EU Risk Management Plan

for

ARIKAYCE liposomal 590 mg nebuliser dispersion

RMP version to be assessed as part of this application:	
RMP version number:	1.3
Data lock point for this RMP:	27-Sep-2024
Date of final sign off:	21-Nov-2024
Rationale for submitting an updated RMP:	
The RMP was updated to reclassify and remove the important identified risks of Ototoxicity, Nephrotoxicity, and Impaired neuromuscular transmission from the list of safety concerns based on a cumulative review of the relevant safety data obtained for these risks since the initial marketing approval in the EU on 27-Oct-2020 until the data lock point for this RMP on 27-Sep-2024, and in the context of the cumulative patient exposure to Arikayce liposomal in the clinical trial and post-marketing setting.	
Summary of significant changes in this RMP:	
This RMP update includes the following significant change: - Part II: Module SVII - Important identified risks of Ototoxicity, Nephrotoxicity, and Impaired neuromuscular transmission were removed from the list of safety concerns. This change was reflected in Parts III, V.1, V.3, and Annex 4 of the RMP, as applicable. Changes introduced to the body of document were reflected in Part VI of the RMP, as applicable.	
Other RMP versions under evaluation:	
RMP version number:	Not applicable
Submitted on:	Not applicable
Procedure number:	Not applicable
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Version number:	1.0
Approved with procedure:	EMEA/H/C/005264/0000
Date of approval (opinion date):	23-Jul-2020

QPPV name: Helle Tolstrup Myschetzky

The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV. The electronic signature is available on file.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

ADR	adverse drug reaction
AE	adverse event
ALIS	amikacin liposome inhalation suspension
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATU	Temporary Authorisation for Use
ATS/IDSA	American Thoracic Society / Infectious Diseases Society of America
AUC_{t1-t2}	area under the plasma concentration-time curve from time zero to time of last measurable concentration
cf.	*confer/conferatur* (compare with)
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CTCAE	Common Terminology Criteria for Adverse Events
CUP	Compassionate Use Programme
DNA	deoxyribonucleic acid
EEA	European Economic Area
EU	European Union
GLP	Good Laboratory Practice
HIV	human immunodeficiency virus
LAI	liposomal amikacin for inhalation
IR	incidence rate
ISS	Integrated Summary of Safety
MAC	*Mycobacterium avium* Complex
MDR	multidrug regimen
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
NOAEL	no-observed-adverse-effect level
NTM	non-tuberculous mycobacteria
NPU	Named Patient Use
PL	Package Leaflet
PSUR	Periodic Safety Update Report
PT	Preferred Term (of MedDRA)
PTA	Post-Trial Access
QPPV	Qualified Person for Pharmacovigilance

RGM	rapid-growing mycobacteria
RMP	Risk Management Plan
rRNA	ribosomal ribonucleic acid
SGM	slow-growing mycobacteria
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SYE	Subject Years of Exposure
TEAE	treatment-emergent adverse event
TFLs	Tables, Figures and Listings
UK	United Kingdom
ULN	upper limit of normal
US	United States

Part I: Product(s) Overview

Table 1: Product Overview

Active substance(s) (INN or common name)	Amikacin sulfate
Pharmacotherapeutic group(s) (ATC Code)	Antibacterials for systemic use, other aminoglycosides. (ATC code: J01GB06)
Marketing Authorisation Holder	Insmed Netherlands B.V.
Medicinal products to which this RMP refers	One
Invented name(s) in the European Economic Area (EEA)	Arikayce liposomal
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** Aminoglycoside antibacterial
	Summary of mode of action: Amikacin binds to a specific receptor protein on the 30S subunit of bacterial ribosomes and interferes with an initiation complex between mRNA and the 30S subunit resulting in inhibition of protein synthesis.
	Important information about its composition: Inhaled liposomal amikacin is a suspension of amikacin sulfate encapsulated in liposome consisting of dipalmitoylphosphatidylcholine and cholesterol, which are both naturally occurring lipids in human lung.
Hyperlink to the Product Information	Arikayce liposomal Product Information (Module 1.3)
Indication(s) in the EEA	**Current**: 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. Consideration should be given to official guidance on the appropriate use of antibacterial agents.
	Proposed: Not applicable

Dosage in the EEA	**Current**: The recommended dose is one vial (590 mg) administered once daily, by oral inhalation.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	**Current**: Nebuliser dispersion. Each vial contains amikacin sulfate equivalent to 590 mg amikacin in a liposomal formulation. The mean delivered dose per vial is approximately 312 mg of amikacin.
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

ATC = anatomical therapeutic chemical; EEA = European Economic Area; EU = European Union; INN = international non-proprietary name; mRNA = messenger ribonucleic acid; RMP = Risk Management Plan; RNA = ribonucleic acid.

Part II: Safety Specification

Part II: Module SI - Epidemiology of the Indication(s) and Target Population(s)

Nomenclature

The acronym ALIS is used to represent amikacin liposome inhalation suspension. Previously, the product has been referred to as liposomal amikacin for inhalation (LAI). As such, the acronym LAI may be found throughout documents in the marketing authorisation application. Prior designations may also have been used, such as Arikayce (a previously proposed proprietary name).

Readers should consider LAI, ALIS, Arikayce and Arikayce liposomal to be synonymous in the context of this Risk Management Plan (RMP).

Indication

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.

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

Incidence and Prevalence

The prevalence of human disease attributable to NTM has increased over the past two decades (Khan et al, 2007; Khan et al, 2008; Marras et al, 2007). NTM epidemiological data should be interpreted with caution since NTM infection is not notifiable in most countries (Chalmers et al, 2018), therefore, numbers of cases are likely to be underestimated.

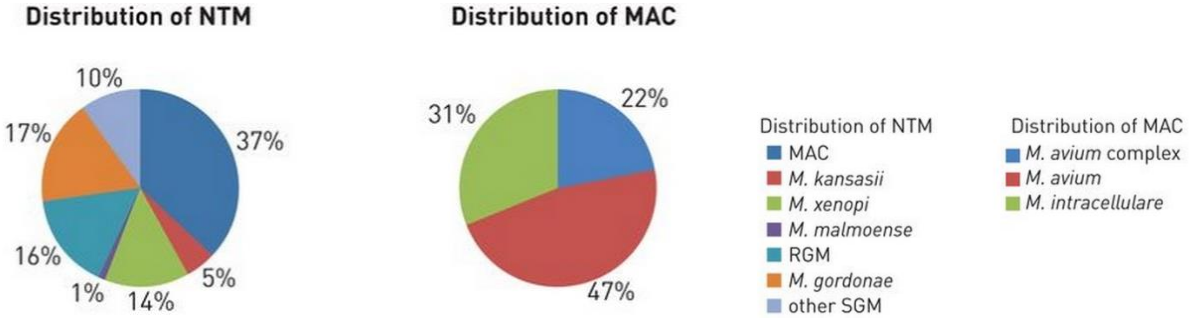
The prevalence of NTM lung infection in the European Economic Area (EEA) is 0.6 per 10,000 population (Insmed Orphan Drug Designation for amikacin sulfate for the treatment of NTM lung disease, (EU/3714/1259); Wagner et al, 2014).

The NTM-Network European Trials Group study conducted in 62 laboratories in 30 countries across 6 continents and found MAC bacteria predominated in most countries, followed by *M gordonae* and *M xenopi* (Figure 1). In Germany, the documented prevalence of NTM pulmonary disease increased from 2.3 cases/100,000 to 3.3 cases/100,000 population from 2009 to 2014, with a strong association with advanced age and chronic obstructive pulmonary disease (Ringshausen et al, 2016). However, a prediction model algorithm, using historical health claims data, estimated the prevalence of both diagnosed and undiagnosed NTM to be 19.1 cases/100,000 population (Ringhausen et al, 2021). In France, a retrospective analysis of nationwide claims and hospitalisation data between 2010 and 2017 estimated the prevalence of NTM as 5.9 cases/100,000 population, in line with the EU prevalence (Veziris et al, 2021). In the United Kingdom (UK), the estimated prevalence of NTM was 4.7 cases/100,000 population in 2016 using electronic healthcare record (Axson et al, 2018). The analysis of data from a machine learning-based algorithm, using data from an electronic medical records primary care database, estimated the prevalence of both diagnosed and undiagnosed NTM in UK to 9 to16 cases/100,000 population in 2016 (Doyle et al, 2020).

Data from the UK suggest that the incidence of pulmonary NTM-positive cultures increased from 4.0/100,000 in 2007 to 6.1/100,000 in 2012. 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 (Shah et al, 2016).

Figure 1: Distribution of Non-tuberculous Mycobacteria in Europe



Source: The NTM-Network European Trials Group study (Hoefsloot et al, 2013)
MAC = *Mycobacterium avium* Complex; NTM = non-tuberculous mycobacteria; RGM = rapid-growing mycobacteria; SGM = slow-growing mycobacteria.

The annual prevalence of NTM lung disease in the United States (US) doubled from 1997 to 2007 from approximately 20 to 47 cases per 100,000, or 8.2% per year, and increased from 2008 to 2015 to 70.2 cases per 100,000 in the US Medicare beneficiaries (Adjemian et al, 2012, Winthrop et al, 2018). At least 80% of definite pulmonary NTM infections in the US (as defined as at least two sputum samples positive for 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) are caused by MAC (Prevots et al, 2010).

Improved detection methods and enhanced physician awareness could explain some of the observed increase in NTM-positive cultures. Other potential explanations include: declining rates of *M. tuberculosis* infection potentially reducing population immunity to mycobacteria; increases in environmental exposure to NTM through more permissive temperature settings of home water heaters and more contact with shower aerosols; increased long-term antibiotic usage in inflammatory lung diseases, potentially creating a more favourable lung niche for NTM; greater use of medications that might impair host immunity to NTM; and the potential impact of person-to-person transmission of certain NTM species in some patient cohorts (e.g., in cystic fibrosis) (Haworth et al, 2017).

Demographics of the Population in the Authorised Indication – Age, Gender, Racial and/or Ethnic Origin and Risk Factors for the Disease

Earlier studies noted a male preponderance in patients with pulmonary disease, but later reports have found a female preponderance. (Iseman et al, 1991; Prince et al, 1989).

Risk factors for NTM pulmonary disease can be grouped into those that influence either NTM exposure or host susceptibility.

Studies have suggested that, for any given level of host susceptibility, there might be a threshold exposure level for NTM associated with the development of disease. Thus, some, but not all, studies show associations with activities potentially increasing exposure to NTM in water (swimming), soils (gardening) and aerosols (showering, hot tubs) (Haworth et al, 2017).

NTM infection is more common in individuals with chronic lung diseases such as asthma, prior tuberculosis, chronic obstructive pulmonary disease (COPD), lung damage due to occupational exposure to dusts (e.g., mining), cystic fibrosis or heterozygosity for a cystic fibrosis mutation, and

α-1-antitrypsin deficiency. Immunodeficiency due to human immunodeficiency virus (HIV)-infection or immunosuppression due to cancer or chemotherapy or following organ transplantation are risk factors for *Mycobacterium avium* bacteraemia (Falkinham et al, 2001).

Many studies, predominantly US-based, have described a series of characteristic features of patients with nodular-bronchiectatic NTM lung disease, who were more likely to be white, postmenopausal, thin, tall women with pectus excavatum and mitral valve prolapse who develop predominantly middle lobe and lingula bronchiectasis; a cluster of features described as 'Lady Windermere Syndrome' (Iseman et al, 1991).

A number of other comorbidities may potentially contribute to the development of NTM lung disease, including the presence of gastro-oesophageal reflux disease, rheumatoid arthritis, low vitamin D, low body mass index, and malnutrition (Haworth et al, 2017).

Immunodeficiencies that have been associated with NTM infection include inherited disorders of the IFNγ-IL12 pathway (e.g., IFNγR1 mutations), other cytokine signalling (e.g., STAT mutations), and macrophage and dendritic cell function (e.g., GATA2, NRAMP1), as well as acquired immunodeficiencies including HIV-AIDS (acquired immunodeficiency syndrome) and functional anti-interferon gamma antibodies (Haworth et al, 2017).

Some medications have been shown to be associated with a higher risk of the development of NTM lung disease. These include immunosuppressants (corticosteroids, tumour necrosis factor alfa inhibitors, drugs used to prevent organ transplant rejection and cancer chemotherapy); azithromycin, inhaled antibiotics, and proton pump inhibitors (Haworth et al, 2017).

The Main Existing Treatment Options

Macrolides (clarithromycin and azithromycin) are the key components in treatment regimens for MAC pulmonary disease (Daley et al, 2020).

The 2020 Guideline, a joint guideline of the American Thoracic Society, European Respiratory Society, European Society of Clinical Microbiology and Infectious Diseases, and Infectious Diseases Society of America, recommends the use of a 3-drug regimen including a macrolide and ethambutol, in patients with macrolide-susceptible nodular/bronchiectatic MAC pulmonary disease (Daley et al, 2020). The recommended 3-drug combination include azithromycin/clarithromycin, rifampicin/rifabutin, and ethambutol. In patients with newly diagnosed disease, azithromycin-based regimen is recommended rather than clarithromycin-based regimen. When azithromycin is not available or not tolerated, clarithromycin is an acceptable alternative. A 3-times-weekly administration is recommended for this treatment regimen.

In patients with cavitary or advanced/severe bronchiectatic MAC pulmonary disease or in patients with macrolide-resistant MAC pulmonary disease, a parenteral aminoglycoside (amikacin or streptomycin) is recommended to be added to the initial oral treatment regimen. The parenteral agent is typically administered for at least 2 to 3 months. If solely the oral regimen is used in these patient populations, a daily administration is recommended. If a parenteral aminoglycoside is added, a 3-times-weekly administration is recommended.

In general, patients should be treated for at least 12 months after culture conversion. In patients who have failed therapy after at least 6 months of guideline based therapy for macrolide-susceptible MAC pulmonary disease, the 2020 guideline recommendation is to add ALIS to the oral regimen.

In the setting of disease caused by macrolide-resistant MAC, the 2020 Guideline suggests seeking expert consultation and for the use of parenteral aminoglycoside in initial treatment regimen does not provide any specific treatment recommendations (Daley et al, 2020).

The British Thoracic Society guidelines (Haworth et al, 2017) advise that nebulised amikacin may be considered in place of an injectable aminoglycoside when intravenous/intramuscular administration is impractical, contraindicated or when longer-term treatment with an aminoglycoside is required for the treatment of MAC pulmonary disease.

Treatment with ALIS, as part of multidrug therapy, should be continued for a minimum of 12 months after culture conversion.

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity

Non-tuberculous mycobacteria are environmental opportunistic pathogens that are ubiquitous in soil (Brooks et al, 1984) and drinking water (Falkinham et al, 1980; Falkinham et al, 2001). Chronic pulmonary disease is the most common clinical manifestation of NTM disease (Griffith et al, 2007).

NTM lung disease, caused by MAC, is a life-threatening condition associated with productive cough, shortness of breath, fatigue, lung function decline, and reduced life-expectancy. MAC infection is a complication of debilitating comorbid lung diseases such as bronchiectasis, COPD, and cystic fibrosis. Pulmonary disease associated with MAC in subjects without predisposing pulmonary pathology tends to be more common in elderly white women (Kim et al, 2008).

The 5-year all-cause mortality associated with NTM lung disease has been reported in the literature to range from 5.4% (Hayashi et al, 2012) to 39.7% (Andréjak et al, 2010). In retrospective studies, the failure to achieve negative sputum cultures in patients with MAC lung disease was associated with higher mortality rates. The 5-year mortality 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 conversion was 53.7% compared to 0% in the untreated group. Although this is an indirect measure of treatment success, these data suggest that treatment followed by sputum conversion decreases mortality risk (Ito et al, 2012). Another study evaluated the outcomes of patients with macrolide-resistant MAC lung disease and found that one-year mortality was 34% for patients who remained sputum culture positive compared to 0% for patients who converted. Another study evaluated the outcomes of patients with macrolide-resistant MAC lung disease and found that one-year and two-year mortality for patients who remained sputum culture positive was 34% and 45%, respectively. Of the patients whose sputum converted to negative, the one-year as well as two-year mortality was 0% (Griffith et al, 2006).

The 5-year all-cause mortality in patients with MAC lung disease has been estimated to be 27%. Predictors of mortality risk were male sex, presence of comorbidities, and advanced patient age (Diel et al, 2018).

Important Co-morbidities

Lung disease due to NTM occurs most commonly in patients with structural lung disease, such as chronic obstructive pulmonary disease, bronchiectasis, cystic fibrosis (CF), pneumoconiosis, prior tuberculosis, pulmonary alveolar proteinosis, and in patients with oesophageal motility disorders. Abnormal CF genotypes and α-1-antitrypsin phenotypes may predispose some patients to NTM infection.

Part II: Module SII - Non-clinical Part of the Safety Specification

Non-clinical Studies

The non-clinical toxicity and toxicokinetic profiles of ALIS were characterised in a number of *in vitro* and *in vivo* studies:

Table 2: ALIS Non-Clinical Studies

Type of Study/Study No.	Route of Administration	Test System
Repeat-Dose		
28-Day Range Finding/ 667621 (Rat) 667637 (Dog)	Inhalation	Rat and Dog
1-Month Toxicity/ 667396 (Rat) 667574 (Dog) [(a)]	Inhalation	Rat and Dog
3-Month Toxicity/07-6307	Inhalation	Mouse
3-Month Toxicity/07-6306	Inhalation	Dog
6-Month Toxicity/07-6308	Inhalation	Rat
9-Month Toxicity/11-6400	Inhalation	Dog
Genetic toxicity		
Ames/7522-100	*In vitro*	*Salmonella* and *E coli*
Chromosomal Aberration/7522-101	*In vitro*	Chinese Hamster Ovary Cells
Gene Mutation/7522-102	*In vitro*	Mouse Lymphoma L5178Y Cell Line
Micronucleus/07-6315	Inhalation	Rat
Carcinogenicity		
2-Year Carcinogenicity/09-6345	Inhalation	Rat
Other Toxicity Studies		
Immunotoxicity Report No.: AMIK-BRD-2005-19-TOX	Inhalation	Rat
Immunotoxicity/ Report No.: AMIK-BIO-2009-16-MAC, Rev. 1	Inhalation	Rat

[a] Includes cardiovascular and respiratory function assessments.
Source: Module 2.6.7 Table 1

Repeat-dose toxicity

In the 6-month nose-only inhalation toxicity study with ALIS in rats, amikacin doses of 0 (1.5% NaCl control), 10, 30, and 90 mg/kg were administered daily; the study included a 3-month interim evaluation and a 3-month recovery period. All doses of ALIS were well tolerated in this study. Macrophage accumulation in the lungs was the principal postmortem finding at all doses after 3 and 6 months of dosing. In addition, tubular nephropathy was observed with an increased incidence and/or severity at 90 mg/kg/day.

The lung changes were considered an adaptive response to clear inhaled particulates associated with the ALIS drug/lipid formulation. In addition to the adaptive changes, multiple foci of sub-acute/chronic active inflammation were present in the lungs at 30 and 90 mg/kg/day following

13 weeks of dosing and at all doses following 26 weeks of dosing; at the two highest doses, the inflammation was accompanied by regenerative hyperplasia of the alveolar epithelium. The adverse pulmonary inflammatory and hyperplastic changes were considered secondary to chronic exposure to inhaled particulates from ALIS (drug/lipid) leading to a high lung burden of particulates, a phenomenon to which rodents are particularly sensitive compared with non-rodent species (Module 2.4 Section 5.1). Findings in the upper respiratory tract at all ALIS doses included degenerative changes in the nasal turbinates and tracheal epithelium (consistent with local irritation secondary to prolonged administration of ALIS by daily nose-only inhalation) and squamous/ squamoid metaplasia/hyperplasia of the epithelium in the larynx (considered to be non-specific responses to inhaled ALIS). Regarding the kidney, the incidence and/or severity of cortical tubular nephropathy was increased at 90 mg/kg/day. Nephropathy was expected since the kidney is a known target organ for amikacin and other aminoglycoside antibiotics. The no-observed-adverse-effect level (NOAEL) for changes in the upper respiratory tract was < 10 mg/kg/day. Based on the sub-acute/chronic inflammation and/or alveolar epithelial hyperplasia that accompanied the macrophage infiltration, the NOAEL for changes in the lung was < 10 mg/kg/day. The NOAEL for nephropathy was 30 mg/kg/day.

In the 9-month inhalation toxicity study in dogs with facemask administration, amikacin doses of 0 (1.5% NaCl control), 0 (Empty Liposome Control; ELC), 5, 10 and 30 mg/kg/day were administered daily; the study included a 6-month interim evaluation (in-life findings only) and a 3-month recovery period. ALIS was well tolerated at all doses in this study; there were no treatment-related in-life findings. The principal postmortem finding was an accumulation of foamy macrophages in the lungs. In addition, intracytoplasmic brown pigment in the renal proximal tubules was observed. Foamy pulmonary macrophages were characterised by vacuolated cytoplasm that often contained basophilic granules and were considered an adaptive response by the lungs to clear inhaled particulates associated with the drug/lipid formulation. Importantly, it was not associated with tissue necrosis, squamous metaplasia, or proliferative/neoplastic changes. The brown pigment in the kidneys was not associated with other cellular changes or changes in clinical pathology parameters and thus was considered non-adverse. The NOAEL in this study was 30 mg/kg/day.

In an investigative study in rats, ALIS was administered by inhalation for 3 cycles of 1-month on drug/1-month off drug at doses of 0 (1.5% NaCl) or 90 mg/kg/day, to evaluate the effects of ALIS on alveolar macrophage function. ALIS did not inhibit or alter the normal cellular functions of alveolar macrophages when administered in this dosing regimen.

Reproductive/developmental toxicity

Inhalation reproductive toxicology studies with ALIS were not considered necessary to support safety in humans as systemic exposure to amikacin is much less following inhalation of ALIS compared with parenteral amikacin and no evidence of impaired fertility and/or harm to the foetus was observed with amikacin in rats, mice, and rabbits (Akutsu, 1982; Matsuzaki, 1975; Matsuzaki, 1975a). In addition, no adverse effects on reproductive organs were observed in repeat-dose inhalation toxicology studies in rodents and dogs with ALIS.

Nephrotoxicity

It is known that the kidney is a target organ for aminoglycoside antibiotic toxicity. Renal changes following the chronic administration of amikacin and other drugs in this class are expected.

In the 6-month rat study, the incidence and/or severity of cortical tubular nephropathy was increased at 90 mg/kg/day. Of note, this nephropathy was not associated with any evidence of

tubular degeneration or necrosis and was almost completely reversible. The NOAEL for nephropathy in the kidneys was 30 mg/kg/day in this 6-month rat study.

In the 3-month dog study, accumulation of eosinophilic droplets within the renal proximal tubules, which may indicate renal uptake of amikacin, was observed at 30 mg/kg/day and was considered non-adverse. In the 9-month dog study, intracytoplasmic brown pigment in the renal proximal tubules was present at all doses and was also considered non-adverse. In both dog studies, the renal observations were completely reversible.

Hepatotoxicity

Amikacin is not metabolised (Bodey et al, 1974). After parenteral administration, amikacin is excreted in the urine unchanged, primarily by glomerular filtration (Contrepois et al, 1985). In addition, the liver was not identified as a target organ in repeat-dose inhalation toxicology studies in animals up to 6 months (rats) and 9 months (dogs) duration and in clinical trials in humans administered ALIS.

Genotoxicity

No evidence of mutagenicity was observed *in vitro* in a microbial mutagenicity test with *Salmonella typhimurium* (*S. typhimurium*) and *Escherichia coli* (*E. coli*) with or without metabolic activation. No evidence of clastogenicity was observed *in vitro* in a chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells with or without metabolic activation. In addition, there was no evidence of genotoxicity in an *in vitro* mouse lymphoma assay or an *in vivo* micronucleus assay in rats following 3 days of inhalation dosing. Based on the results of the battery of completed studies, it is concluded that ALIS is not genotoxic and therefore, is unlikely to pose a genotoxic risk to humans.

Carcinogenicity

During the 2-year non-clinical carcinogenicity study with ALIS in rats, squamous cell carcinoma of lung was observed in 2 of 120 rats (0/60 males and 2/60 females) administered the highest dose tested (45 mg/kg/day). This dose is 6-fold above the clinical dose when normalised on a lung weight basis.

In the rat carcinogenicity study, histopathological findings in the lungs of rats included a cascade of events from foamy macrophage accumulation, acute/subacute/chronic alveolar inflammation, to bronchioloalveolar epithelial hyperplasia, leading to neoplasia. The early histopathological changes were seen across the ALIS toxicology programme with the severity of each increasing with higher doses and longer exposures. The cascade of pulmonary findings described in the rat studies with ALIS is consistent with the concept of particulate overload and is in alignment with the existence of a threshold for adverse pulmonary effects related to the high lung burden of particulates from ALIS (Module 2.4 Section 5).

These findings in rats must be considered in the context of the entire toxicology programme for ALIS and its relevance to larger animal species, including humans. Important biological and anatomical differences exist in lung structure and function between rats and larger species (Mauderly, 1986). In rats, the bronchioloalveolar junction appears to be the main site of inhaled drug deposition, which is beyond the mucociliary layer (Kato et al, 2003; Patton et al, 2010) and the rat alveolar surface area is much smaller (approximately 210 to 230-fold) compared with that of larger species such as dogs and humans (0.39 m^2 in rats; 90 m^2 in dogs, and 82 m^2 in humans). Other factors contributing to the differentiation between the rat and larger species include fewer

alveoli and alveolar macrophages, and a larger surface area patrolled by each macrophage in the rat lung.

The inflammatory and hyperplastic/neoplastic lung changes seen in the rat lung were not reproduced in the dog studies of up to 9 months duration at comparable or higher lung burdens of particulates from ALIS. The dog is an animal model more likely to be predictive of reactions in humans. As a result, the effect of particle overload observed in rats is of questionable relevance for adult patients with NTM lung disease.

General safety pharmacology

As part of a 4-week repeat-dose Good Laboratory Practice (GLP) toxicology study in dogs, respiratory parameters were assessed, and electrocardiograms (ECG) were recorded (Module 2.6.2 Section 4.2).

No additional safety pharmacology evaluations were conducted as it was not considered necessary to use additional animals in safety pharmacology studies with ALIS because no substantive drug-related changes in organs outside the respiratory tract have been observed in repeat-dose toxicology studies in animals administered ALIS. Of note, in the 4-week GLP toxicology study in dogs in which safety pharmacology assessments were conducted, the systemic exposure at the top-dose of 31 mg/kg/day was similar to that in humans at 590 mg, which is the nominal inhaled daily dose proposed for Arikayce liposomal (Module 2.6.6 Section 3.4). Further, the steady-state lung exposures at this top-dose in the 4-week GLP toxicology study in dogs was estimated to be 12-fold higher than that in humans at 590 mg, the clinical dose. In addition, amikacin is well characterized and there is extensive experience from clinical use of systemically administered amikacin. Furthermore, local delivery of ALIS to the lungs (i.e., exposure to amikacin is much higher in sputum compared to serum in patients administered ALIS [Module 2.7.2]), low systemic exposure to amikacin relative to parenteral amikacin (i.e., $AUC_{0\text{-}24h}$) values following IV administration of amikacin are more than 10-fold higher than those following ALIS administration [Module 2.7.2]), and the sustained release characteristic of ALIS suggest low potential for important adverse effects on vital organ systems.

Drug interactions

It was not considered necessary to use additional animals in pharmacodynamic drug interaction studies with ALIS as there had been no evidence of drug interactions with ALIS in clinical trials in which ALIS was taken concomitantly with pancreatic enzymes, dornase alpha, hypertonic saline, short and long-acting bronchodilators, systemic and inhaled steroids and systemic antibiotics.

Other toxicity related information

Alveolar macrophages from ALIS-treated rats demonstrated normal cellular functions (phagocytosis, yeast cell killing and cytokine expression) when challenged with appropriate stimulation. Therefore, it can be concluded that ALIS, administered in a manner comparable to that in humans, does not inhibit or alter the normal cellular functions of alveolar macrophages.

Antigenicity (hypersensitivity), phototoxicity, dependence, and mechanistic studies, have not been identified as a safety issue with amikacin in current professional literature and thus further studies were deemed unnecessary from both a scientific and ethical perspective.

Conclusions on non-clinical data

Toxicology studies with ALIS confirmed the kidney as a target organ as seen before with amikacin and other aminoglycoside antibiotics.

During the 2-year non-clinical carcinogenicity study with ALIS in rats, squamous cell carcinoma of lung was observed in 2 of 120 rats (0/60 males and 2/60 females) administered the highest dose tested (45 mg/kg/day). This dose is 6-fold above the clinical dose when normalised on a lung weight basis.

In the rat carcinogenicity study, histopathological findings in the lungs included a cascade of events from foamy macrophage accumulation, acute/subacute/chronic alveolar inflammation, to bronchioloalveolar epithelial hyperplasia, leading to neoplasia. The early histopathological changes were seen across the ALIS toxicology programme with the severity of each increasing with higher doses and longer exposures. The cascade of pulmonary findings described in the rat studies with ALIS may be the result of a high lung burden of particulates from ALIS in the rat lung.

These findings in rats must be considered in the context of the entire toxicology programme for ALIS and its relevance to larger animal species, including humans. Important biological and anatomical differences exist in lung structure and function between rats and larger species (Mauderly, 1986). In rats, the bronchioloalveolar junction appears to be the main site of inhaled drug deposition, which is beyond the mucociliary layer (Kato et al, 2003; Patton et al, 2010) and the rat alveolar surface area is much smaller (approximately 210 to 230-fold) compared with that of larger species such as dogs and humans (0.39 m^2 in rats; 90 m^2 in dogs, and 82 m^2 in humans). Other factors contributing to the differentiation between the rat and larger species include fewer numbers of alveoli and alveolar macrophages, and a larger surface area patrolled by each macrophage in the rat lung. The inflammatory and hyperplastic/neoplastic lung changes seen in the rat lung were not reproduced in the dog studies of up to 9 months duration at comparable or higher lung burdens of particulates from ALIS. The highest dose employed in this 9-month dog study was 30 mg/kg/day, a dose that is 11-fold above the clinical dose of 590 mg when normalised on a lung weight basis. The dog is an animal model more likely to be predictive of reactions in humans. As such, these biological and anatomical differences that exist between species support that the effect of particle overload observed in rats is of questionable relevance for adult patients with NTM lung disease.

Part II: Module SIII - Clinical trial exposure

Clinical studies with Arikayce liposomal have been conducted in subjects with NTM lung disease, cystic fibrosis with *Pseudomonas* infection, and bronchiectasis with *Pseudomonas* infection.

The safety and efficacy of Arikayce liposomal have been evaluated in 15 studies in all indications. Fourteen studies were completed at the data lock for this RMP (27-Sep-2024), and one phase 3 study in subjects with NTM lung disease (INS-416) was ongoing. The safety data set includes data from the completed studies in patients with NTM lung disease.

The overall safety data set covering all indications includes the following studies:

- Four completed studies in subjects with NTM lung disease comprising:
    - A multiple-dose Phase 2 study (TR02-112);
    - Two multiple-dose Phase 3 studies (INS-212 and INS-312).
    - A multiple-dose Phase 3 study (INS-415).
- Two completed single-dose Phase 1 studies comprising:
    - One healthy volunteer study (RD 201/23924);
    - One study in subjects with cystic fibrosis and *Pseudomonas* infection (TR02-101).
- One completed multiple-dose Phase 3 study in subjects with non-cystic fibrosis bronchiectasis with *Pseudomonas* infection (TR02-107).
- Seven completed multiple-dose studies in subjects with cystic fibrosis with *Pseudomonas* infection (TR02-103, TR02-104, TR02-105, TR02-105EXT, TR02-106, TR02-108, TR02-110).

A total of 884 subjects (including 6 healthy volunteers) have received at least one dose of Arikayce liposomal during the completed clinical trials. Amongst these subjects, 452 were treated for NTM lung infection in studies TR02-112, INS-212, INS-312, and INS-415. Detailed demographic characteristics of subjects exposed to Arikayce liposomal in the completed clinical trials as of 27-Sep-2024 are provided in Table 3 (by age group and gender) and Table 4 (by racial group).

Detailed demographic characteristics of subjects exposed to either Arikayce liposomal or placebo (Empty Liposome Control) in the ongoing double-blinded clinical trial INS-416 as of 27-Sep-2024 are provided in Table 5 (by age group and gender) and Table 6 (by racial group).

Table 3: Cumulative Subject Exposure to Arikayce Liposomal in the Completed Clinical Trials, Stratified by Age Group and Gender

Age Group (Years)	Number of Subjects[a]		
	Male	Female	Total
<18	68	87	**155**
18 to 65	199	285	**484**
66 to 75	51	126	**177**
>75	16	46	**62**
Total	**334**	**544**	**878**

[a] Does not include six healthy volunteers from study RD 201/23924.

Table 4: Cumulative Subject Exposure to Arikayce Liposomal in the Completed Clinical Trials, Stratified by Racial Group

Racial Group	Number of Subjects[a]
Asian	103
Black	9
Caucasian	742
Other[b]	16
Unknown	8
Total	**878**

[a] Does not include six healthy volunteers from study RD 201/23924.

[b] Includes subjects who do not identify in the other racial groups listed.

Table 5: Cumulative Subject Exposure to Either Arikayce Liposomal or Placebo in the Ongoing Double-Blinded Clinical Trial INS-416, Stratified by Age Group and Gender

Age Group (Years)	Number of Subjects		
	Male	Female	Total
< 18	0	0	**0**
18 to 65	26	113	**139**
66 to 75	33	134	**167**
> 75	19	53	**72**
Total	**78**	**300**	**378**

Ongoing study INS-416.

Table 6: Cumulative Subject Exposure to Either Arikayce Liposomal or Placebo in the Ongoing Double-Blinded Clinical Trial INS-416, Stratified by Racial Group

Racial Group	Number of Subjects
Asian	126
Black	2
Caucasian	235
Other	3
Multiple	1
Missing	11
Total	**378**

Ongoing study INS-416.

Part II: Module SIV - Populations not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Hypersensitivity to amikacin, or other aminoglycosides

Reason for exclusion: Subjects who have known hypersensitivities to amikacin or any component of the product regardless of the route of administration must not receive Arikayce liposomal. Cross-sensitivity to other aminoglycosides may also occur in subjects with hypersensitivity to amikacin.

Is it considered to be included as missing information?: No

Rationale: Arikayce liposomal is contraindicated in subjects who may be hypersensitive to any of the constituents of the product.

Subjects with neuromuscular weakness

Reason for exclusion: Subjects with neuromuscular weakness, including those with a diagnosis of myasthenia gravis, were excluded from clinical studies. Aminoglycosides may aggravate muscle weakness by blocking the release of acetylcholine at neuromuscular junctions particularly in subjects with myasthenia gravis, and those that may have received non-depolarising muscle relaxants during general anaesthesia.

Is it considered to be included as missing information?: No

Rationale: Neuromuscular blockade is a well-established complication of all aminoglycosides, including amikacin.

Subjects with renal dysfunction

Reason for exclusion: Subjects with serum creatinine > 2 × the upper limit of normal (ULN) were excluded from clinical studies. Reversible, mild nephrotoxicity has been reported in studies in animals. The risk of nephrotoxicity is greater in patients with impaired renal function, and in those who receive high doses, or in those whose therapy is prolonged.

Is it considered to be included as missing information?: No

Rationale: Renal toxicity is a well-established complication of all aminoglycosides, including amikacin.

Subjects with significant hearing loss or vestibular dysfunction

Reason for exclusion: Subjects with significant hearing loss or vestibular dysfunction where the potential risk of aminoglycoside toxicity outweighs the potential benefit (as determined by the Investigator) were excluded from clinical studies. High frequency deafness usually occurs first and can be detected by audiometric testing. Vertigo may occur and may be evidence of vestibular injury. The risk of ototoxicity due to aminoglycosides increases with the degree of exposure to either persistently high peak or high trough serum concentrations. Subjects who develop cochlear or vestibular damage may not have symptoms during therapy to warn of developing eighth cranial nerve toxicity, and total or partial irreversible bilateral deafness or disabling vertigo may occur after treatment has been discontinued. Aminoglycoside-induced ototoxicity is usually irreversible.

Is it considered to be included as missing information?: No

Rationale: Ototoxicity (both vestibular and auditory) is a well-established complication of all aminoglycosides, including amikacin.

Subjects with hepatic dysfunction

Reason for exclusion: Subjects with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3 × ULN or total bilirubin ≥ 2 × ULN were excluded from clinical studies. Subjects with evidence of hepatic dysfunction were excluded to limit confounding of interpretation of safety data.

Is it considered to be included as missing information?: No

Rationale: Hepatotoxicity is not a known complication of treatment with amikacin. Amikacin is not metabolised by the liver. Hepatic dysfunction is not a clinically relevant risk for patients receiving amikacin.

Pregnancy and lactation

Reason for exclusion: Aminoglycosides can cause harm to the unborn child. Aminoglycosides have been associated with total, irreversible, bilateral congenital deafness in children whose mothers also received streptomycin during pregnancy.

Is it considered to be included as missing information?: No

Rationale: Foetal toxicity is an established complication of all aminoglycosides, including amikacin.

Paediatric use

Reason for exclusion: MAC lung infection in patients < 18 years, without underlying cystic fibrosis, is very uncommon. Children and adolescents were excluded from clinical studies.

Is it considered to be included as missing information?: No

Rationale: A Paediatric Investigation Plan has been completed to investigate the safety and efficacy of Arikayce liposomal in young people with NTM lung infection, including those with underlying cystic fibrosis. No trends have been observed to date from reports describing the use of Arikayce liposomal in the paediatric population and/or adverse events that occurred and were reported in this population.

Immunosuppression/immunodeficiency

Reason for exclusion: Patients with known or suspected acquired immunodeficiency syndromes (e.g., HIV-positive subjects regardless of CD4 counts) and other immunodeficiency syndromes that may interfere with study participation as determined by the Investigator were excluded from all clinical studies. These subjects were excluded to limit potential confounding of the interpretation of efficacy and safety endpoints.

Is it considered to be included as missing information?: No

Rationale: There are no grounds to assume Arikayce liposomal may lead to outcomes that may be materially different in this population.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

Four hundred and fifty-two (452) subjects with NTM lung infection were exposed to Arikayce liposomal during the clinical development programme within completed clinical trials. Adverse drug reactions (ADRs) with a true frequency lower than approximately 1 in 130 would not be expected to be quantifiable with a data set of this size, even if they may be observed.

Around 23% of the subjects with NTM lung infection have been treated with Arikayce liposomal for more than one year, all of whom were enrolled in studies INS-212 and INS-312 (Module 5.3.5.3 RMP TFLs Table SIII.1).

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by exposures greater than those observed in clinical studies. While the maximum duration of exposure to Arikayce liposomal has been more than one year, the probability of detecting ADRs due to exposures of this duration will diminish in proportion to the number of patients treated for prolonged periods. This is because there are fewer patients exposed for longer periods than for shorter periods in clinical development studies. ADRs occurring in subjects with NTM lung infection treated with Arikayce liposomal for 12 months or more with a true frequency lower than approximately 1 in 34 would not be expected to be quantifiable with a data set of this size, even if they may be observed.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

Table 7: Exposure of Special Populations Included or not in Clinical Development

Type of special population	Exposure
Pregnant women	Pregnant women and women nursing an infant were excluded from clinical studies.
Breastfeeding women	
Patients with relevant comorbidities:	
Patients with hepatic impairment	Subjects with AST or ALT ≥ 3 × ULN or total bilirubin ≥ 2 × ULN were excluded from clinical studies.
Patients with renal impairment	Subjects with serum creatinine > 2 × ULN were excluded from clinical studies.
Immuno-compromised patients	Not included in the clinical development programme.
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development programme.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method Used to Calculate Exposure

Estimated post-authorisation exposure includes exposure through commercial use of Arikayce as well as through expanded-access programmes (i.e., Compassionate Use Programmes [CUPs], Named Patient Use [NPU], French Temporary Authorisation for Use [ATU], and Post-Trial Access [PTA]).

Arikayce liposomal supply and recommended dose of one vial (590 mg) administered once a day is consistent in all the labels in all regions/countries. The 590 mg/day is the defined daily dose (DDD) of amikacin by the World Health Organization and provides the standard for calculating patient exposure based on the DDD and expressed in patient-years. However, the recommended duration of treatment as per EU/EEA and UK label is 12 months after sputum culture conversion without exceeding a maximum duration of 18 months, or 6 months if sputum culture conversion has not been confirmed by then. The recommended duration of treatment is not defined in labels for the US and Japan.

Patient exposure estimated in the RMP is presented in patient-years of exposure based on the number of dispensed vials, with the assumption that all patients are treated according to the dosage recommendation and schedule.

In order to calculate the estimated number of patients on Arikayce liposomal, the number of vials distributed is divided by 365.25 days as the average length of the year to express the estimated patient-years of exposure.

SV.1.2 Exposure

The estimated cumulative patient exposure data are presented in Table 8 by region[redacted] in which Arikayce liposomal is marketed or distributed since the International Birth Date for amikacin sulfate on 28-Sep-2018 until the data lock point for this RMP on 27-Sep-2024.

The estimated patient exposure to Arikayce liposomal in the post-marketing setting since the International Birth Date until the DLP for this RMP (including data from the CUPs, NPU, French ATU, and PTA) was 10,349.06 patient-years.

Data populated by age, sex, or other demographic characteristics are not available for patients receiving Arikayce liposomal in the post-marketing setting.

Table 8: Estimated Patient Exposure in the Post-Marketing Setting

Region Country	Estimated Patient Exposure since IBD until 27-Sep-2024	
	Vials	**Patient-years**
EU/EEA		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Sub-total EU/EEA	**226,744**	**620.79**
Non-EU/EEA		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Subtotal non-EU/EEA	**3,553,249**	**9,728.27**
Total	**3,779,993**	**10,349.06**

EEA = European Economic Area; EU = European Union; IBD = International Birth Date; MA = marketing authorisation; [redacted]

Part II: Module SVI - Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

Given the mechanism of action of the active substance and its indication, the potential for misuse or abuse for illegal purposes is considered negligible. No such misuse has been identified since the International Birth Date until the DLP for this RMP.

Part II: Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

The clinical data presented in this section come from the pivotal studies TR02-112, INS-212 (through the data cut-off date on 25-Oct-2018), and INS-312, which were conducted in subjects with refractory NTM lung infection caused by MAC (patients who did not achieve negative sputum cultures after a minimum of 6 consecutive months of a multidrug background regimen therapy).

SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason for not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP:

Risks with Minimal Clinical Impact on Patients (in Relation to the Severity of the Indication Treated):

The following undesirable effects are expected to have a minimal impact when viewed from the perspective of the seriousness and severity of NTM lung infection itself:

- Laryngitis
- Vocal cord inflammation
- Throat irritation
- Oral candidiasis
- Tinnitus
- Anxiety
- Headache
- Dizziness
- Dysgeusia
- Aphonia
- Balance disorder
- Diarrhoea
- Nausea
- Vomiting
- Dry mouth
- Decreased appetite
- Rash
- Pruritus
- Arthralgia

- Myalgia
- Fatigue
- Pyrexia
- Chest discomfort
- Weight decreased

Tinnitus, dizziness, and balance disorder are discussed below under "Known risks - ototoxicity".

Adverse Reactions with Clinical Consequences, even Serious, but Occurring with a Low Frequency and Considered to be Acceptable in Relation to the Severity of the Indication Treated:

- Chronic Obstructive Pulmonary Disease
- Infective exacerbation of bronchiectasis
- Pneumonitis

The crude incidence of infective exacerbation of underlying pulmonary disease in the safety population, comprising subjects treated for MAC lung disease in clinical studies, was higher in subjects treated with Arikayce liposomal (27.0%) compared with controls (14.6%). The incidence of infective exacerbation of bronchiectasis was higher in subjects treated with Arikayce liposomal (17.8%) compared with controls (10.8%). The incidence of chronic obstructive pulmonary disease was higher in subjects treated with Arikayce liposomal (7.2%) compared with controls (3.2%). The incidence of infective exacerbation of chronic obstructive pulmonary disease with Arikayce liposomal (0.5%) was similar to that observed in controls (0.6%). The incidence of pneumonitis was higher in subjects treated with Arikayce liposomal (1.5%) compared with controls (0.0%) (Module 5.3.5.3, ISS Table 512) (pneumonitis is also considered in the context of the important identified safety concern "allergic alveolitis" in SVII.3.1).

In the absence of immunosuppression, MAC lung infection rarely occurs in subjects who do not have established, often severe, pulmonary disease. Immunosuppressed subjects were excluded from clinical studies; therefore, most of the subjects in the clinical study safety data set for MAC lung infection had chronic pulmonary disease. Exacerbations of pulmonary disease in this population are common as part of the disease natural history even in the absence of exposure to Arikayce liposomal. This is reflected in the high crude incidences of infective exacerbation of bronchiectasis and COPD in the control group.

The crude incidences of infective exacerbation of underlying pulmonary disease exaggerate the differences between Arikayce liposomal and controls because they do not take the longer duration of exposure to Arikayce liposomal into account. The cumulative duration of exposure to Arikayce liposomal in the MAC lung disease clinical study safety data set (327 subject-years) was longer than that of controls (87 subject-years) (Module 5.3.5.3 RMP TFLs Table SIII.1). When the incidence of exacerbation of underlying pulmonary disease is corrected for the duration of exposure, the difference between Arikayce liposomal and controls becomes considerably smaller (33.4 events per 100 years observation cf. 26.6 events per 100 years observation) (Module 5.3.5.3 ISS TFLs Table 5171.6). The exposure-adjusted incidence of infective exacerbation of underlying pulmonary disease remains higher than that observed amongst controls, but the difference in incidence attributable to Arikayce liposomal is low (6.8 events per 100 years observation).

- Dysphonia
- Dyspnoea
- Cough
- Oropharyngeal pain
- Wheezing
- Productive cough
- Sputum increased
- Bronchospasm

The frequencies of these events in subjects treated for MAC lung disease in clinical studies are shown in Table 9.

Table 9: Treatment-Emergent Adverse Events in Subjects Treated for MAC Lung Disease

Preferred Term	NTM Lung Infection			
	Arikayce Liposomal		Control	
	N = 404		N = 157	
	n	(%)	n	(%)
Dysphonia	181	(44.8)	5	(3.2)
Dyspnoea	79	(19.6)	11	(7.0)
Cough	146	(36.1)	23	(14.6)
Oropharyngeal pain	47	(11.6)	3	(1.9)
Wheezing	25	(6.2)	4	(2.5)
Productive cough	21	(5.2)	3	(1.9)
Sputum increased	22	(5.4)	2	(1.3)
Bronchospasm	110	(27.2)	17	(10.8)

MAC = *Mycobacterium avium* Complex; NTM = non-tuberculous mycobacteria.
Source: Module 5.3.5.3 ISS Table 511 and Module 5.3.5.3 Table 5171

Inhalation of Arikayce liposomal is commonly associated with the development of respiratory symptoms during administration of treatment. These events were not usually serious, but cough, dysphonia and dyspnoea were the reason for discontinuation of treatment in MAC lung disease clinical studies in 1.5%, 1.7% and 3.0% respectively of subjects treated with Arikayce liposomal, compared with no discontinuations in control subjects (Module 5.3.5.3 ISS TFLs Table 551). Cough, dysphonia, dyspnoea and oropharyngeal pain were also more commonly associated with interruption of treatment in 7.7%, 14.6%, 6.7% and 2.5% respectively of subjects treated with Arikayce liposomal, compared with no treatment interruptions in control subjects (Module 5.3.5.3 ISS TFLs Table 5191).

- Haemoptysis

The frequency and exposure-adjusted incidence rate of haemoptysis in subjects treated for MAC lung disease in clinical studies are shown in Table 10.

Table 10: Frequency and Exposure-corrected Incidence of Haemoptysis in Clinical Studies with Arikayce Liposomal

Adverse Event Group	Event Frequency				Number of Subjects with Event per 100 Years Observation	
	Arikayce Liposomal		Control		Arikayce Liposomal	Control
	N = 404		N = 157		N = 404	N = 157
	n	(%)	n	(%)	SYE = 327	SYE = 87
Haemoptysis	76	(18.8)	21	(13.4)	23.5	24.3

SYE = Subject Years of Exposure
Source: Module 2.7.4. Section 2.1.4.3 Adverse events of special interest

Haemoptysis is a common complication of chronic severe lung disease, particularly bronchiectasis. Subjects with a history of severe haemoptysis were excluded from participation in clinical studies.

The crude incidence of haemoptysis in the safety population, comprising subjects treated for MAC lung disease in clinical studies, was higher in subjects treated with Arikayce liposomal (18.8%) compared with controls (13.4%).

The cumulative duration of exposure to Arikayce liposomal in the MAC lung disease clinical study safety data set (327 subject-years) was longer than that of controls (87 subject-years) (Module 5.3.5.3 RMP TFLs Table SIII.11). When the incidence of haemoptysis is corrected for the duration of exposure, the difference between Arikayce liposomal and controls becomes very small (23.5 events per 100 years observation cf. 24.3 events per 100 years observation) (Module 5.3.5.3 ISS TFLs Table 5171.6). Haemoptysis was less likely to be serious in Arikayce liposomal-treated subjects (2.5%) than in controls (3.2%) (Module 5.3.5.3 ISS TFLs Table 531). Despite the similarity of the exposure–adjusted incidence rates, haemoptysis associated with Arikayce liposomal was more likely than controls to lead to interruption of treatment (4.0% cf. 0%) (Module 5.3.5.3 ISS TFLs Table 5191).

- Anaphylactic reactions
- Hypersensitivity reactions

The crude incidence of adverse events (AE) in the Medical Dictionary for Regulatory Activities (MedDRA) Standardised MedDRA Queries (SMQs) for Hypersensitivity and Anaphylactic reaction in the safety population, comprising subjects treated for MAC lung disease in clinical studies, was higher in subjects treated with Arikayce liposomal (28.5%) compared with controls (17.8%) (Module 2.7.4 Section 2.1.5.2).

In the clinical development programme, one serious adverse event (0.4%) of drug hypersensitivity was observed in Study INS-212 in a patient taking Arikayce liposomal and one serious adverse event (0.9%) in a patient in the control group. There were no events of anaphylaxis observed in the overall population exposed to Arikayce liposomal.

Arikayce liposomal was placed on the market in the US on 01-Oct-2018. Up to 31-Jan-2020, 416 post-authorisation spontaneous case reports were retrieved using the SMQ Hypersensitivity; in 49 of these case reports the suspected reaction was reported to be hypersensitivity or drug hypersensitivity, including one anaphylactic reaction. Thirteen of the 49 case reports were assessed as serious and possibly related to Arikayce liposomal, including one anaphylactic reaction. Thirty-one of the 49 case reports were assessed as non-serious and possibly related to Arikayce

liposomal. In a total of 367 case reports the reported event was not consistent with hypersensitivity or drug hypersensitivity, but the case reports contained at least one term that was also included in the SMQ for Hypersensitivity.

Known Risks that Require no Further Characterisation and are Followed up via Routine Pharmacovigilance Namely Through Signal Detection and Adverse Reaction Reporting, and for which the Risk Minimisation Messages in the Product Information are Adhered to by Prescribers (e.g., Actions Being Part of Standard Clinical Practice in each EU Member State Where the Product is Authorised):

None

Known Risks that do not Impact the Risk-benefit Profile:

None

Other Reasons for Considering the Risks not Important:

- Leucopenia
- Neutropenia

Leucopenia and neutropenia are not labelled risks in the Summary of Product Characteristics (SmPC) section 4.8, nor are they important potential safety concerns for Arikayce liposomal, nor are they known to be associated with the administration of parenteral amikacin.

Data from clinical studies in subjects with NTM lung infection provide no evidence of an effect of Arikayce liposomal on either leucocytes or neutrophils.

At baseline, in the NTM lung infection population, low leukocyte counts were reported in 41 (10.1%) patients in the ALIS group, and 13 (8.3%) patients in the placebo group. Low neutrophils were reported in 23 (5.7%) patients in the ALIS group and in 5 (3.2%) patients in the placebo group (Module 5.3.5.3. ISS Table 602.2).

In the total NTM lung infection population, low leukocyte counts at any post-baseline visit were seen in 51 (15.5%) patients in the ALIS arm, and 9 (7%) patients in the placebo arm. Low neutrophil counts at any post-baseline visit were seen in 31 (9%) patients in the ALIS arm and 8 (6%) patients in the placebo arm (Day120_Q77_Luco_Neutro).

In most patients, low leukocyte or neutrophil counts did not persist on treatment from one visit to the next, and despite continued treatment, often returned to within normal limits (Day120_Q77_Leukocytes_F1, Day120_Q77_Neutrophils_F2).

Most low counts were very close to the lower limit of normal and were not clinically significantly decreased. There were only two patients with counts below levels that apply for Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 events (2,000/mm^3 for leukocytes and 1,000/mm^3 for neutrophils). [redacted]

Leucopenia and neutropenia events were rare in clinical studies and occurred sporadically with no evidence of a temporal or causal relationship to treatment.

Reports of leucopenia and neutropenia received in association with use of the commercial product will continue to be monitored with routine pharmacovigilance measures including medical review

of case reports and signal detection. Leucopenia and neutropenia will be reviewed and reported in Periodic Safety Update Reports (PSURs).

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risk: Allergic Alveolitis

In clinical studies with Arikayce liposomal for the treatment of NTM lung disease the percentage of subjects in whom allergic alveolitis was reported was 3.2% (13 cases), which was higher than the percentage in subjects that were not treated with Arikayce liposomal in the same studies (1.3%; 2 cases) (Table 12). The incidence of allergic alveolitis corrected for exposure in subjects treated with Arikayce liposomal was also higher than that of controls (4.0 subjects per 100 years' observation cf. 2.3 subjects per 100 years' observation). Nine of the 13 cases reported with Arikayce liposomal were serious, and more than half (8 cases) were severe (CTCAE Grade 3 or greater). There were no fatal cases. Nine of the cases recovered, [redacted]

Allergic alveolitis is an important safety concern because it may contribute to the respiratory burden in a population with significant respiratory pathology. Risk minimisation measures including discontinuation of treatment with Arikayce liposomal and administration of glucocorticoids lead to complete resolution of allergic alveolitis and appear to be effective in most cases.

Risk-benefit Impact:

The benefit of effective treatment of MAC lung infection outweighs the risk of allergic alveolitis.

Important Identified Risk: Ototoxicity

Amikacin was introduced into clinical practice in 1976 for parenteral use (intravenous or intramuscular) for the treatment of severe infections with multidrug-resistant, aerobic Gram-negative bacteria, especially *Pseudomonas*, *Acinetobacter*, *Enterobacter*, *E. coli*, *Proteus*, *Klebsiella*, and *Serratia*. Parenteral amikacin also has an established place for the treatment of NTM infections and tuberculosis (if caused by sensitive strains) that do not respond to treatment with first line antimycobacterial medicines. Amikacin is usually administered in combination with other antimycobacterial medicines.

Ototoxicity is a safety concern common to all aminoglycoside antibiotics. It is reasonable to assume that inhaled liposomal amikacin shares this risk, even if the probability of it occurring may be less than that associated with parenteral administration due to the low systemic concentrations of amikacin achieved with inhaled administration. The management of ototoxicity due to aminoglycoside antibiotics is embedded into medical practice.

Table 11 summarises the crude frequencies and incidence corrected for duration of exposure to Arikayce liposomal for adverse events (AEs) compared with controls from the three multiple-dose studies (TR02-112, INS-212, and INS-312) conducted in subjects with NTM lung disease.

Adverse events consistent with ototoxicity (including deafness, dizziness, presyncope, tinnitus, and vertigo) were reported in 72 of 404 (17.8%) NTM subjects treated with Arikayce liposomal compared with 16 of 157 (10.2%) control subjects. [redacted] The incidence rate was 22.0 subjects per 100 years' exposure (95% confidence interval [CI] - 17.2, 27.8) for Arikayce liposomal, and 18.5 subjects per 100 years' exposure (95% CI - 10.6, 30.0) for

controls. The difference in exposure-adjusted incidence rates is small and the confidence intervals for the Arikayce liposomal and control incidences are overlapping (Module 5.3.5.3 RMP TFLs Table SIII.7).

The data show that the overall incidence of ototoxicity is higher in subjects treated with Arikayce liposomal, but most of the apparent difference can be explained by a longer duration of exposure to Arikayce liposomal than to control treatment in clinical studies.

The risk of ototoxicity attributable to Arikayce liposomal appears to be only marginally greater than the risk in unexposed comparator groups.

Table 11: Frequency and Exposure-corrected Incidence of Ototoxicity, Nephrotoxicity and Neuromuscular Blockade in Clinical Studies with Arikayce Liposomal

Adverse Event Group	Event Frequency				Number of Subjects with Event per 100 Years Observation	
	Arikayce Liposomal		Control		Arikayce Liposomal	Control
	N = 404		N = 157		N = 404	N = 157
	n	(%)	n	(%)	SYE = 328	SYE =87
Ototoxicity	72	(17.8)	16	(10.2)	22.0	18.5
Nephrotoxicity	17	(4.2)	4	(2.5)	5.2	4.6
Neuromuscular blockade	12	(3.0)	1	(0.6)	3.7	1.2

SYE = Subject Years of Exposure
Source: Module 5.3.5.3 RMP TLFs Table SIII.7.1; Module 5.3.5.3 RMP TLFs Table SIII.6; Module 5.3.5.3 RMP TLFs Table SIII.5.1

Risk-benefit Impact:

The benefit of Arikayce liposomal as an effective treatment for patients with NTM lung infection with limited alternative treatment options, outweighs the important identified risk of ototoxicity that can be monitored and managed in clinical practice.

Important Identified Risk: Nephrotoxicity

Nephrotoxicity is a safety concern common to all aminoglycoside antibiotics. The management of nephrotoxicity due to aminoglycoside antibiotics is embedded into medical practice.

Adverse events consistent with nephrotoxicity (including haematuria, proteinuria, renal failure, blood creatinine increased, creatinine renal clearance increased, glomerular filtration rate abnormal, glomerular filtration rate decreased, red blood cells urine positive, urinary casts present, and leukocyturia) were reported in 17 of 404 (4.2%) NTM subjects treated with Arikayce liposomal compared with 4 of 157 (2.5%) control subjects. None of these events was reported to be serious. The incidence rate, which takes duration of exposure into account (i.e., the number of subjects with an event per 100 years' cumulative exposure) was 5.2 subjects per 100 years' exposure (95% CI - 3.0, 8.3) for Arikayce liposomal, and 4.6 subjects per 100 years' exposure (95% CI - 1.3, 11.8) for controls. The difference in exposure-adjusted incidence rates is small and the confidence intervals for the Arikayce liposomal and control incidences are overlapping (Module 5.3.5.3 RMP TLFs Table SIII.6).

The data show that the overall incidence of nephrotoxicity is higher in subjects treated with Arikayce liposomal, but most of the apparent difference can be explained by a longer duration of exposure to Arikayce liposomal than to control treatment in clinical studies.

The risk of nephrotoxicity attributable to Arikayce liposomal appears to be only marginally greater than the risk in unexposed comparator groups.

Risk-benefit Impact:

Arikayce liposomal is contraindicated in patients with severe renal impairment.

The benefit of Arikayce liposomal as an effective treatment for patients with NTM lung infection with limited alternative treatment options, outweighs the important identified risk of nephrotoxicity that can be monitored and managed in clinical practice.

Important Identified Risk: Impaired Neuromuscular Transmission

Impaired neuromuscular transmission is a safety concern common to all aminoglycoside antibiotics. The management of this safety concern due to aminoglycoside antibiotics is embedded into medical practice.

Adverse events consistent with impaired neuromuscular transmission (reported as muscle weakness, neuropathy peripheral and balance disorder) were reported in 12 of 404 (3.0%) NTM subjects treated with Arikayce liposomal compared with one of 157 (0.6%) control subjects. [redacted] Among the 12 events reported, only one event suggestive of impaired neuromuscular transmission (PT Muscular weakness) was reported in a subject treated with Arikayce liposomal in Study 212. For comparison, one control subject in study 112 also reported one event coded to the preferred term “muscular weakness”. Both events were assessed as non-serious and mild in severity. The remaining events in subjects treated with Arikayce liposomal were coded to either balance disorder or peripheral neuropathy. The incidence rate was 3.7 subjects per 100 years’ exposure (95% CI - 1.9, 6.4) for Arikayce liposomal, and 1.2 subjects per 100 years’ exposure (95% CI - 0, 6.4) for controls. The difference in exposure-adjusted incidence rates is smaller than the difference in crude frequency, and the confidence intervals for the Arikayce liposomal and control incidences are overlapping (Module 5.3.5.3 RMPF TFLs Table SIII.5).

The data show that the overall incidence of impaired neuromuscular transmission is higher in subjects treated with Arikayce liposomal, but most of the apparent difference can be explained by a longer duration of exposure to Arikayce liposomal than to control treatment in clinical studies.

The risk of impaired neuromuscular transmission attributable to Arikayce liposomal appears to be only marginally greater than the risk in unexposed comparator groups.

Risk-benefit Impact:

The benefit of Arikayce liposomal as an effective treatment for patients with NTM lung infection with limited alternative treatment options, outweighs the important identified risk of impaired neuromuscular transmission that can be monitored and managed in clinical practice.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Removal of important identified risks from the list of safety concerns in the RMP

The risks of ototoxicity, nephrotoxicity, and impaired neuromuscular transmission, previously classified as important identified risks are proposed to be removed from the list of safety concerns, based on the rationale discussed below.

Rationale:

The risks of ototoxicity, nephrotoxicity, and impaired neuromuscular transmission are safety concerns common to all aminoglycoside antibiotics including amikacin. Amikacin was introduced into clinical practice in 1976 for parenteral use (intravenous or intramuscular) for the treatment of severe infections with multidrug-resistant, aerobic Gram-negative bacteria, especially *Pseudomonas*, *Acinetobacter*, *Enterobacter*, *E. coli*, *Proteus*, *Klebsiella*, and *Serratia*. Parenteral amikacin also has an established place for the treatment of NTM infections and tuberculosis (if caused by sensitive strains) that do not respond to treatment with first line antimycobacterial medicines.

The management of these 3 risks due to aminoglycoside antibiotics is well integrated into medical practice with the routine risk communication adequately addressed in the SmPC (Section 4.3, 4.4, 4.5, 4.8), package leaflet (PL; Section 2 and 4), and risk minimisation measures (legal status, treatment initiated and managed by physicians experienced in the treatment of the targeted population). The recognised NTM Clinical Practice Guidelines recommend the use of Arikayce liposomal in the authorized indication and provide guidance for the monitoring for adverse reactions, including recommendations specific to the risk of ototoxicity and nephrotoxicity with the product (Daley et al, 2020).

The new data acquired from the clinical trials (completed INS-415 study and ongoing INS-416 study) did not identify any new information to these risks that were already well characterised in the initial RMP based on the pivotal clinical trial data including potential mechanism, frequency/incidence, severity, reversibility/outcomes, risk factors, and preventability.

Since the approval of initial RMP and implementation of routine pharmacovigilance activities, a request was received to update the Product Information to address a class effect, the increased risk of ototoxicity in patients with mitochondrial DNA mutations. The Arikayce liposomal Product Information in the EU was updated accordingly within procedure no. EMEA/H/C/PSUSA/00010882/202309 and implemented on 29-Jun-2023. The Product Information update was also endorsed by the Medicines and Healthcare products Regulatory Agency in the UK within procedure PLGB47434/0001-0011 and implemented on 11-Aug-2023. No other changes to the pharmacovigilance and risk minimisation plan were deemed needed by the MAH and/or health authorities for these risks.

The use of targeted follow-up questionnaires did not identify any new risk factors or new significant safety information in the post-marketing setting. For each of these risks, the frequency, severity, seriousness and outcomes were reviewed over time and found to be stable, if not improving, as documented in the annual PSURs and the quarterly signal detection reports that focus on each risk as an Adverse Event of Special Interest. An up-to-date characterisation of each risk is presented in the Addendum to Clinical Overview (reporting interval 27-Oct-2020 to 27-Sep-2024) submitted within the renewal procedure.

The benefit of Arikayce liposomal as an effective treatment for patients with NTM lung infection with limited alternative treatment options outweighs these risks that are fully characterised, does not require outstanding additional pharmacovigilance activities and is appropriately monitored and managed in clinical practice.

Based on the available information to date, the risks of ototoxicity, nephrotoxicity, and impaired neuromuscular transmission are considered fully characterised including in the post-marketing setting and further active characterisation effort is unlikely to bring an impact on the risk-benefit balance of Arikayce.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk: Allergic Alveolitis

Potential Mechanisms:

Allergic alveolitis (currently referred to as hypersensitivity pneumonitis) is an inflammatory and/or fibrotic disease affecting the lung parenchyma and small airways that typically results from an immune-mediated reaction provoked by an overt or occult inhaled antigen in susceptible individuals (Raghu et al, 2020, Raghu et al, 2021).

Evidence Source(s) and Strength of Evidence:

This identified risk is based on the findings from the clinical trials TR02-112, INS-212 and INS-312 in patients with refractory NTM lung infection caused by MAC. The percentage of subjects treated with Arikayce liposomal for NTM lung disease (N = 404) in whom allergic alveolitis was reported was 3.2%, which was higher than the percentage in subjects that received placebo (N = 157) in the same studies (1.3%).

The evidence from these randomised, controlled clinical trials is considered to be a reliable predictor of how subjects will respond to treatment in clinical practice, by convention.

Characterisation of the Risk:

Clinical Trials

The following tables display the frequency, percentage, and incidence rates for allergic alveolitis in the NTM lung infection safety data set. Outcomes and severities are also shown for these case reports. Data have been pooled from 3 multiple-dose studies conducted with Arikayce liposomal (TR02-112, INS-212 and INS-312) (Table 12 and Table 13). The algorithm used to identify cases retrieved all case reports with at least one event coded to the MedDRA Preferred Terms (PTs): allergic alveolitis, eosinophilic pneumonia, interstitial lung disease, pneumonitis, or respiratory disorder.

No events of allergic alveolitis were reported in the completed clinical trial INS-415 in patients with newly diagnosed NTM lung infection caused by MAC (N = 48).

Table 12: 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 cut-off date (25-Oct-2018) for study INS-212.
NTM subjects from TR02-112, INS-212, and INS-312.
Note: Placebo consists of empty liposomes + MDR in Study TR02-112, and MDR alone in Study INS-212
*ALIS + MDR in NTM Studies TR02-112, INS-212, and INS-312
IR = Incidence Rate (number of patients with event per 100 years of cumulative exposure); CI = Confidence Interval for IR
SYE = Subject Years of Exposure; TEAE = treatment-emergent adverse events.
SYE were rounded for display purposes. Calculations were based on actual values. SYE is time subjects were taking study treatment, removing off treatment cycles.
Data Source: Module 5.3.5.3 RMP TFLs Table SIII.8

Table 13: Characterisation of Risk of Treatment-Emergent Adverse Events of Special Interest Category Alveolitis Allergic – Multiple Dose Studies – Safety Population – Outcomes and Severity

	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}**
Event Outcome		
Unknown/Missing	0	0
Recovered/Resolved	9 (2.2%) [2.8] {1.3, 5.2}	1 (0.6%) [1.2] {0, 6.4}
Recovering/Resolving	0	0

	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}**
Recovered/Resolved with sequelae	1 (0.2%) [0.3] {0, 1.7}	0
Not recovered/Not resolved	3 (0.7%) [0.9] {0.2, 2.7}	0
Fatal	0	1 (0.6%) [1.2] {0, 6.4}
Maximum Severity CTCAE		
Grade 1	1 (0.2%) [0.3] {0, 1.7}	0
Grade 2	4 (1.0%) [1.2] {0.3, 3.1}	0
Grade 3	6 (1.5%) [1.8] {0.7, 4.0}	1 (0.6%) [1.2] {0, 6.4}
Grade 4	2 (0.5%) [0.6] {0.1, 2.2}	0
Grade 5 (Death)	0	1 (0.6%) [1.2] {0, 6.4}
Grade 3, 4, and 5	8 (2.0%) [2.4] {1.1, 4.8}	2 (1.3%) [2.3] {0.3, 8.4}

Data presented through the cut-off date (25-Oct-2018) for study INS-212.
NTM subjects from TR02-112, INS-212, and INS-312.
Note: Placebo consists of empty liposomes + MDR in Study TR02-112, and MDR alone in Study INS-212
*ALIS + MDR in NTM Studies TR02-112, INS-212, and INS-312
IR = Incidence Rate (number of patients with event per 100 years of cumulative exposure); CTCAE = Common Terminology Criteria for Adverse Events; CI = Confidence Interval for IR SYE = Subject Years of Exposure.
SYE were rounded for display purposes. Calculations were based on actual values. SYE is time subjects were taking study treatment, removing off treatment cycles.

Data Source: Module 5.3.5.3 RMP TFLs Table SIII.8

Post-authorisation Experience

A comprehensive analysis of data collected during the post-authorisation experience does not indicate a change in the characterisation of the risk.

Risk Factors and Risk Groups:

Risk factors for the development of allergic alveolitis in response to treatment with inhaled Arikayce liposomal have not been identified.

In the general population, repeated exposure to inhaled organic materials including inhaled medicines increases the risk of development of allergic alveolitis.

Preventability:

There are no known effective preventive measures apart from avoidance of the allergen. If allergic alveolitis develops in a subject treated with Arikayce liposomal, the treatment should be discontinued to prevent worsening of the condition. The evidence from clinical studies with Arikayce liposomal suggests that allergic alveolitis should resolve with appropriate medical management including treatment with corticosteroid therapy.

Impact on the Risk-benefit Balance of the Product:

Allergic alveolitis was reported to occur with a crude incidence of 3.2% in clinical studies with Arikayce liposomal administered to patients with refractory NTM lung infection caused by MAC (Table 12). The condition appears to resolve with discontinuation of treatment with Arikayce liposomal and the administration of corticosteroids. Further characterisation of the risk is unlikely to have an impact on the perceived risk-benefit balance for Arikayce liposomal.

Public Health Impact:

Arikayce liposomal is intended to be used in subjects with MAC lung infection for which there are limited effective alternative treatments. MAC lung infection is a rare disease. The public health impact of allergic alveolitis associated with treatment with Arikayce liposomal is, therefore, predicted to be minimal.

SVII.3.2. Presentation of the Missing Information

Not applicable.

Part II: Module SVIII - Summary of the Safety Concerns

Table 14: Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	Allergic alveolitis
Important potential risks	None
Missing information	None

Part III: Pharmacovigilance Plan (Including Post-authorisation Safety Studies)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific Adverse Reaction Follow-up Questionnaire for Allergic Alveolitis:

A specific follow-up questionnaire has been developed to obtain detailed information on reports of suspected ADRs involving allergic alveolitis (Annex 4). This questionnaire is distributed to reporters of cases including the MedDRA PTs Acute interstitial pneumonitis, Alveolar lung disease, Alveolitis, Eosinophilic pneumonia, Eosinophilic pneumonia acute, Eosinophilic pneumonia chronic, Hypersensitivity pneumonitis, Interstitial lung disease, Idiopathic pulmonary fibrosis, Lung opacity, Lung disorder, Pneumonitis, Pulmonary fibrosis, Pulmonary toxicity, and Respiratory disorder.

The incidence of this important identified safety concern has been adequately characterised for Arikayce liposomal in the clinical study safety data set. Participants in clinical studies are recruited selectively. The purpose of the follow-up questionnaire is to obtain information on the characteristics of the safety concern when adverse reactions have been reported during use in clinical practice in a less selective environment.

Over and above the information provided in initial case reports, the follow-up questionnaire aims to obtain detailed risk factors for the specific safety concern reported.

The data obtained from detailed follow-up of the important identified safety concern will undergo medical review for causality assessment, and identification of potential risk factors. The data will be reviewed periodically according to the applicant's standard pharmacovigilance procedures and will be reported cumulatively in PSURs.

III.2 Additional Pharmacovigilance Activities

No additional pharmacovigilance activities are planned.

III.3 Summary Table of Additional Pharmacovigilance Activities

Not applicable.

Part IV: Plans for Post-authorisation Efficacy Studies

Not applicable.

Part V: Risk Minimisation Measures (Including Evaluation of the Effectiveness of Risk Minimisation Activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table 15: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation 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 restricted medical prescription. Treatment initiated and managed by physicians experienced in the treatment of the targeted population.

V.2. Additional Risk Minimisation Measures

Patient Alert Card – allergic alveolitis

Objectives:

The purpose of the patient card is to raise awareness of the risk of allergic alveolitis and to encourage patients to seek medical advice promptly when symptoms develop.

Rationale for the Additional Risk Minimisation Activity:

NTM lung infection is a rare disease, which usually develops in subjects with chronic lung conditions. It is therefore important to detect allergic alveolitis at the earliest opportunity, to minimise the risk of further lung injury. The patient card will serve as a reminder to the patient to be observant for potential symptoms of allergic alveolitis. It will also serve as a reminder to medical attendants; patients will be advised to show the card at any contact with a health professional.

Target Audience and Planned Distribution Path:

The target audience is the patient.

The card is included in every carton containing Arikayce liposomal.

Text:

The text showing on the card (Annex 6) is included in the labelling.

Plans to Evaluate the Effectiveness of the Interventions and Criteria for Success:

Effectiveness of this additional risk minimisation measure is evaluated using outcome measures as follows:

- follow-up of all case reports suggestive of allergic alveolitis with a structured questionnaire for important details that might help to identify risk factors for this safety concern. The questionnaire is also be used to assess the impact of the card on patient's knowledge and behaviour regarding allergic alveolitis.
- estimate the reporting incidence and secular trends for allergic alveolitis with the commercial product and report this in PSURs.
- assess the reporting incidence of allergic alveolitis with the commercial product in the NTM lung infection population and compare it, to the extent possible, with the expected incidence from clinical studies conducted with Arikayce liposomal.

V.3 Summary of Risk Minimisation Measures

Table 16: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

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 restricted medical 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

Part VI: Summary of the Risk Management Plan

Summary of risk management plan for Arikayce liposomal (amikacin sulfate)

This is a summary of the Risk Management Plan (RMP) for Arikayce liposomal. The RMP details important risks of Arikayce liposomal, how these risks can be minimised, and how more information will be obtained about Arikayce liposomal's risks and uncertainties (missing information).

Arikayce liposomal's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Arikayce liposomal should be used.

Important new concerns or changes to the current ones will be included in updates of Arikayce liposomal's RMP.

I. The Medicine and What it is Used for

Arikayce liposomal is authorised for the treatment of adults with *Mycobacterium avium* Complex lung infection (see SmPC for the full indication). It contains amikacin sulfate as the active substance, and it is given by oral inhalation.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Arikayce liposomal, together with measures to minimise such risks and the proposed studies for learning more about Arikayce liposomal's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Arikayce liposomal is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Arikayce liposomal are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which

there is sufficient proof of a link with the use of Arikayce liposomal. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List Of Important Risks and Missing Information	
Important identified risks	Allergic alveolitis
Important potential risks	None
Missing information	None

II.B Summary of Important Risks

Important Identified Risk: Allergic Alveolitis	
Evidence for linking the risk to the medicine	This identified risk is based on the findings from the clinical trials TR02-112, INS-212 and INS-312 in patients with refractory NTM lung infection caused by MAC. The percentage of subjects treated with Arikayce liposomal for NTM lung disease (N = 404) in whom allergic alveolitis was reported was 3.2%, which was higher than the percentage in subjects that received placebo (N = 157) in the same studies (1.3%). The evidence from these randomised, controlled clinical trials is considered to be a reliable predictor of how subjects will respond to treatment in clinical practice, by convention.
Risk factors and risk groups	Risk factors for the development of allergic alveolitis in response to treatment with inhaled Arikayce liposomal have not been identified. In the general population, repeated exposure to inhaled organic materials including inhaled medicines increases the risk of development of allergic alveolitis.

Risk minimisation measures	*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 restricted medical prescription. Treatment initiated and managed by physicians experienced in the treatment of the targeted population. *Additional risk minimisation measures:* Patient Alert Card

II.C Post-authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Arikayce liposomal.

II.C.2 Other Studies in Post-authorisation Development Plan

There are no studies required for Arikayce liposomal.

Part VII: Annexes

Table of Contents

Annex 4 – Specific Adverse Drug Reaction Follow-up Forms

Table of contents:

Allergic alveolitis questionnaire

Event as reported:

A. Medical history			
1.	Airway hyperresponsiveness?	☐ Yes ☐ No	Date of diagnosis (mm/dd/yyyy):
2.	Atopy?	☐ Yes ☐ No	Date of diagnosis (mm/dd/yyyy):
3.	Environmental or occupational exposure to dust, mold, chemical agents?	☐ Yes ☐ No	Date of diagnosis (mm/dd/yyyy):
4.	Does the patient have recurrent symptoms such as fever, cough, shortness of breath, fatigue that could be related to certain places or following certain activities started prior Arikayce commencement?	☐ Yes ☐ No	Date of diagnosis (mm/dd/yyyy):
5.	Any other relevant medical history?	☐ Yes ☐ No	If yes, please specify and provide date of diagnosis: _____

B. Event description	
1.	Please provide start date of therapy with Arikayce or provide duration of treatment prior to event onset. Start date of suspect drug (mm/dd/yyyy): _____ Duration of treatment: _____
2.	Please provide onset date of the event: _____
3.	Was the diagnosis of allergic alveolitis (hypersensitivity pneumonitis) established? ☐ Yes ☐ No If yes, please provide the date and specify clinical course of the disease: (mm/dd/yyyy) _____ Clinical course: ☐ acute (manifestation 4-8h following exposure/ symptoms resolved within hours to days)

	☐ subacute (gradual manifestation over the course of weeks/resolved within weeks or months) ☐ chronic
4.	Please provide all concomitant medications (including medications that were commenced and stopped within 3 months before diagnosis of allergic alveolitis) : _____
5.	Please provide results of chest X-ray, computed tomography, pulmonary function testing, bronchoalveolar lavage, complete blood count, lung biopsy, immunology testing: _____
6.	Was there any corrective treatment administered due to the reported event(s)? ☐ Yes ☐ No If yes, please provide details and duration of treatment: _____
7.	Was the suspect drug discontinued or interrupted? ☐ Yes ☐ No If yes, please indicate the date of interruption or discontinuation: _____
8.	Please provide the final outcome of the reported event: ☐ not recovered ☐ recovered If recovered, please provide date of recovery: _____
9.	Was the treatment with the suspect drug reintroduced? ☐ Yes ☐ No Did the event reoccur? ☐ Yes ☐ No

C. Please populate if case report originated from EU or UK	
1.	Did the patient ever demonstrate awareness about the patient alert card (PAC): (the patient was keeping the PAC at all times, the patient showed this PAC to you (or any doctor, pharmacist, nurse), the patient made a reference to the PAC when contacting you (or any doctor, pharmacist, nurse), etc.) ☐ Yes ☐ No ☐ I do not know
2.	Did the patient demonstrate knowledge of the information contained in the patient alert card (PAC): (the patient was well aware of the signs or symptoms listed in the PAC and understanding that they should prompt contacting his/her doctor immediately) ☐ Yes ☐ No ☐ I do not know
3.	The patient contacted a health care professional (yourself or any doctor, pharmacist, nurse) immediately or within 2-3 days after the start of signs/symptoms ☐ Yes ☐ No ☐ I do not know

D. Additional information

Annex 6 – Details of Proposed Additional Risk Minimisation Activities

Approved Key Messages of the Additional Risk Minimisation Measure:

Patient Alert Card

Arikayce liposomal may be associated with the development of an allergic lung condition (allergic alveolitis)

Contact your doctor immediately if you develop any signs or symptoms such as:

- Fever, cough, worsening breathlessness, weight loss
- Lung condition gets worse, affecting your breathing or overall health

Be sure to notify any health care professional you see that you are being treated with Arikayce liposomal and show them this card.

Annex 7 – Other Supporting Data (Including Referenced Material)

List of Publications and Other Bibliographic Material Referenced in This RMP

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