOC of skin and subcutaneous disorders (≥ 1.5 percentage points difference between groups within either population)

	NTM Lung Infection				Safety Population			
	ALIS		Placebo		ALIS		Placebo	
	N = 404		N = 157		N = 818		N = 212	
Preferred term within SOC	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Any within SOC	**77**	**(19.1)**	**21**	**(13.4)**	**104**	**(12.7)**	**25**	**(11.8)**
Dermatitis	1	(0.2)	3	(1.9)	2	(0.2)	3	(1.4)
Pruritus	10	(2.5)	4	(2.5)	11	(1.3)	6	(2.8)
Rash	14	(3.5)	1	(0.6)	20	(2.4)	2	(0.9)

Discontinuation due to adverse events

In the NTM population, AEs leading to discontinuation were reported in 96 (23.8%) in the ALIS group vs. none in the placebo group. Almost half of AEs leading to discontinuation were within the SOC of respiratory, thoracic and mediastinal disorders. The most commonly reported MedDRA PT was dyspnoea, in 12 (3.0%) patients. In INS-212 it seems that only one ALIS patient discontinued due to drug hypersensitivity.

In the NTM population, AEs leading to interruption were reported in 191 (47.3%) ALIS patients vs. 4 (2.5%) in the placebo group (in TR02-112).

Table 35: Treatment-emergent adverse events leading to discontinuation by MedDRA PT (≥ 1.5% in any group)

	NTM Lung Infection				Safety Population			
	ALIS N = 404		Placebo N = 157		ALIS N = 818		Placebo N = 212	
Preferred term	n	(%)	n	(%)	n	(%)	n	(%)
Infective exacerbation of bronchiectasis	7	(1.7)	–	–	7	(0.9)	–	–
Infective pulmonary exacerbation of cystic fibrosis	5	(1.2)	–	–	22	(2.7)	–	–
Cough	6	(1.5)	–	–	8	(1.0)	–	–
Dysphonia	7	(1.7)	–	–	10	(1.2)	–	–
Dyspnoea	12	(3.0)	–	–	16	(2.0)	–	–

The majority of AEs leading to interruption of ALIS were within the SOC of respiratory, thoracic and mediastinal disorders (127 [31.4%]) followed by AEs in the SOC of infections and infestations (49 [12.1%]). The most commonly reported MedDRA PT was dysphonia in 59 (14.6%).

Within INS-212106/223 (47.5%) of ALIS patients had a drug interruption. In 72 cases this was due to AEs within the respiratory system, most often dysphonia, dyspnoea and cough. Six had an interruption due to tinnitus and 2 due to rash.

Table 36: Treatment-emergent adverse events leading to interruption by MedDRA PT (≥ 1.5 % in any group)

	NTM Lung Infection				Safety Population			
	ALIS N = 404		Placebo N = 157		ALIS N = 818		Placebo N = 212	
Preferred term	n	(%)	n	(%)	n	(%)	n	(%)
Any	191	(47.3)	4	(2.5)	228	(27.9)	4	(1.9)
Tinnitus	9	(2.2)	-	-	9	(1.1)	-	-
Nausea	6	(1.5)	-	-	8	(1.0)	-	-
Fatigue	11	(2.7)	-	-	11	(1.3)	-	-
Infective exacerbation of bronchiectasis	12	(3.0)	1	(0.6)	12	(1.5)	1	(0.5)
Infective pulmonary exacerbation of cystic fibrosis	5	(1.2)	-	-	24	(2.9)	-	-
Laryngitis	6	(1.5)	-	-	6	(0.7)	-	-
Pneumonia	6	(1.5)	1	(0.6)	6	(0.7)	1	(0.5)
Aphonia	6	(1.5)	-	-	6	(0.7)	-	-
Headache	8	(2.0)	-	-	9	(1.1)	-	-
Chronic Obstructive Pulmonary Disease	10	(2.5)	-	-	10	(1.2)	-	-
Cough	31	(7.7)	-	-	33	(4.0)	-	-
Dysphonia	59	(14.6)	-	-	59	(7.2)	-	-
Dyspnoea	27	(6.7)	-	-	30	(3.7)	-	-
Haemoptysis	16	(4.0)	-	-	22	(2.7)	-	-
Oropharyngeal pain	10	(2.5)	-	-	10	(1.2)	-	-

Post marketing experience

ALIS was granted accelerated approval by the FDA on 28 September 2018 for the *treatment of MAC in adults as part of a combination antibacterial drug regimen in patients who do not achieve negative sputum cultures after a minimum of 6 consecutive months of a multidrug background regimen therapy*.

There is an *Arikares patient support programme* in operation in the US and most reports seem to have come via this system.

Post-marketing safety data from 28 September 2018 to 31 December 2019 were provided during the procedure. There was an emerging safety issue for hypersensitivity and anaphylactic reactions that has been reflected in the final SmPC.

2.6.1. Discussion on clinical safety

Safety database

The critical data come from the NTM/MAC patients exposed during randomised comparative phases in INS-212 (223; since 1/224 was not treated) and TR02-112 (44). The total NTM/MAC patients exposed includes another 90 initially randomised to MDR alone in INS-212 who opted to enrol in INS-312 and 43 from the initial placebo group in TR02-112 who opted to receive open-label ALIS in the extension phase. These numbers give a total of 400 NTM/MAC patients exposed to ALIS, to which the applicant added the 4 patients who enrolled in the scintigraphy sub-study and continued on ALIS for 3 months.

Safety in comparative phases

When reviewing the tables, it is important to note that the applicant denotes 157 NTM patients as being in the "placebo" group. This number comprises 45 assigned to placebo (empty liposomes) in the randomised phase of TR02-112 (43 of whom later received ALIS in the open-label phase) plus 112 patients in the MDR alone group in INS-212, 90 of whom opted to receive ALIS in INS-312. Thus, the AEs listed for the NTM "placebo" group would have been captured only during the comparative phases. In INS-212, any comparisons between treatments after month 8 are limited by the fact that only 65 in the ALIS group and 10 in the MDR group were allowed to continue on study.

Adverse event profile

The new data from INS-212 and from those who initiated ALIS in INS-312 support the previous conclusions drawn from TR02-112 on the generally poor tolerability of Arikayce. Much, but not all, of the burden of total AEs, AEs related to treatment and severe AEs reflects airway intolerance and elicitation of lung reactions. Most patients who felt unable to continue with ALIS treatment due to AEs withdrew during the first 6 months; hence there were few withdrawals due to AEs in patients previously exposed to ALIS in INS-212 who chose to enter INS-312.

The additional data provide important information on the safety of longer-term exposure in NTM/MAC patients. The combined randomised and open-label phases of TR02-112 limited the maximum duration of exposure to 168 days. Some patients randomised to ALIS in INS-212 who switched to INS-312 at month 8 could have received a total of up to 20 months. Those who were randomised to ALIS in INS-212 and had SCC by month 6 (hence received 12 months after achieving SCC at latest at month 4) could have received up to 16 months (although the median was 7.8 months). The additional data point to aminoglycoside-related AEs that were not evident during shorter-term exposures in TR02-112 but emerged with longer-term exposures to relatively low serum levels of amikacin in INS-212.

Respiratory AEs

ALIS was associated with much higher rates of cough, dysphonia, dyspnoea, bronchospasm and oropharyngeal pain as well as exacerbations compared to placebo or to MDR alone. There were also higher rates of haemoptysis with ALIS. These AEs also explained much of the difference between treatments in total rates for AEs considered treatment related.

Allergic alveolitis was identified as a potential identified risk in the prior application. In the current application the applicant reports 13 cases in patients given ALIS (3.2%) and 2 in those who did not receive ALIS (1.3%). After correcting for duration of exposure, there remains an excess risk for

ALIS-treated patients. Discontinuation of ALIS with/without use of steroids has resolved most cases. The overall data also suggest a higher rate of interstitial lung disease in ALIS patients. In the ALIS group, 15 patients had an AE within the SMQ of ILD of which 12 were included in the 13 with allergic alveolitis.

Ototoxicity, nephrotoxicity and other possible aminoglycoside issues
Despite the low systemic exposures to amikacin, nephrotoxicity, tinnitus, hearing impairment and vestibular disorders were all more common with ALIS. Furthermore, neuromuscular AEs were common in ALIS-treated patients and it is possible that the higher rate of fatigue reported with ALIS could be associated with such issues. However, few patients had more than one AESI and generally few had overlapping events.

Although systemic availability of amikacin may be low, a risk of aminoglycoside-related AEs associated with the long duration of exposure cannot be ruled out. The applicant has provided several analyses of exposure-adjusted AE rates, including AESIs. In most instances these analyses still show a higher risk for ALIS. It should be noted that the marked differences in demographics between NTM/MAC and CF patients means that results for the pooled safety population are not reassuring.

In summary, current evidence points to a conclusion that chronic exposure (up to 20 months) to relatively low serum levels of amikacin constitutes a risk for developing aminoglycoside-related toxicities affecting the ear, kidney and neuromuscular system. The SmPC reflects the need to be vigilant for onset of such events and to consider stopping ALIS.

Other AEs
There were no cases of *Clostridioides difficile*-associated diarrhoea (CDAD) across the development programme but diarrhoea and nausea were considerably more common with ALIS, which may reflect the amount of amikacin that is deposited in the oropharynx and then swallowed. Low leukocyte counts occurred more often in NTM/MAC patients treated with ALIS (17; 4.2%) vs. controls (4; 2.5%). Similarly, low neutrophil counts were reported for 9 (2.2%) vs. 1 (0.6%).

Hypersensitivity
In order to assess AEs possibly representing hypersensitivity without the confounding of respiratory events, the SMQ of Hypersensitivity was re-analysed excluding terms in the SOC of Respiratory, Thoracic and Mediastinal Disorders. The incidence of hypersensitivity AEs was higher in the ALIS group (60 patients; 14.9%) than in the placebo group (17, 10.8%). The difference was due to the incidence of AEs in the SOC of Skin and Subcutaneous Tissue Disorders [42 (10.4%) patients in the ALIS group vs 11 (7.0%) in the placebo group], which was driven by rash. Rash was reported in 14 (3.5%) patients in the ALIS group compared to 1 (0.6%) patient in the MDR group and was considered related to study treatment in 5 (1.2%) patients in the ALIS group and no patients in the MDR group. Rash has been listed as a common ADR in the SmPC.

Furthermore, reflecting also the post-marketing safety data available, the SmPC reflects the potential risk for serious systemic hypersensitivity reactions to occur.

Deaths and SAEs
There was not an excess of deaths in patients exposed to ALIS. While the total SAE rates in NTM/MAC patients were higher for those exposed to ALIS, and while SAEs of the respiratory and infections SOCs predominated, most others occurred in very low numbers.

Discontinuations and interruptions due to AEs
Generally, the predominant AEs leading to discontinuations or interruptions were in the respiratory or infections SOCs or were potential aminoglycoside-related AEs. In the ALIS group, interruption of study treatment was reported in 110 (49%) of patients and interruption of ALIS was reported in 106 (48%) patients. Of patients with interruptions, 25 (23%) also had a treatment-emergent adverse event (TEAE)

leading to discontinuation. This was not meaningfully different from the proportion of patients without drug interruption with a TEAE leading to discontinuation (22/113; 19%). If all-cause discontinuations are considered, patients without interruptions completed the treatment at a little higher rate (73%) vs those who interrupted the treatment due to TEAEs (58%). In the ALIS group, patients with a treatment interruption had lower rates of sustainable conversion (at 12 months of treatment post conversion) and durable conversion (at the 3-month follow-up visit) than the patients who did not interrupt treatment.

2.6.2. Conclusions on the clinical safety

There are several concerns regarding the pulmonary (especially allergic alveolitis) and systemic toxicities (especially nephrotoxicity, ototoxicity and effects on neuromuscular conditions) that may be due to chronic exposure to amikacin. Nevertheless, it was considered that NTM patients are managed in specialised centres and that adequate SmPC contraindications and warnings could suffice to alert physicians. Thus, it appeared that the safety profile is manageable subject to adequate patient supervision by specialists in this field, as advised in section 4.2 of the SmPC.

Furthermore, the safety profile of Arikayce was taken into account when defining the final indication for use.

2.7. Risk Management Plan

Safety concerns

Important identified risks	Allergic alveolitis Ototoxicity Nephrotoxicity Impaired neuromuscular transmission
Important potential risks	None
Missing information	None

Pharmacovigilance plan

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection include specific adverse reaction follow-up questionnaires for all important identified risks: Allergic alveolitis; Ototoxicity; Nephrotoxicity; Impaired neuromuscular transmission.

Routine pharmacovigilance activities are considered sufficient to monitor the safety profile and the product and to monitor the effectiveness of the risk minimisations measures.

Risk minimisation measures

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Important identified risk: Allergic alveolitis	*Routine risk communication:* • Summary of Product Characteristics (SmPC) section 4.4 and 4.8. • Package Leaflet (PL) section 2 and 4. *Routine risk minimisation activities recommending specific clinical measures to address the risk:* • SmPC section 4.4. Recommending treatment discontinuation and management as medically appropriate. *Other routine risk minimisation measures beyond the Product Information:* Legal status - Medicinal product subject to prescription. Treatment initiated and managed by physicians experienced in the treatment of the targeted population. *Additional risk minimisation measures:* Patient Alert Card	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* Specific adverse reaction follow-up questionnaire *Additional pharmacovigilance activities:* None

Important identified risk: Ototoxicity	*Routine risk communication:* • Summary of Product Characteristics (SmPC) section 4.4 and 4.8. • SmPC section 4.5. Interaction potential with other ototoxic medicines • Package Leaflet (PL) section 2 and 4. *Routine risk minimisation activities recommending specific clinical measures to address the risk:* • SmPC section 4.4. Recommending monitoring and potentially treatment discontinuation. *Other routine risk minimisation measures beyond the Product Information:* Legal status - Medicinal product subject to prescription. Treatment initiated and managed by physicians experienced in the treatment of the targeted population. *Additional risk minimisation measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* Specific adverse reaction follow-up questionnaire *Additional pharmacovigilance activities:* None

Important identified risk: Nephrotoxicity	*Routine risk communication:* • Summary of Product Characteristics (SmPC) section 4.3, 4.4, and 4.8. • SmPC section 4.5. Interaction potential with other nephrotoxic medicines • Package Leaflet (PL) section 2 and 4. *Routine risk minimisation activities recommending specific clinical measures to address the risk:* • SmPC section 4.3. Contraindicated in severe renal impairment. • SmPC section 4.4. Recommending close monitoring, potentially treatment discontinuation. *Other routine risk minimisation measures beyond the Product Information:* Legal status - Medicinal product subject to prescription. Treatment initiated and managed by physicians experienced in the treatment of the targeted population. *Additional risk minimisation measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* Specific adverse reaction follow-up questionnaire *Additional pharmacovigilance activities:* None

Important identified risk: Impaired neuromuscular transmission	*Routine risk communication:* • Summary of Product Characteristics (SmPC) section 4.4 and 4.8. • SmPC section 4.5. Interaction potential with other medicines • Package Leaflet (PL) section 2 and 4. *Routine risk minimisation activities recommending specific clinical measures to address the risk:* • SmPC section 4.4. Recommending close monitoring. Use in myasthenia gravis not recommended. *Other routine risk minimisation measures beyond the Product Information:* Legal status - Medicinal product subject to prescription. Treatment initiated and managed by physicians experienced in the treatment of the targeted population. *Additional risk minimisation measures:* None.	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* Specific adverse reaction follow-up questionnaire *Additional pharmacovigilance activities:* None

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

Based on the presence of important identified risks specific to the inhalatory administration, the CHMP is of the opinion that a separate entry in the EURD list for Arikayce liposomal is needed, as it cannot follow the already existing entry for amikacin. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request the alignment of the new PSUR cycle with the international birth date 28.09.2018. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

During assessment of the MAA, the CHMP requested a change of the invented name change as part of the Day 120 LoQ. As part of their answers to the D120 LoQ, the applicant changed the product name into 'Arikayce liposomal', accordingly. This is in line with the EMA guidance and news from 31 July 2019.

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Not applicable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The proposed revised indication for Arikayce liposomal is for the treatment of non-tuberculous mycobacterial (NTM) lung infections caused by *Mycobacterium avium* Complex (MAC) in adults with limited treatment options who do not have cystic fibrosis.

Non-tuberculous mycobacterial (NTM) lung disease caused by MAC is associated with productive cough, shortness of breath, fatigue, lung function decline and mortality. MAC has been implicated in complications of debilitating lung diseases such as bronchiectasis or chronic obstructive pulmonary disease (COPD). Post-menopausal Caucasian women without apparent predisposing conditions have been reported with increasing frequency to have pulmonary disease associated with MAC.

The morbidity associated with NTM lung diseases is significant and has been reported in the literature to have a 5-year all-cause mortality risk ranging from 5.4% to 39.7%. In retrospective studies from the literature, the failure to achieve negative sputum cultures in patients with MAC lung disease has been associated with higher mortality rates. The 5-year mortality rate in one study was 33.3% for untreated MAC lung disease compared to 22.2% for treated MAC lung disease in patients with definite MAC lung disease. In the treated group, sputum culture conversion was 53.7% compared to 0% in the untreated group.

3.1.2. Available therapies and unmet medical need

There are no approved treatments specifically for NTM or for the subset with MAC lung disease in the EU. Treatment guidelines have been developed by the ATS/IDSA and the British Thoracic Society, which have since been adopted by various countries globally and incorporated into local guidelines. The current treatment of NTM lung disease is primarily with a multi-drug regimen (MDR) based on the treatment of tuberculosis. The recommendation for patients with MAC is a 3-drug regimen including a macrolide,

ethambutol and a rifamycin. Treatment is often for 12 to 18 months and selected based on clinical presentation and disease progression but may exceed 18 months.

Specifically, the ATS/IDSA guidelines recommend a 3 times weekly regimen of clarithromycin (1,000 mg) or azithromycin (500 mg), rifampicin (600 mg) and ethambutol (25 mg/kg) for most patients with nodular/bronchiectatic MAC lung disease. For patients with fibrocavitary MAC lung disease or severe nodular/bronchiectatic disease, a daily regimen of clarithromycin (500 to 1,000 mg) or azithromycin (250 mg), rifampicin (600 mg) or rifabutin (150 to 300 mg) and ethambutol (15 mg/kg) with consideration of 3 times weekly IV amikacin or streptomycin early in therapy is recommended. Patients should continue treatment for 12 months after sputum culture conversion (SCC) has been achieved.

The recently updated British Thoracic Society guideline on the management of NTM pulmonary disease provides treatment recommendations similar to the ATS/IDSA guidelines for the NTM species that most commonly fulfil the ATS/IDSA microbiologic criteria for NTM pulmonary disease within the UK, namely MAC, *M. kansasii*, *M. malmoense*, *M. xenopi* and *M. abscessus* complex. The guidance is based on five randomised controlled studies and several non-comparative studies involving individuals (not known to be HIV-positive) with MAC identified in the literature.

More recently, guidance was published recommending addition of ALIS to treatment in patients who have failed to respond after 6 months.

The stated aim of treatment is to achieve 12 months of negative sputum cultures while on treatment. SCC on treatment has been reported to occur in the majority of patients without fibrocavitary disease if they complete a full course of guideline-based treatment. In patients who experience treatment failure and/or have more severe underlying conditions such as fibrocavitary disease, it is more difficult to achieve SCC even with extended treatment, and alternative therapeutic options are limited.

3.1.3. Main clinical studies

The applicant conducted 3 studies in patients with NTM or specifically with MAC.

INS-212 is the single pivotal study to support the indication claimed since it was conducted in the target population of non-CF patients with chronic MAC lung disease and it prospectively followed-up patients eligible to stop all MAC treatment for a total of 12 months off therapy.

The original protocol had a pre-defined primary endpoint of SCC (based on 3 consecutive monthly negative cultures) by month 6 on treatment. Whilst there are some data to suggest that patients with chronic MAC lung disease who achieve on-treatment SCC are less likely to die within prescribed periods than those who do not, the evidence is neither consistent nor conclusive. In contrast, if treatment achieves sustained SCC, such that it is considered possible to stop all anti-MAC therapy after completing treatment for 12 months post-SCC, this would be a clear benefit to the patient since a) no further MAC-associated lung damage would be expected and b) the burden and side effects of treatment would be removed. Therefore, a separate statistical analysis plan was developed for the EU, following CHMP advice that the primary endpoint should be sustained SCC documented at least 3 months after stopping all treatment.

Other design issues that were not considered optimal by CHMP include the following:

- INS-212 was open-label and the possibility that the open-label design influenced the discontinuation or AE reporting rates cannot be dismissed.

- Patients were discontinued at month 8 if they had not had SCC confirmed by month 6. This means that the comparisons of longer-term and post-treatment sustained SCC rates between the initial

randomised treatment groups can be made only between the 65 ALIS and 10 control group patients who achieved SCC by month 6. Whilst the primary analysis is based on the entire ITT population, as advised by CHMP, the interpretation of this analysis rests on the assumption that the post-treatment sustained SCC rate in the patients initially assigned to MDR alone would have been zero if they had continued on MDR alone. Overall, in a population that had mostly received prior unsuccessful treatment for MAC for several years, and given the actual results for the 10 control group patients retained in the study after month 8, it is reasonable to assume that the post-treatment sustained SCC rate on MDR alone would have been zero or, at least, negligible.

- The definitions applied to on-treatment and post-treatment sustained SCC and relapse, which allowed for some broth cultures to have been positive, were not considered appropriate. Any positive culture (agar or broth) post SCC should be counted as a positive for the visit at which the sample was obtained since the result is evidence of residual MAC in the airways.

- Although patients were to have received at least 6 months of treatment for MAC, this could have consisted of only two agents and it could have been stopped < 12 months before screening. Overall, the study population was not confined to patients who had failed to respond to what could be considered an adequate treatment regimen for MAC and could be regarded as a mixture of inadequately treated (some of whom may have been non-adherent) and recalcitrant patients.

- There was no attempt to "optimise" the background multidrug (MDR) regimen at baseline.

INS-312 was an uncontrolled study in which patients enrolled into INS-212 who had failed to achieve SCC by month 6 or had relapsed within that period could elect to receive open-label ALIS for up to 12 months. The aim was to analyse safety and there was follow-up for only one month off-treatment. This study described SCC rates in those who persisted with ALIS or switched to ALIS but does not contribute to the overall understanding of the clinical benefit of adding ALIS to MDR.

TR02-112 did not allow conclusions to be drawn on the possible clinical benefit of ALIS. For example, the duration of the double-blind randomised phase was 84 days, after which patients could elect to receive open-label ALIS for another 84 days of treatment maximum and follow-up was not planned to formally assess efficacy. The study did provide placebo-controlled safety data over 12 weeks and it showed no clear microbiological effect or other benefit in patients with CF or species other than MAC. INS-212 excluded patients with non-MAC infections and those with CF.

3.2. Favourable effects

INS-212 met the pre-defined enrolment target to address the FDA-recommended primary endpoint. Based on the FDA-recommended primary endpoint, SCC by month 6 on treatment was achieved by 65/224 (29%) in the ALIS+MDR group and by 10/112 (8.9%) in the MDR alone group, a difference which reached significance. Only these 75 patients with SCC by month 6 then remained on study beyond month 8 and were to receive 12 months of treatment after SCC had been achieved.

At the time of the month 3 post-treatment visit (the pre-defined EU primary endpoint), and based on the applicant's definitions of continued negative cultures, sustained SCC (based on the ITT population, assuming zero for all 112 MDR alone patients if they had been retained on study) had been documented in 36/224 (16.1%) ALIS and 0/112 (0%) MDR alone patients, which reached significance. Overall, this rate means that ~1/6 patients who commenced ALIS had sustained SCC at month 3 off treatment. All of the 36 ALIS patients considered by the applicant to have post-treatment sustained SCC had initially

achieved SCC by 3 months on treatment and 32/36 had done so by month 2, which suggests that those who respond early are most likely to have a lasting benefit.

The findings also mean that 29 ALIS and all 10 MDR alone patients with on-treatment SCC by month 6 did not sustain SCC at month 3 off treatment. Furthermore, most of those who did not sustain SCC at month 3 off treatment had become culture positive while still on treatment, i.e. at month 12 post-SCC there were 41 ALIS and 3 MDR alone patients who still had SCC (44/75 of those with SCC by month 6).

In the final CSR, complete data are reported for the post-treatment follow-up visit at month 12. According to the applicant's rules, 30/224 (13.4%) in the ALIS + MDR arm vs. 0% in the MDR alone arm had sustained SCC conversion, which equates with about 1/7 of total patients assigned to ALIS.

INS-312 was uncontrolled and cannot support any conclusion drawn on clinical benefit.
However, it provided additional information on tolerability and SCC rates over time that added to information supporting the SmPC advice regarding when to consider stopping ALIS due to it being very unlikely that the individual patient will benefit from continuing treatment.

Firstly, most patients who cannot tolerate Arikayce will withdraw in the first 6 months. Thus, only 3/73 (4%) patients already exposed to ALIS in INS-212 discontinued from ALIS in INS-312 due to AEs vs. 20/90 (22%) not previously exposed. Far fewer patients previously exposed to ALIS achieved SCC in INS-312 while the rate of achieving SCC by month 6 on ALIS in previously unexposed patients was 24/90 (26.7%), very similar to the rate (29%) observed in the ALIS arm in INS-212.

Secondly, a small number of patients randomised to ALIS in INS-212 achieved SCC for the first time during INS-312. However, at end of treatment in INS-312 6/73 (8.2%) prior ALIS vs. 18/90 (20%) prior MDR patients had achieved and sustained SCC on treatment. There were no post-treatment visits beyond month 13 so the study cannot support the primary endpoint in INS-212.

3.3. Uncertainties and limitations about favourable effects

There is no good rationale for the daily dose or for once daily dosing. Since PK-PD analyses cannot be applied to dose-finding in this situation, the only way to select a dose would be from dose-finding studies, which would likely have to rely on an on-treatment SCC rate. The 12-month duration of treatment that was employed in INS-212 and is recommended in the SmPC after confirmed SCC is achieved is in line with recommendations from professional bodies.

Whilst the applicant reported a continued SCC in 36/224 and 30/224 vs. 0/112 at the 3-month and 12-month post-treatment visits, these rates are based on the applicant's counting schema, which is not entirely agreed. The applicant provided on request the serial culture data for 44 patients – 41 initially assigned to ALIS and 3 initially assigned to MDR alone – who had achieved SCC (as defined in the protocol) on treatment so continued in the study on their assigned treatment after month 8 and were solid culture negative at month 12. Of these 44, two were broth culture positive at month 12 and 6 did not have a result. Also, at end of treatment, one ALIS patient was solid culture positive and one MDR alone patient had no result.

Importantly, not all of these 44 patients had MAC cultured from their baseline (as opposed to screening visit) sputum specimen. There were 9 ALIS and 2 MDR patients with completely negative cultures on Day 1. Of these subjects, 6/9 ALIS and one of the 2 MDR patients had no post-baseline positive solid or broth cultures. It cannot be ruled out that on-study treatment with ALIS+MDR or MDR alone made no difference to these 7 patients, leaving 35 and 1 that can be assessed.

Focussing on the 35 ALIS patients for whom an on-treatment SCC could therefore be assessed, and counting any solid or broth culture positive after SCC occurred as failure, there were 30 (13.4%) with sustained SCC at month 3 post-treatment. Similarly, counting any positive as failure, there were 25 (11%) patients with SCC through to Month 12 post-treatment.

In summary, whilst the applicant reports a post-treatment sustained SCC rate of 36/224 (16%) at month 3 and 30/224 (13.4%) at month 12, the Rapporteur's findings indicate rates of 30/224 (13.4%) and 25/224 (11%) at respective visits. Whilst one could argue about how certain patients have been counted by the applicant or by the Rapporteur, it remains the case that, at best, ~1/6 to ~1/10 patients who ever start on Arikayce might have a sustained SCC on treatment that is maintained after stopping all NTM treatment. Thus, the treatment benefit is, at best, modest.

Success rates were comparable for *M. avium* and *M. intracellulare* and, perhaps, may be lower for the unspeciated NTMs that were considered to fall within the MAC complex. Also, success rates were comparable for the US and Japan, where the majority was enrolled. In Europe, <10% of 48 patients had a sustained conversion compared to ~40% of the 24 enrolled in Oceania. However, these differences may have arisen by chance.

3.4. Unfavourable effects

The critical safety data come from the NTM/MAC patients exposed during randomised comparative phases in INS-212 (223; since 1/224 was not treated) and TR02-112 (44). The total NTM/MAC patients exposed includes another 90 initially randomised to MDR alone in INS-212 who opted to enrol in INS-312 and 43 from the initial placebo group in TR02-112 who opted to receive open-label ALIS in the extension phase. When including the scintigraphy sub-study patients, a total of 404 NTM/MAC patients were exposed to ALIS but the minority have been exposed for >8 months.

The data demonstrate the poor tolerability of Arikayce. Much, but not all, of the burden of total AEs, AEs related to treatment and severe AEs reflects airway intolerance and most patients who felt unable to continue with ALIS treatment due to AEs withdrew during the first few months on treatment. The additional data also provide important information on the safety of longer-term exposure of up to 20 months, which allows for an evaluation of the risk of aminoglycoside-related AEs that may emerge during chronic exposure to relatively low serum levels of amikacin.

Respiratory AEs

ALIS was associated with much higher rates of cough, dysphonia, dyspnoea, bronchospasm and oropharyngeal pain as well as exacerbations compared to placebo or to MDR alone. There were also higher rates of haemoptysis with ALIS. These AEs also explained much of the difference between treatments in total rates for AEs considered treatment-related.

Allergic alveolitis was documented in 13 patients given ALIS (3.2%) and 2 who did not receive ALIS (1.3%). After correcting for duration of exposure, there remains an excess risk for ALIS-treated patients. Discontinuation of ALIS and use of steroids has apparently resolved most cases. The time to onset of allergic alveolitis was variable but 8/13 cases had onset within the first 6 months.

Ototoxicity, nephrotoxicity and other possible aminoglycoside issues

Whilst most patients have relatively low plasma amikacin exposures when compared to parenteral dosing, there is chronic exposure to the agent during inhalational treatment. Nephrotoxicity, tinnitus, hearing impairment and vestibular disorders were all more common with ALIS. Furthermore, neuromuscular AEs were common in ALIS-treated patients and it is possible that the higher rate of fatigue reported with ALIS could be associated with such issues. The applicant clarified that most patients with

these potentially aminoglycoside-related AEs had only one such event. There were too few PK samples obtained to be able to investigate the relationship between such events and serum amikacin.

The applicant provided several analyses of exposure-adjusted AE rates, including AESIs. In most instances, these analyses still show a higher risk for ALIS. There was no clear relationship found between serum creatinine and any specific concomitant medications. However, it should be noted that the median (range) creatinine clearance in patients with NTM was 86.3 (63.3 to 140) mL/min/1.73 m^2 in TR02-112 and 88.4 (57.4 to 124) mL/min/1.73 m^2 in INS-212.

In summary, chronic exposure (up to 20 months) to relatively low serum levels of amikacin constitutes a risk for developing aminoglycoside-related toxicities.

Other AEs

Low leukocyte counts occurred more often in NTM/MAC patients treated with ALIS (17; 4.2%) vs. controls (4; 2.5%). Similarly, low neutrophil counts were reported for 9 (2.2%) vs. 1 (0.6%).

The assessment of AEs possibly representing hypersensitivity to amikacin is complicated by the fact that some respiratory AES could represent airway irritation rather than true hypersensitivity (e.g. bronchospasm). However, an analysis of non-respiratory AEs that could represent hypersensitivity reactions showed rates of 14.9% in the ALIS group vs. 10.8% in the placebo group, with a difference that reflected rash, which was reported in 14 (3.5%) patients in the ALIS group compared to 1 (0.6%) patient in the MDR group. Rash was considered related to study treatment in 5 (1.2%) patients in the ALIS group and no patients in the MDR group and it has been added as a common ADR in section 4.8 of the SmPC. Furthermore, based also on post-marketing experience, it was apparent that severe systemic hypersensitivity reactions can occur during use of ALIS, which has been reflected in the SmPC.

3.5. Uncertainties and limitations about unfavourable effects

The CSR for TR02-112, where treatment with ALIS or placebo was fixed at a maximum of 84 days, presented the safety data separately for the double-blind randomised phase. These data clearly showed that amikacin was per se a bronchial irritant. In INS-212, any comparisons between treatments after month 8 are limited by the fact that only 65 in the ALIS group and 10 in the MDR group were allowed to continue on study. On request, separate tabulations were provided for AEs for the ALIS+MDR vs. MDR alone groups only for the first 8 months of the study. This comparison strongly underlined the poor airway tolerability of Arikayce but it also showed higher rates of AEs with Arikayce in many other SOCs and for multiple specific non-respiratory PTs.

There have not been any cases of *Clostridioides difficile*-associated diarrhoea (CDAD) across the development programme but diarrhoea and nausea were considerably more common with ALIS, which may reflect the amount of amikacin that is deposited in the oropharynx and then swallowed.

Thus far, there has not been an excess of deaths in patients exposed to ALIS. There were higher rates for SAEs considered related to assigned treatment in NTM/MAC patients, mostly driven by respiratory events.

3.6. Effects table

Table 37: Effects table for Arikayce (data from INS-212 up to 25 October 2018)

Effect	Short Description	Unit	Treatment ALIS+MDR	Control MDR	Uncertainties/ Strength of evidence	References
Favourable Effects						
Sustained SCC at 3 months post-treatment	Can be estimated only in those with SCC by month 6	n/N (%)	36/224 (16.1%) 36/65 with SCC by month 6	0/112 (0%) 0/10 with SCC by month 6	All patients without SCC by month 6 were discontinued at month 8	INS-212
SCC by month 6 on therapy			65/224 (29.0%)	10/112 (8.9%)	Only these 75 patients were followed in INS-212	
Sustained SCC at 28 days, 6 and 12 months off treatment	As for primary analysis above		Day 28 37/224 (16.5%) Month 6 33/224 (14.7%) Month 12 30/224 (13.4%)	0 at each time point	The Rapporteur's count for the post-treatment visit at month 3 is 30/224 (13.4%) and at final visit at month 12 after treatment it is 25/224 (~11%).	
Unfavourable Effects						
AE rate		n/N (%)	400/404 (99%)	141/157 (89.8%)	Differences mainly reflect AEs mapping to the respiratory and infections SOCs, especially cough, dysphonia, dyspnoea and oropharyngeal pain	TR02-112, INS-212 and INS-312
AE related rate			330/400 (81.7%)	17/157 (10.8%)	Control rate is from the placebo-controlled TR02-112 (empty liposomes)	
SAE rate			109/400 (27%)	27/157 (17.2%)		
Moderate Severe			47.3% 20.8%	31.8% 8.9%		
Hypersensitivity Bronchospasm Haemoptysis Allergic alveolitis Ototoxicity Tinnitus Vestibular disorder Nephrotoxicity Neuromuscular Interstitial lung disease			28.5% 27.2% 18.8% 13 (3.2%) 17.8% 6.9% 10.4% 4.2% 3.0% 3.7%	17.8% 10.8% 13.4% 2 (1.3%) 10.2% 1.9% 5.8% 2.5% 0.6% 2.5%	Excess risk with ALIS mostly remains after correcting for duration of exposure Hypersensitivity may be confounded by bronchospasm rates, which may be irritant rather than allergic reactions	

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

There are no agents specifically licensed in the EU for treatment of chronic MAC lung disease but agents licensed or at least used to treat tuberculosis are widely used in combination. There is significant morbidity and mortality and some publications report that the latter is reduced by treatments that achieve SCC. However, the benefit of achieving on-treatment SCC remains uncertain and unquantified. In contrast, if SCC is sustained throughout and after stopping treatment there is a clear benefit to the patient since no further lung damage due to MAC would be expected and the burden of MAC treatment regimens is removed.

Current evidence suggests that approximately 1/8 patients who commence ALIS in addition to MDR will achieve and sustain SCC at month 3 after completing 12 months of treatment post-SCC. However, the rate may drop to 1/10 by month 12 post-treatment. Some of these patients may have a relapse while others may have a reinfection. It is not surprising that adding a single inhaled agent to patients who have failed to respond to prior treatment (but for a range of reasons) is not dramatically effective. Nevertheless, in a population that has already failed to respond to guideline-recommended first-line regimens, and in light of the serious nature of uncontrolled NTM, this modest benefit may be of importance to a select patient subset.

Treatment with Arikayce is accompanied by significant local tolerability and systemic safety issues. In the first months of treatment discontinuation rates due to AEs or patient decision is considerable. Thus, the current safety data also support use of Arikayce only in a very restricted patient group and under careful supervision of experts in the field of NTM management.

3.7.2. Balance of benefits and risks

Taking into account the modest efficacy of Arikayce in NTM/MAC patients and the safety profile, it was concluded that the benefit-risk relationship could be favourable only in patients who have limited treatment options as reflected in the final indication for use. Furthermore, usage should be under supervision of experts in the field and clear stopping rules are appropriate for section 4.2 of the SmPC.

3.7.3. Additional considerations on the benefit-risk balance

Lung squamous cell carcinomas were observed in 2 of 120 animals at study termination in the high dose group in the non-clinical carcinogenicity study conducted in rat. The applicant suggests that this finding is of questionable clinical relevance. However, the non-clinical data available are not sufficient to conclude on the clinical relevance of these findings and it is not foreseen that additional non-clinical studies will clarify this risk.

3.8. Conclusions

The overall B/R of Arikayce is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Arikayce liposomal is favourable in the following indication:

treatment of non-tuberculous mycobacterial (NTM) lung infections caused by Mycobacterium avium Complex (MAC) in adults with limited treatment options who do not have cystic fibrosis (see sections 4.2, 4.4 and 5.1).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

The MAH has developed a patient alert card which will be included in the outer carton. The wording of the alert card is part of the labelling - please see Annex III, A. LABELLING.

The purpose of the alert card is to inform patients that the use of Arikayce liposomal may be associated with the development of allergic alveolitis.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.