



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

## Withdrawal assessment report

### Arikayce

International non-proprietary name: amikacin

Procedure No. EMEA/H/C/003936/0000

### Note

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



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## List of abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATS	American Thoracic Society
BID	Twice a day
BLQ	Below limit of quantification
BMI	Body mass index
CF	Cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFU	Colony forming units
CI	Confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
DPPC	Dipalmitoylphosphatidylcholine
FEF <sub>25-75%</sub>	Forced expiratory flow during mid-portion of expiration
FEV <sub>1</sub>	Forced expiratory volume in 1 second
FEV <sub>1</sub> % predicted	Forced expiratory volume in 1 second, % predicted
FVC	Forced vital capacity
GGT	Gamma glutamyl transferase
GRH	Global Rating of Health
IDSA	Infectious Disease Society America
IV	Intravenous
LAI	Liposomal Amikacin for Inhalation (formerly called "Arikace")
MAC	<i>Mycobacterium avium</i> complex
Mab	<i>Mycobacterium abscessus</i>
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum inhibitory concentration
mITT	Modified intent-to-treat
NTM	Nontuberculous mycobacteria
<i>P. aeruginosa</i>	<i>Pseudomonas aeruginosa</i>
PK	Pharmacokinetics
PT	Preferred term
QD	Once a day
QOL	Quality of life
RSSQ	Respiratory and Systemic Symptom Questionnaire
SAE	Serious adverse event
SD	Standard deviation
SMQ	Standard MedDRA Query
SOC	System organ class
SQS	Semi-Quantitative Scale
TEAE	Treatment-emergent adverse event
TIS	Tobramycin Inhalation Solution
TOBI	Tobramycin Solution for Inhalation
ULN	Upper limit of normal

## 1. Recommendation

Based on the review of the data on quality, safety and efficacy, the CHMP considers that the application for Arikayce, an orphan medicinal product, for the revised indication:

*treatment of Mycobacterium avium Complex (MAC) lung disease in adult patients who have persistent positive sputum cultures despite the use of medically appropriate first-line therapy*

**is not approvable** since Major Objections have been identified, which preclude a recommendation for marketing authorisation at the present time.

### **New active substance status**

Amikacin is not a new active substance.

## 2. Executive summary

### 2.1. Problem statement

Non-tuberculous Mycobacteria (NTM) are ubiquitous in the environment. The pulmonary infection caused by these organisms has features that overlap with tuberculosis, but disease definition can be more complex as recovery of a single isolate from the airway secretions does not necessarily indicate disease. In contrast to tuberculosis, there is no convincing evidence of person-to-person spread. It appears that the prevalence of human disease attributable to these organisms over the past 2 decades is increasing.

Pulmonary disease due to NTM was traditionally reported as primarily upper lobe fibrocavitary disease occurring in male smokers with emphysema. More recently, certain disease and demographic populations seem to be particularly susceptible to nodular bronchiectatic pulmonary disease with predominant infection of the anterior aspect of the mid-lung. In CF, the prevalence of NTM (~75% *Mycobacterium avium* complex [MAC], 20% *M. abscessus*) in the lower airways is 13%, and increases with age. Elderly, Caucasian women without apparent predisposing conditions have been reported with increasing frequency to have pulmonary disease associated with MAC, and one community pulmonary practice reported this to be a prominent cause of chronic cough with infiltrates.

Signs and symptoms of NTM pulmonary infection are variable and nonspecific. They include chronic cough, sputum production, and fatigue. Less commonly, malaise, dyspnea, fever, hemoptysis, and weight loss can also occur, usually with advanced NTM lung infection.

Evaluation is often complicated by the symptoms caused by co-existing lung diseases. These conditions include chronic obstructive airway disease (COPD) associated with smoking, bronchiectasis, previous mycobacterial diseases, CF, and pneumoconiosis.

Treatment guidelines for patients with MAC lung infection in the recently published ATS/Infectious Diseases Society of America (IDSA) consensus document were based primarily on small uncontrolled or non-comparative studies in patients with predominantly severe or recalcitrant MAC disease. Guidelines from the Brompton Hospital (London) provide similar recommendations. Overall, there remains a lack of sufficiently powered, prospective clinical trials aimed at the treatment of pulmonary MAC infection. There were no sufficient clinical trials for pulmonary *M. abscessus* infection upon which to base treatment recommendations; the guidelines list drugs which may be effective based on either in-vitro susceptibility or efficacy shown in skin and soft tissue infections. Many of the drugs used in these prolonged, multi-drug regimens are expensive and poorly tolerated. It is clear from single-site studies that more effective, less-toxic therapeutic options are needed.

### 2.2. About the product

Amikacin is a well-established aminoglycoside that is administered intravenously. As with other aminoglycosides it is associated with adverse effects on hearing, balance and renal function. There is no formulation approved for the inhalation route of administration. The liposomal formulation of amikacin was developed specifically for inhalation with the aim of overcoming the rapid clearance of drug from lung tissue, so allowing once daily dosing, shortening the duration of inhalation and achieving improved penetration of biofilms without significant systemic (plasma) exposures.

Proposed revised indication and posology:

Arikayce is indicated for:

- treatment of *Mycobacterium avium* Complex (MAC) lung disease in adult patients who have persistent positive sputum cultures despite the use of medically appropriate first-line therapy

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

Arikayce should be added to existing therapy and should not be used as monotherapy.

### Posology

#### *MAC lung disease in adults*

The recommended dose for adult patients with MAC lung disease is 590 mg of Arikayce administered once daily, by oral inhalation.

Treatment with Arikayce, as part of multidrug therapy, should be continued until the microbiological goal is obtained (12 months of negative sputum cultures while on therapy).

In patients who do not achieve sputum culture conversion, physician discretion should be used to determine the length of treatment. The benefits of treatment in this population and the safety of Arikayce when dosed continuously for more than 168 days have not been established.

In the event of a missed dose the patient should administer the dose as soon as possible. Otherwise the patient should wait for their next scheduled dose. The patient should not administer two doses on the same day to make up for the missed dose.

#### *Patients with renal impairment and the elderly*

Renal function should be monitored in patients with known or suspected renal impairment, including elderly patients with potential age-related decreases in renal function (see section 4.4).

#### *Patients with hepatic impairment*

There is no experience with Arikayce in patients with hepatic impairment.

#### *Paediatric population*

The safety and efficacy of Arikayce for the treatment of MAC lung infections in paediatric patients aged less than 18 years of age has not been established. There are no data.

### Method of administration

Oral inhalation.

Arikayce should only be used with the ® (nebuliser handset and aerosol head). It must not be administered using any other nebulisation system.

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

CHMP advice was initially sought in 2008 regarding the CF programme. Protocol Assistance was obtained regarding the design for the Phase 3 study TR02-108.

Further and separate advice was sought from CHMP in 2013 but only after near completion of the Phase 2 study in non-tuberculous mycobacterial (NTM) infections.

After filing this application dossier the applicant also requested CHMP advice on the design of a Phase 3 study, which had already commenced.

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

### **GMP**

The product manufacturing site has been inspected by the MHRA in June 2014. The GMP inspection had included the complex liposome manufacturing process. The applicant has provided a GMP certificate from the FDA.

### **GLP**

All pivotal nonclinical toxicity studies were conducted consistent with International Conference on Harmonisation (ICH) Nonclinical Testing Guidelines and in compliance with the Good Laboratory Practice (GLP) Regulations.

### **GCP**

The Clinical Overview contains the following statement:

*All clinical studies were conducted with respect for the individual participants according to the respective protocol, the World Medical Association Declaration of Helsinki, and Good Clinical Practice guidelines and in accordance with International Conference on Harmonisation E6 and local regulatory requirements.*

In addition, Module 1 contains a compliance statement regarding GCP compliance of studies conducted outside of the EU.

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

- Legal basis
  - This is a full dossier submitted under Article 8(3): known active substance.
  - Eligibility to the Centralised Procedure was in accordance with the Mandatory Scope – Article 3(1) of regulation (EC) No. 726/2004 (Annex 4, Orphan drug).
  - Eligibility was confirmed on January 23rd 2014.

- Orphan medicinal products

Arikayce has EU Orphan Drug Designation for:

- Treatment of cystic fibrosis patients with *Pseudomonas aeruginosa* lung infections (EU/3/06/387) (The indication on cystic fibrosis was withdrawn by the applicant)
- Treatment of non-tuberculous mycobacterial lung infections (EU/3/14/1259).

There are no licensed medications with orphan drug status for the NTM indication.

- Significance of paediatric studies
  - There is an agreed PIP for the treatment of chronic *Pseudomonas aeruginosa* lung infection/colonisation in cystic fibrosis patients (EMA-000525-PIP01-08-M01).
  - The inclusion of the NTM indication into the approved PIP was submitted on 27 May 2014 by means of a PIP modification application. There are no data on treatment of NTM in patients aged < 18 years.

### 3. Scientific overview and discussion

#### 3.1. Introduction

Arikayce (liposomal amikacin for inhalation; LAI) was previously known as either *SLIT Amikacin* or *Arikace*. In this report the assessors often use the term LAI (see formulations below). LAI is presented for clinical use as a sterile aqueous liposomal suspension of amikacin as the sulfate. The 10 mL vial of the suspension for nebulisation presentation initially referred to a delivered dose of 8 mL per vial of 70 mg/mL amikacin (as LAI), which equates to a delivered dose of 560 mg amikacin. A review of 24 later lots showed that the average volume delivered from the vials to the nebuliser was actually 8.43 mL, i.e. the applicant concluded that the delivered dose using the commercial presentation is 590 mg amikacin.

#### 3.2. Quality aspects

##### Drug Substance

Amikacin sulfate is a semi-synthetic aminoglycoside antibiotic derived from kanamycin A. The drug substance is a white to almost white crystalline powder that is freely soluble in water. Its limited solubility in ethanol contributes to the high encapsulation efficiency achieved during manufacture of Liposomal Amikacin for Inhalation (LAI).

Amikacin sulfate complies with Ph. Eur. requirements for amikacin sulfate Ph. Eur. and additional in-house specifications as per the ASMF. Test and acceptance criteria are mainly those described in ASMF. The Active Substance Master File (ASMF) procedure is used and is provided by the ASMF holder. Amikacin sulfate. Information on structural characterisation of amikacin sulfate has been provided and discussion on elucidation of structure and other characteristics is considered not necessary. The structure and identification of stereochemistry is adequately demonstrated.

Major Objections had been initially raised regarding clarity of the starting material and the source of the manufacture and controls of the starting material, however these have been resolved.

The proposed specification for the drug substance is in line with the Ph. Eur. with additional tests. This is accepted. The analytical methods have been adequately described in the ASMF, however although the method validation has been discussed in the QOS (AP) of the ASMF, the validation of these methods the relevant section 3.S.4.3 of the DMF does not seem to have been submitted. This has been requested.

Regarding stability data, accelerated and long-term stability data indicate that amikacin sulfate is stable. It is recommended that amikacin sulfate be stored below 25°C. A re-test period of 60 months has been established. The stability protocol was provided.

Stability studies were carried out on nine batches of amikacin sulfate according to the "Guideline on stability testing: Stability Testing of Existing Active Substance und Related Finished Product " (CPMP/QWP/122/02 rev.1). The container system used for stability testing of bulk drugs was representative of the proposed packaging material. The analytical methods used to analyse each batch put on stability and the specifications are the ones reported in the analytical monograph and used for batch release. Stability data over 6 months stored under accelerated conditions (40°C ± 2°C and 75 % ± 5 % RH) and long-term stability data (25°C ± 2°C and 60 % ± 5 % RH) over 60 months were submitted for 3 batches.



The stability data provided show no significant trend and justify the re-test period of 60 months stored below 25°C.

### **Drug product**

Liposomal Amikacin for Inhalation (LAI) is a suspension consisting of amikacin sulfate encapsulated in liposomes. The liposomes are composed of two lipids, which are dispersed in sodium chloride solution. The drug product is filled into a 10-mL, 20-mm borosilicate Type I flint glass single-use vial, stoppered with a bromobutyl stopper and sealed with an aluminum flip off–tear off cap. The vial contains 9.3 grams (8.9 mL) of LAI to deliver 8.4 mL to a product-specific nebulizer. LAI is delivered through the mouthpiece of the Nebulizer System.

The aim of the pharmaceutical development was the development of a liposomal nebulizer suspension of amikacin sulfate in an aqueous based formulation. The development of the product as a liposomal suspension for nebulisation is to manipulate the pharmacokinetics to permit once-a-day dosing and to target delivery of amikacin to the lungs. The liposomes are comprised of naturally derived lipids which are the basis of lung surfactant replacement therapies indicating a high degree of lung biocompatibility; an important property for an inhaled formulation that is to be administered repeatedly.

A discussion of the nebulizer systems that have been used in the clinical development of Liposomal Amikacin for Inhalation (LAI) is provided in Nebulizer Development Report. A summary of the certification of the nebulizer system (CE mark) is provided in Section 3.2.R Medical Device.

The development is generally in line with the Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products – EMEA/CHMP/QWP/49313/2005 Corr in relation to pharmaceutical development studies for products nebulisation.

### *Control of excipients*

The drug product manufacturer receives the liposome forming excipients raw materials with a copies of the certificate of analysis.

### *Manufacturing*

The proposed manufacturing process for Liposomal Amikacin for Inhalation (LAI) was developed to provide the required physiochemical properties. LAI is manufactured using a process in which an amikacin sulfate solution is combined with a lipid solution to form liposomes. Liposomal Amikacin for Inhalation (LAI) is a sterile formulation manufactured by an aseptic process. The proposed commercial manufacturing process, the approximate batch size and process controls for Liposomal Amikacin for Inhalation (LAI) have been described. Initially a major objection is raised concerning the absence of manufacturing process validation at this scale. The manufacturing process validation was then completed and the data presented. The process validation is considered acceptable; however a major object regarding the justification for proposed process and the comparative data on the level of one of the liposome forming excipient is outstanding.

### *Control of product*

The following tests are included in the product specification: identification, determination of total and free amikacin, aerodynamic particle size distribution (APSD), and the determination of content uniformity, amikacin degradation products, content uniformity (Delivered Dose), the liposome forming excipients concentration, lipid degradation products, residual ethanol, liposome particle size determination, aerodynamic Particle Size Distribution (APSD) post nebulization (NGI), percent associated amikacin post nebulization, determination of in vitro release of liposomal amikacin for inhalation. These are accepted; however a major point is outstanding concerning the provision of

validation data for the in vitro release test method and the insufficient comparative bridging study data between the original method and the final validated method which has been provided to demonstrate the equivalency of the two methods.

### *Stability*

The stability of LAI has been evaluated by monitoring 13 registration batches as per ICH guidelines. Data is provided for four batches at the proposed shelf life of 36 months at labeled storage conditions of 2-8°C. Nine batches were evaluated in the upright orientation only and an additional four batches were evaluated at both upright and inverted orientations. Accelerated studies were performed at 25°C for all thirteen batches and four batches were stored at 40°C. After storage for 24 months at 2-8°C, samples are transferred to 25°C and tested after up to 3 months storage. Additionally, the three batches that have reached 36 months were also transferred to 25°C and tested for sterility.

The results of real time stability data at the proposed storage conditions, as well as the accelerated stability studies support the proposed expiration dating for LAI of 36 months when stored under refrigerated conditions (2-8°C), with up to 1 month storage at ambient conditions (25°C). LAI does not need to be protected from light and cannot be frozen throughout shelf life storage and shipment.

## **3.3. Non clinical aspects**

### **Pharmacology**

Two in-vitro and 2 in-vivo studies were submitted. These are described in the Clinical Pharmacology section.

### **Pharmacokinetics**

The pulmonary deposition, retention and clearance of amikacin after single or multiple doses of liposomal amikacin for Inhalation (LAI) and single doses of free amikacin (FA) or tobramycin (FT) were evaluated in rats (primarily CD(R)IGS; the same strain used in toxicology studies) via nose-only inhalation. The Applicant states early investigative studies focused entirely on the use of tissue, serum and urine amikacin concentrations determined using an Abbott TDx™ automated fluorescence immunopolarisation assay (TDx) to describe the disposition of inhaled LAI. Follow-on studies used fluorescent immunostaining, fluorescent probes, fluorescence microscopy and spectrofluorometry to further investigate the biodistribution of LAI.

It was shown that amikacin from LAI, as for FA, undergoes biphasic clearance from the lungs. Compared to free aminoglycosides, LAI delivered higher lung levels of amikacin and a slower clearance of amikacin over time was noted. The Applicant hypothesises that the initial loss of amikacin from the lung is due to clearance of small amounts of FA that are present in the LAI preparation.

The pulmonary deposition, retention and clearance of dual-labelled LAI (amikacin-TAMRA and DiIC18(5)DS) was evaluated in rats. Female animals were exposed to LAI daily for 27 days. One set of animals was exposed to 10 mg/kg/day LAI and another group was given 90 mg/kg. On Day 28, 12 rats in each group were given a single, 90-mg/kg dose of LAI via inhalation while the remaining 24 rats in each group received a single, 90-g/kg dose of dual-labelled LAI via inhalation. The dual-labelled LAI contained approximately 0.2% (w/w) DiIC18(5)DS and 0.2% (w/w) of amikacin-TAMRA.

The amount of amikacin in the lungs after 28 days of dosing was dose-dependent. C<sub>max</sub>, AUC<sub>0-672hr</sub> and t<sub>1/2</sub> values for amikacin at 90 mg/kg were approximately 2-fold higher than at 10 mg/kg/day. The rate of clearance of amikacin from the lung was approximately 5-fold higher at 90 mg/kg/day compared to 10 mg/kg/day (i.e. approximately 5 µg/hr and 1 µg/hr, respectively). The amount of amikacin deposited per gram of lung tissue (cranial, accessory, and median right lung lobes and

sections from the top, middle, and bottom of the left lung) as well as clearance was the same (i.e. there was uniform deposition and clearance). Cmax and AUC values in urine were greater than those in serum.

Total plasma concentrations of amikacin are lower compared to intravenous dosing and therefore free plasma concentrations of amikacin would also be expected to be lower. However, it cannot be agreed that free concentrations would be lower in tissues, as liposomes can give rise to increased tissue concentrations. The Applicant is required to provide a detailed discussion of the distribution to tissues e.g. liver, kidney, spleen, heart and brain and with comparison to the distribution of free amikacin, where available.

Lung PK parameters for amikacin-TAMRA (AUC0-24hr, AUC0-672hr, T1/2 beta (hr)) did not show a dose-related increase (that was observed for unlabelled amikacin). PK parameters at 10 mg/kg were equal to or greater than those at 90 mg/kg; this was the same for DiIC18(5)DS in the lung.

The applicant states that the reason for this difference is unclear but it may be related to reduced capacity of animals at 90 mg/kg to retain amikacin and lipids of the dual-labeled LAI. Similar serum and urine levels of amikacin-TAMRA were seen at both doses. It is stated that this was expected as serum and urine amikacin levels are attributed primarily to the clearance of amikacin from the last administered dose which was the same for both groups. The clearance of DiIC18(5)DS from the lung was slower than amikacin-TAMRA and resulted in no measurable levels in serum or urine.

The fraction of amikacin released during nebulisation of LAI (approximately 40%) was cleared rapidly with an estimated pulmonary half-life ( $\alpha$ ) of  $\leq 7$  hours. The estimated half-life ( $\beta$ ) of the fraction of amikacin remaining in the lung following LAI exposure was approximately 400 hours. It is stated that the lipid was cleared slowly from the lung and the lack of measurable levels of DiIC18(5)DS in the serum or urine suggested that the lipid is cleared primarily through cellular processing. Amikacin was shown to be uniformly distributed throughout the lung.

In an inhaled biodistribution study in rats it was also shown that >50% of the total recovered dose for LAI and FA was found in the stomach and intestinal contents. It is known that aminoglycosides are not absorbed after oral administration and require administration by intravenous injection or by inhalation.

There appears to be active reabsorption of amikacin by the kidney. Comprehensive examinations of the data have been conducted in relation the transporter responsible for the reabsorption. It is currently not known which transporter responsible for the reabsorption.

No metabolism studies have been submitted with LAI. The Applicant states that as amikacin is not metabolised so no metabolism studies were conducted.

## **Toxicology**

### Inhalation studies in rats

In the 1-month GLP study animals were given 10, 30 and 100 mg/kg/day of amikacin (LAI) via nose-only inhalation. Another group was given free amikacin (FA) for the same duration at 100 mg/kg/day. Lung weights were increased at 100 mg/kg/day FA and at 30 and 100 mg/kg/day LAI. Diffuse alveolar foamy macrophage accumulation was seen in the lungs at all doses (minimal-mild at 10 mg/kg/day, mild-moderate at 30 mg/kg/day FA and 30 mg/kg/day LAI, and moderate at 100 mg/kg LAI). Minimal to moderate Bronchial Clara cell hypertrophy was seen in all animals given amikacin. Minimal/mild focal alveolar foamy macrophage accumulation was also observed in animals given the empty liposomes (ELC).

Lipid staining of lung sections did not provide any evidence of excessive accumulation of phospholipids; the staining, according to the Applicant, was more consistent with neutral fat. Evidence of upper

respiratory irritation (nasal cavity, larynx, and trachea) was observed with animals given FA and at all doses of LAI. This was considered to reflect non-specific local irritation, commonly observed in nose-only inhalation studies in rats with a range of test items. Following a 1-month post-dose period, all findings were reversed or showed evidence of reversibility. The NOAEL in this study was considered to be 100 mg/kg/day.

In the 6-month study, animals were given LAI once daily via nose-only inhalation for up to 240 minutes at targeted daily doses of 10, 30 and 90 mg/kg/day of amikacin. Increased absolute neutrophils were seen at 30 and 90 mg/kg/day (also after 3 months of dosing), increased serum phosphorous in females at 30 and 90 mg/kg/day, and decreased serum triglycerides in males and decreased serum globulins in females at 90 mg/kg/day were also noted. After both 3 and 6 months, increased lung weights were noted at all doses and tan/white foci in the lungs were noted at 30 and 90 mg/kg/day.

Test article-related microscopic changes were present in the lungs, nasal turbinates, larynx, trachea and kidneys after both 3 and 6 months of dosing. In the lungs, foamy macrophage accumulation was observed at all doses following 3 and 6 months of dosing (e.g., slight at 10 mg/kg/day, mostly moderate at 30 mg/kg/day, and mostly marked at 90 mg/kg/day after 6 months of dosing). Multiple foci of subacute/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 30 and 90 mg/kg/day, the inflammation was accompanied by regenerative hyperplasia of the alveolar epithelium.

The applicant states that the inflammation was likely a response to macrophage degeneration secondary to overload of the phagocytic function of the cells.

Findings in the upper respiratory tract at 10, 30, and/or 90 mg/kg/day following 3 and 6 months of dosing included degenerative changes in the nasal turbinates, squamous/squamoid metaplasia/hyperplasia of the pseudostratified columnar epithelium in the larynx, and degenerative changes of the tracheal epithelium. The applicant states that the changes in the nasal turbinates and trachea were consistent with local irritation secondary to prolonged administration of LAI by daily nose-only inhalation whereas the laryngeal findings were considered to be non-specific responses to inhaled LAI (reference supplied Boorman *et al.* 1990).

In the kidneys, minimal nephropathy was evident in several males at 9 mg/kg/day after 13 weeks of dosing. After 26 weeks of dosing, minimal to slight nephropathy was evident in most males at 90 mg/kg/day and several females at this dose; minimal nephropathy was also observed in several controls (both sexes) and one male at 10 mg/kg/day. The applicant states that the nephropathy was not unexpected since the kidney is a known target organ for amikacin and other aminoglycosides.

After 12 weeks of recovery, several clinical-laboratory changes were still evident in females (increased serum phosphorous at 30 and 90 mg/kg/day and decreased serum globulins at 90 mg/kg/day). Histopathological changes were largely completely reversed at 10 mg/kg/day and showed evidence of reversibility at 30 and 90 mg/kg/day. Findings in the lungs that were not present after 3 or 6 months of dosing at 90 mg/kg/day included a single minimal focus of alveolar fibrosis in two animals and minimal foci of subacute/chronic inflammation/fibrosis of the visceral pleural capsule in 4 animals. These changes were considered by the applicant as secondary to inflammation associated with the alveolar macrophage accumulation.

Based on the subacute/chronic inflammation and/or alveolar epithelial hyperplasia that accompanied the macrophage infiltration, the NOAEL for changes in the lung was considered to be < 10 mg/kg/day. The NOAEL for nephropathy was 30 mg/kg/day. All changes were reversed or showed evidence of reversibility following a 3-month recovery period. It was clear that foamy macrophage accumulation

was associated with inflammation in this study. This inflammation was accompanied by regenerative hyperplasia of the alveolar epithelium.

In addition findings in the upper respiratory tract at 10, 30, and/or 90 mg/kg/day following 3 and 6 months of dosing consisted of degenerative changes in the nasal turbinates, squamous/squamoid metaplasia/hyperplasia of the pseudostratified columnar epithelium in the larynx, and degenerative changes of the tracheal epithelium and considered a non-specific response. After the 12 week recovery period at 90 mg/kg/day single minimal focus of alveolar fibrosis was noted in two animals and minimal foci of subacute/chronic inflammation/fibrosis of the visceral pleural capsule in 4 animals. Over all these findings were considered by the applicant as an adaptive response to clear inhaled particulates associated with the drug/lipid formulation. The macrophage accumulation was considered non-adverse.

There are concerns regarding the subacute/chronic active inflammation and regenerative hyperplasia of the alveolar epithelium and exacerbation of these findings seen in the 6 month rat study.

While the Applicant provides some evidence that the findings of the rat studies with LAI were species (rat) specific and that 1) the cause could be due to lung burden and 2) a threshold effect could exist and these findings were not seen in the dog, the relevance of the rodent data to humans is still unknown (response to Day 120 questions). The Applicant acknowledges that the currently available safety database does not include data on patients dosed continuously for more than 168 days, however proposes the following in the product literature

*Treatment with Arikayce, as part of multidrug therapy, should be continued until the microbiological goal is obtained (12 months of negative sputum cultures while on therapy) in patients who achieve culture conversion.*

*In patients who do not achieve sputum culture conversion, physician discretion should be used to determine the length of treatment. The benefits of treatment in this population and the safety of Arikayce when dosed continuously for more than 168 days has not been established*

This is not considered acceptable. See the nonclinical conclusions and outstanding clinical Major Objection.

In addition, the applicant argues that humans do not appear to be as susceptible to adverse particle overload responses as those described in rats. In light of those arguments, and for further assessment of the clinical relevance of the rat lung findings, the Applicant is requested to discuss these findings also considering the disease to be treated itself; i.e. to discuss whether the disease itself affects the sensitivity of the human lung.

#### Inhalation studies in dogs

At Day 120 the applicant was asked to fully address the changes seen in the upper respiratory tract (such as the focal erosions in the larynx of animals in the 9 month dog study) and the possible relevance to the clinical situation. In addition it has been shown that lymph node reactions such those seen in these studies (perivascular/peribronchiolar lymphoid cell infiltration) are not readily reversible and lymphoid findings associated with foamy macrophages can indicate an adverse effect (Lewis *et al*). The Applicant was asked to fully address the clinical relevance of the foamy macrophage accumulation and associated lymph node finding seen in the 1, 3 and 9 month dog studies.

In relation to the findings of the dog studies, Applicant argues that the presence of intracytoplasmic basophilic granules (ICBG) in epithelial cells at the apex of the tracheal bifurcation/tracheal epithelium seen the 9-month study was not associated with other microscopic changes such as degeneration, inflammation or proliferation and that since the tracheal bifurcation is the site of greatest particle

impact during inhalation therapy, the ICBG probably represents deposition and epithelial uptake of LAI at this anatomical location.

Perivascular and/or peribronchiolar infiltration were observed in the lung in all dog studies. In contrast to the macrophage accumulation in dogs, increased amounts of perivascular and peribronchiolar infiltrates was observed in the 1-month study in dogs, but was not seen in the 3 and 9 month studies. Therefore the Applicant argues that the infiltration may have been either a transient occurrence or an incidental finding in the 1-month study. This is agreed.

In the regional lymph nodes (bronchial and mediastinal), foamy macrophages (often containing ICBG in the 3- and 9-month studies) were seen however there was no associated signs of inflammation. The Applicant goes onto say that the migration of foamy macrophages to lymph nodes has been considered a nonspecific immune response to inhalation of poorly soluble particles (literature reference); however, given that the main route of clearance of macrophages from the lungs is via the interstitium/lymphatics, these findings in dogs appear consistent with the normal clearance of macrophages from the lung rather than an immune response.

Minimal to moderate degeneration of the respiratory and olfactory epithelium was seen in the nasal turbinates in the 9 month dog study (not seen in the 1- and 3-month studies) and the Applicant argues that these findings were not severe and not associated with more damaging changes such as necrosis. The Applicant go onto say that given that LAI was administered with a closed face mask system, it is likely that the method of administration contributed to the development of these changes. In adult humans, LAI is administered via a mouth piece, thus preventing direct access to the nasal turbinates during dosing.

Finally the Applicant discusses the changes seen in the larynx; that they were minor and were only observed in only one or two dogs at the high in the 1 and 3 month studies and were similar in severity and there were no laryngeal changes in the 9 month study. Thus, the earlier changes may represent low incidence (i.e., only 3 of 72 dogs dosed with LAI in repeat-dose studies had laryngeal changes) or transient occurrences given that they were not present in the 9-month study. The applicant states that this was consistent with the findings in the Phase 2 (TR02-112) clinical study in patients with non-tuberculous mycobacteria (NTM) lung disease. Symptoms such as dysphonia and oropharyngeal pain were common (> 10%) and reported early, but only led to one discontinuation in a subject experiencing oropharyngeal pain. Further, reports of dysphonia and oropharyngeal pain decreased over time.

It can be agreed that given the presence of intracytoplasmic basophilic granules (ICBG) in epithelial cells at the apex of the tracheal bifurcation/tracheal epithelium noted in the 9-month study was not associated with other microscopic changes such as degeneration, inflammation or proliferation, this finding is unlikely to be clinically relevant. In addition given that perivascular and/or peribronchiolar infiltration was only noted in the 1 month study and not in longer term studies, it was most like a an incidental finding in the 1-month study. In addition it is also agreed that the respiratory and olfactory epithelium was seen in the nasal turbinates in the 9 month dog study is unlike to pose a risk, as LAI is administered via a mouth piece in humans so prevents direct access to the nasal turbinates during dosing. It is also agreed that the changes seen in the larynx were over-all seen at a low incidence and were not present in the 9 month study. The Applicant has adequately addressed this objection.

## **Genotoxicity**

LAI formulations were shown not to be genotoxic in a standard battery of tests.

## **Carcinogenicity**



Neoplastic changes considered directly related to LAI were seen in the lung. At 45 mg/kg/day squamous cell carcinomas were observed in two females. The tumours were observed at terminal sacrifice after almost 2 years of dosing and thus were not the cause of death in these rats. A keratinizing pulmonary cyst was also present in a female at 45 mg/kg/day and squamous metaplasia of the alveolar epithelium was present in two females at 45 mg/kg/day. Lung concentrations of amikacin were not determined in this study; however, the 45 mg/kg dose (associated with lung tumours) is within 2-fold of that used in humans when normalised on a body surface area or lung weight basis.

Bronchiole/alveolar adenoma was observed in one male (grossly evident at necropsy) and one female at 45 mg/kg/day. This finding was considered of uncertain relationship to LAI administration since the incidence was within the HLS historical background range. Other neoplastic changes in animals given LAI included squamous cell carcinoma of the palate region of the head in one male and one female at 5 mg/kg/day and one male at 45 mg/kg/day (this was the cause of death in these rats). Increased incidences of tumours in the endocrine pancreas (islet cell carcinomas and combined islet cell adenomas and carcinomas) were observed in males at 45 mg/kg/day. The incidences of the tumours in the palate region of the head and pancreas were not statistically significantly increased, were within the HLS historical background range, and/or lacked a dose-response relationship. The applicant provided adequate evidence that the incidence of bronchiolo/alveolar adenoma, islet cell adenoma and islet cell carcinoma observed in the rat carcinogenicity study (HLS Study No. 09-6345) was in the range of well documented historical control data.

Non-neoplastic test article-related changes (degenerative changes in the nasal cavity, squamous metaplasia and epithelial hyperplasia, moderate inflammation, foamy alveolar macrophages, alveolar/interstitial inflammation, and alveolar epithelial hyperplasia and foamy macrophages in mediastinal and bronchial lymph nodes) were also noted in this study. The applicant ascribed these findings to chronic irritation in rats. Foamy alveolar macrophages associated with inflammation demonstrate an adverse effect.

There are no margins of safety exposure over the expected clinical doses/exposures for any of the findings seen in this study.

### **Reproductive and developmental toxicity**

Studies in juvenile animals with LAI were not conducted in support of this submission. The Applicant states that C<sub>max</sub> and AUC values for amikacin following the inhalation of LAI are 17 times and 11 times lower than C<sub>max</sub> and AUC values for amikacin following intravenous or intramuscular injection in humans. See the Major Objections, which relate to all proposed populations and ages.

### **Environmental toxicology**

Using refined F<sub>pen</sub> values that reflect the prevalence of CF and NTMLD in the EU, a total PEC for amikacin was calculated as 37 ng/L. This is higher than the Phase I action level of 10 ng/L and as a result a Phase II Tier A testing program was initiated. The results from the structure activity determination of octanol:water partitioning indicate that the log K<sub>ow</sub> value is expected to be low; therefore, a PBT assessment is not required. Further, the PEC concentrations are well below the minimum inhibitory concentrations for efficacious antimicrobial activity.

Only the results of the ready biodegradability study are currently available. In the ready biodegradability study, it was determined that amikacin was not readily biodegradable (SMV Study 14071.6100). The final reports for the following seven studies were submitted (at day 120). Predicted environmental concentrations exceeded the action limit of 0.01 µg/L and triggering a Phase II – Tier A for amikacin. The applicant provided final ecotoxicological studies reports: biodegradation (301B),

Activated Sludge, Respiration Inhibition Test (OECD 209), Daphnia Reproduction (OECD 211), Algae Toxicity (OECD 201), Fish Early Life Stage (OECD 210), Sorption/Desorption (OECD 106), Aerobic and Anaerobic Transformation in Aquatic Sediment Systems (OECD 308). Partition Coefficient (n-octanol/water): Shake Flask Method (OECD 107) study was carried out as a part of Phase I.

Ecotoxicological expert calculated predicted environmental concentration ( $PEC_{\text{SURFACEWATER}}$ ) of LAI by the EMA guideline pre-screening equation. Default values of  $F_{\text{pen}}$ ,  $WASTEW_{\text{inhab}}$ ,  $DILUTION$  were included in the initial  $PEC_{\text{SURFACEWATER}}$  calculation. The  $DOSE_{\text{ai}}$  was defined for maximum dosage of drug substance as 590 mg/day. The result of such approach was  $PEC_{\text{SURFACEWATER}} = 2.95 \mu\text{g/L}$  above the trigger value of  $0.01 \mu\text{g/L}$ . Thus the action limit of  $0.01 \mu\text{g/L}$  is not applicable and the environmental risk assessment Phase II is required. Besides the initial PEC calculation the revised  $PEC_{\text{SURFACEWATER}}$  was estimated by applying refined  $F_{\text{pen}}$ . Based on the report author clarifications, the use of amikacin is expected to be much lower than the default  $F_{\text{pen}}$  of 1% as the LAI is intended only for treatment of two rare diseases (cystic fibrosis and nontuberculous mycobacterial lung disease) – EU Orphan Drug Designation. The idea of  $PEC_{\text{SURFACEWATER}}$  recalculation is supported by Co-Rapp. Revised  $PEC_{\text{SURFACEWATER}}$  was calculated separately for CF and NTMLD. Revised  $PEC_{\text{SURFACEWATER}}$  of  $0.019 \mu\text{g/L}$  was deduced from the  $F_{\text{pen}} = 0.00013$  of CF. Revised  $PEC_{\text{SURFACEWATER}}$  of  $0.018$  was corresponded to the  $F_{\text{pen}} = 0.00006 \mu\text{g/L}$  of NTMLD. The estimation of the total revised  $PEC_{\text{SURFACEWATER}} = 0.037 \mu\text{g/L}$  was derived from the sum of the  $PEC_{\text{SURFACEWATER}}$  for both rare diseases, respectively. For the refinement of  $F_{\text{pen}}$  values the ERA report author used data included in the EMA two public summary of opinion on orphan designation: EMA/COMP/97247/2014 Rev.1 and EMA/COMP/428207/2006 Rev.2. In line with "Questions and answers on 'Guideline on the environmental risk assessment of medicinal products for human use'" EMA/CHMP/SWP/44609/2010, for orphan drug submissions,  $F_{\text{pen}}$  can be refined based on the prevalence on which the medicinal orphan drug designation, as adopted by the Committee for Orphan Medicinal Product (COMP), was based. Thus the source of data is considered sufficient.

Amikacin was investigated for its biodegradation in the SMV Study 14071.6100. Mean cumulative net percent  $\text{CO}_2$  evolved from aqueous test medium fortified with amikacin was -13,78% on day 28. Amikacin was not considered readily biodegradable. The transformation of  $[^3\text{H}]$ amikacin in sediments and natural water was assessed in two different water/sediment systems under aerobic conditions at a temperature of  $20 \pm 2^\circ\text{C}$  continuously in the dark for 100 days (SV Study No. 14071.6112). The half-lives of  $[^3\text{H}]$ amikacin in the water fraction and in the sediment extractables were >1 year for the Taunton River and the Weweantic River aerobic test systems. The half-lives of  $[^3\text{H}]$ amikacin in the total water/sediment test systems were >3 years for the Taunton River aerobic test system and for the Weweantic River aerobic test system. No transformation products were observed for the Taunton River and Weweantic River aerobic test samples. All validity criteria provided in the OECD 308 guideline and the protocol were met. The adsorption and desorption of  $[^3\text{H}]$ amikacin sulfate was evaluated using five solids at  $21 \pm 1^\circ\text{C}$  in the SV Study No. 14071.6108 performed according to the OECD 106 guideline. Following preliminary and adsorption and desorption testing,  $K_d$ ,  $K_{oc}$  and  $K_{des}$  values for  $[^3\text{H}]$ amikacin sulfate were determined. In the definitive adsorption study the average  $K_{oc}$  value was 33.8 mL/g for soils and 36.7 mL/g for sludges. Based on these  $K_{oc}$  values amikacin was considered to be highly mobile in soil and sludge according to the McCall classification scale. This suggests that amikacin may move through soils to reach groundwater. Amikacin treatment of activated sludge obtained from a sewage treatment plant resulted in a dose-dependent inhibition of sludge respiration. Study (SV Study No. 14071.6107) was conducted in accordance with Activated Sludge, Respiration Inhibition Test (OECD 209). The  $EC_{10}$  and  $EC_{50}$  values were 0.3 and 114 mg/L, respectively. Toxicity data on algae, daphnia and fish were submitted as outcomes of aquatic effect studies set (SV Study No. 14071.6104, 14071.6105, 14071.6106).

The procedures employed were in line with OECD 201, OECD 211, OECD 210 guidelines, respectively. The individual predicted no effect concentrations ( $PNEC_{\text{SURFACEWATER}} = 0.17 \mu\text{g/L}$ ;  $PNEC_{\text{MICROORGANISM}} = 30$



µg/L;  $PNEC_{GROUNDWATER} = 120 \text{ µg/L}$ ;) were deduced from the NOEC values of anit-microbial effect study and long-term toxicity studies. In compliance with EMEA/CHMP/SWP/4447/00 guideline and REACH guidance on the environmental risk assessment (Guidance on information requirements and chemical safety assessment Chapter R.10: Characterisation of dose [concentration]-response for environment, 2008), all above PNEC values were also calculated by adopting default assessment factor ( $AF = 10$ ) to the NOEC values from relevant studies. As all ratios ( $PEC_{SURFACEWATER} / PNEC_{SURFACEWATER} = 0.22$ ;  $PEC_{GROUNDWATER} / PNEC_{GROUNDWATER} = 0.000078$ ;  $PEC_{SURFACEWATER} / PNEC_{MICROORGANISM} = 0.0012$ ) were clearly below the recommended threshold values indicated in the regulatory guidelines it could be concluded that amikacin is unlikely to represent a risk to the aquatic environment and microorganisms. The co-rapporteur supports the MAH's conclusion that the risk characterization based on estimated PEC/PNEC ratios did not reveal any risk either to aquatic environment or microorganisms. Thus no further testing was needed in Phase II, Tier B.

Bioaccumulation potential was investigated as part of phase I. Firstly the  $\log K_{ow} = -8.78$  for amikacin was estimated by applying US Environmental Protection Agency EpiSuite software (KowWin version 1.68). Secondly the  $K_{ow}$  value of amikacin was determine experimentally by using shake flask method. According to the study report No. 14071.6103 provided by the applicant the mean  $\log K_{ow}$  for amikacin was determined to be  $< -2.00$  at pH 4, 7 and 9. This is consistent with the highly water soluble nature of this substance. This very low partition coefficient indicates no important partitioning to organic matter and suggests that the substance should not bioaccumulate. From experimental and *in silico* point of view stated  $\log K_{ow}$  was  $< 4.5$  and the substance is not considered to be bio-accumulative. Thus the significant potential to accumulate in aquatic organisms and/or in soils can be concluded as low. In line with EMEA/CHMP/SWP/4447/00 corr2<sup>1</sup>\*guideline screening for persistence, bioaccumulation and toxicity (PBT) was not required since both estimations of amikacin  $\log K_{ow}$  gave the value below the cut-off of 4.5.

The active ingredient amikacin sulfate shows a  $DT50 > 1$  year in water and in sediment and is therefore classified as very persistent in the environment.

The ERA report was supported by information on development of drug-resistant microorganisms and potential environmental effects of tobramycin. For amikacin the margin of approximately 27000 (efficacious antimicrobial concentration/total revised  $PEC_{SURFACEWATER}$ ) was deduced. The comparative ecotoxicological data suggest that the amikacin should be less toxic to alga species than tobramycin. The provided supportive information can be considered as part of environmental monography for amikacin.

Since the studies on transformation in aquatic sediment system revealed shifting of the amikacin to the sediment the Applicant has stated that the toxic study with the sediment-dwelling larvae of *Chironomus riparius* (SV Study No. 14071.6114) according to OECD 218 guideline is underway and the final report will be submitted post approval.

A new blue-green algae (Cyanophyta) test (according to OECD 201) is requested by DE as the validity criterion "mean CV for section-by-section specific growth rates" in the control replicates is not met. The Rapporteurs' do not agree. Another blue-green algae (Cyanophyta) study is not warranted. Although not all of the criteria were meant for the study provided, the data from this study are acceptable and are valid enough to be used in effective environmental risk assessment. In addition DE requests that the applicant is asked to complete the study on transformation in water sediment (OECD 308) with the structural formula and the position of the radiolabel. Again this is not agreed as the data from this study are acceptable and are valid enough to be used in effective environmental risk assessment.

## Conclusion

The Applicant provides some evidence that the findings of the rat studies with LAI were species-specific and that 1) the cause could be due to lung burden and 2) a threshold effect could exist (these findings were not seen in the dog). However, the relevance of the rodent data to humans is still unknown. A Phase 3 study (INS-212) is currently in progress in which patients with NTM lung disease will be dosed continuously for up to 16 months. If the Phase 3 results should support an approval then appropriate guidance on duration of therapy will be considered based on the evidence. At that time, the decision on the duration of therapy should take into account the nonclinical findings as well as the safety profile observed in patients in the Phase 3 study. In this regard, it should be noted that the Phase 3 study is not vs. placebo but compares SOC alone with SOC+Arikayce. Nevertheless, Arikayce will almost certainly be the only inhaled antibacterial agent so the study design should still allow for an assessment of the adverse reactions in the respiratory tract. In addition the Applicant is requested to discuss these findings also considering the disease to be treated itself; i.e. does the disease itself affect the sensitivity of the human lung.

## Clinical aspects

### Pharmacokinetics

Pharmacokinetic data were obtained from six clinical studies conducted in CF patients with *P. aeruginosa*.

Study	Dose and nebuliser	Design	Numbers and age
TR02-101	Single dose via PARI LC Star: 90, 270, 500 mg	Double-blind, placebo-controlled, ascending	N=17 Mean 29.1 y (range 19-45)
TR02-103	PARI LC Star 500 mg QD for 14 days	Open-label	N=13 13-17 y: n=5; ≥18 y: n=8
TR02-104	PARI LC Star 500 mg QD for 14 days	Open-label	N=11 20 – 38 y
TR02-105 (with extension)	PARI LC Star* 280, 560 mg or placebo QD for 28 days	Double-blind, placebo-controlled, ascending	N=64 (42 active; 21 560 mg QD Mean 16.6 y (range 6-29)
TR02-106	PARI LC Star* 70, 140, 560 mg or placebo QD for 28 days	Double-blind, placebo-controlled, parallel	N=41 (27 active; 15 560 mg QD 9 – 68 y
TR02-108 (extension study TR02-110)	LAI 560 mg QD PARI Investigational eFlow TOBI 300 mg BID PARI LC PLUS 3 cycles (28 days on/off)	Phase 3, open-label, randomized, active-controlled	300; 30 PK evaluable Mean 14.3 y (range 6-36)

\*In other tables in the submission the nebuliser used in these studies is described as PARI eFlow.

Additional data were obtained as follows:

- In RD 201/23824 PK and pulmonary deposition data were obtained from healthy subjects who received a single dose of radiolabelled material.
- In TR02-107 PK data were obtained and reported from patients with non-CF bronchiectasis.
- In TR02-112 serum and sputum PK data were obtained from a subset of 16 patients with non-tuberculous mycobacterial (NTM) infections. Serum data were analysed for 14 and sputum data for 12.

Amikacin was assayed in serum, sputum and urine using validated LC-MS/MS methods. POPPK reports were provided for these CF studies and also for CF plus NTM patient data. Due to the revised indication the following describes the POPPK report that included the data from TR02-112, which became available during the procedure.

An integrated POPPK analysis was conducted using the data from the CF studies and from 14 NTM patients (2 had underlying CF and 12 did not have CF). The NTM population was treated with the final LAI formulation and nebulisation system. The population in this study was very predominantly female

and older (mean age 55.8 years) with lower CLcr values (mean 87.7 mL/min) compared to all CF study populations sampled. Most NTM patients had only one serum sample and the maximum was 3.

The population PK model from the previous analyses provided an adequate fit to the pooled dataset. The only change from the model applied to the individual datasets was to alter the residual error model for serum concentrations to add a proportional term. This addition resulted in a small improvement in the fit over the previous model, which had modelled the residual error for serum using an additive model only. In general, the inter-individual variability (IIV) in the population PK parameters was moderately high, ranging from 43.2% for  $k_a$  to 68.4% for CL. The precision of the population PK parameters was generally high (<25%) with the exception of the IIV in  $k_a$ , which was estimated poorly (%SEM of 120%). The estimated C<sub>max</sub> and AUC on day 1 and at steady state are shown below, comparing NTM with CF study patients.

**Table 6.** Summary statistics [Mean (%CV) and Median (Min. – Max.)] for dose-normalized amikacin serum exposure parameters, stratified by study

	Study 105	Study 106	Study 108	Study 112	Combined
	N = 42 <sup>a</sup>	N = 27	N = 29 <sup>b</sup>	N = 14	N = 112 <sup>a,b</sup>
AUC <sub>24</sub>	12.4 (71.5%)	11.1 (51.6%)	5.3 (46.1%)	17.5 (72.1%)	10.9 (77.6%)
Day 1 (µg•h/mL)	10.4 (2.69 - 42.9)	10.1 (3.42 - 23.1)	4.67 (2.21 - 12.1)	14.6 (2.48 - 41)	7.8 (2.21 - 42.9)
AUC <sub>24</sub>	12.8 (75.7%)	11.3 (51.9%)	9.94 (44.4%)	20.5 (69.7%)	12.7 (71.6%)
Steady-State (µg•h/mL)	10.2 (2.7 - 48.7)	10 (3.46 - 23.2)	9.02 (4.36 - 23.2)	17.6 (2.86 - 52.1)	10.4 (2.7 - 52.1)
C <sub>max</sub>	1.95 (73.2%)	1.73 (53.9%)	0.774 (47.5%)	1.65 (83.4%)	1.55 (77.2%)
Day 1 (µg/mL)	1.6 (0.398 - 7.26)	1.52 (0.534 - 4.12)	0.707 (0.293 - 1.77)	1.08 (0.355 - 5.19)	1.12 (0.293 - 7.26)
C <sub>max</sub>	2 (74.3%)	1.71 (52.3%)	1.5 (46.9%)	1.89 (75.9%)	1.79 (66.4%)
Steady-State (µg/mL)	1.66 (0.406 - 7.23)	1.58 (0.537 - 4.13)	1.37 (0.577 - 3.4)	1.46 (0.339 - 5.28)	1.47 (0.339 - 7.23)

Note: Abbreviations are provided in the Abbreviation Listing. All exposures normalized to a LAI dose of 560 mg once daily.

a. One patient from Study 105 did not have steady-state estimates for AUC<sub>24</sub> or C<sub>max</sub>.

b. Two patients from Study 108 did not have steady-state estimates for AUC<sub>24</sub> (last sample was drawn ~2h after the steady-state dose).

A further breakdown that compared the non-CF NTM patients with the Phase 3 CF study population demonstrated higher predicted exposures in the former than the latter.

**Summary statistics [Mean (%CV) and Median (Min.–Max.)] for dose-normalised amikacin serum exposure**

	Study TR02-112		Study TR02-108
	NTM non-CF	CF	CF
	N = 12	N = 2	N = 29 <sup>a</sup>
Mean Age	60.3	28.5	14.1
AUC <sub>(0-24)</sub> Day 1	20.8 (61.5%)	4.01 (49.3%)	5.3 (46.1%)
(µg•h/mL)	16.6 (6.82 - 43.2)	4.01 (2.61 - 5.4)	4.67 (2.21 - 12.1)
AUC <sub>(0-24)ss</sub>	24.5 (58.3%)	4.33 (43.1%)	9.94 (44.4%)
(µg•h/mL)	22.7 (7.64 - 54.9)	4.33 (3.01 - 5.65)	9.02 (4.36 - 23.2)
C <sub>max</sub> Day 1	1.92 (77.2%)	0.617 (55.6%)	0.774 (47.5%)
(µg/mL)	1.31 (0.587 - 5.47)	0.617 (0.374 - 0.859)	0.707 (0.293 - 1.77)
C <sub>maxss</sub>	2.22 (68.4%)	0.638 (62.2%)	1.5 (46.9%)
(µg/mL)	1.68 (0.669 - 5.56)	0.638 (0.358 - 0.919)	1.37 (0.577 - 3.4)

a. Two from 108 did not have steady-state estimates for AUC<sub>(0-24)</sub> (last sample was drawn ~2h after the steady-state dose)

The applicant states that the mean steady-state AUC<sub>(0-24)</sub> in the patients with non-CF NTM included in the PK analysis in TR02-112 was >10 times lower than the mean AUC<sub>(0-24)</sub> reported in the literature by Byl *et al.* for patients with CF given amikacin 30 mg/kg IV once daily (20.8 µg•h/mL compared with 235 µg•h/mL, respectively).

The only continuous covariate of statistical importance was body weight, which was associated with a significant reduction in the IIV in CLr. The only other covariate identified was diagnosis such that patients with CF had a faster total body clearance and renal clearance. There was a clear relationship between indication (CF vs. NTM) and apparent clearance (CLt/F) such that the population mean CLt/F was estimated to be approximately 2.5-fold higher in patients with CF relative to patients with NTM. The report stated that it is not possible to draw definitive conclusions on the mechanism behind these differences but it is probable that increased absorption from the lungs in NTM patients may explain some of the observed differences.

In general, the addition of diagnosis into the population PK model reduced the IIV in CLr modestly (approximately 2%). Despite improving the overall fit of the model, the addition of the covariate relationships for CLt/F actually increased the IIV in CLt/F from 68.4% in the structural model to 73.4% in the final model. The large IIV for CLt/F was thought likely due to the variability in absorption after inhalational administration. After construction of the covariate model, it was necessary to revert to the original residual error model (additive only for both serum and urine) in order to maintain an unbiased fit.

The report concluded that NTM patients exhibited lower apparent oral amikacin clearance after LAI administration. This lower clearance translated into slightly higher predicted exposures in NTM patients. The fact that patient age was not a significant covariate suggested that the observed differences between patients with CF and patients with NTM is an inherent PK difference (i.e. the diagnosis is not masking some other difference in the populations). Ultimately, it is not possible to determine if the decrease in clearance in NTM patients is due to a reduced ability to clear the drug from systemic circulation or an increase in absorption (i.e., an increase in systemic bioavailability). However, given the unique pathology of the lungs of patients with CF, the latter was considered to be a more likely explanation.

### Bioavailability of amikacin in NTM patients

Absolute bioavailability after LAI administration has not been estimated. In the scintigraphy study in healthy subjects using a different nebulisation system compared to that in NTM patients, the report stated that 15.5% of the loaded dose was deposited in lungs. If the estimated bioavailability based on urinary excretion data from CF patients is correct (up to ~12%), then it implies that in some patients a large proportion of the amikacin that reaches the lungs is absorbed (this assumption takes into account minimal absorption of amikacin that is swallowed). The applicant estimated from these data that bioavailability may be 78% of the deposited dose in healthy adults. During the procedure the applicant stated that preliminary data from the scintigraphy sub-study from TR02-112 demonstrated that approximately 43% of the loaded dose using a nebuliser (using the electronic vibrating mesh) was deposited in the lung.

### Distribution

In the initial scintigraphy study six healthy male subjects received 120 mg  $^{99m}\text{Tc}$ -radiolabelled amikacin loaded into liposomes and delivered via a nebuliser. A ventilation scan was performed using  $^{81m}\text{Kr}$  radioactive gas to characterise the deposition of the amikacin-loaded liposomes by defining the ventilated area of the lungs. The margins of the lungs that were defined were used as a template to permit accurate determination of pulmonary deposition of radiolabelled drug. Five subjects completed inhalation of the dose. The mean recovery of radioactivity was 102%. The mean fraction of the emitted dose impacting in the oropharyngeal region and swallowed was 12.3% whereas 47.8% of the emitted dose was deposited on the exhalation filter and mouthpiece.

For all 6 subjects the mean emitted dose to lungs was 39.9% (with means of 32.3% and 47.5% in the nebuliser subgroups). Based on the measured fraction of the loaded dose retained within the nebuliser (mean 61.2%) and the fraction of the emitted dose delivered to lungs it was calculated that 15.5% of the loaded dose was deposited in lungs. Hence the mean dose of amikacin reaching the lungs was 17.2 mg. The calculations were very similar for the three subjects who were dosed in conjunction with two different systems (mean doses of amikacin reaching lungs were 17.9 mg and 16.5 mg, respectively).

The time-dependent retention curve of radiolabelled liposomes was biphasic. There was an initial rapid reduction in counts over 3h followed by a slower phase up to 48 h. Mean retention of radiolabelled liposomes within the lung at 48 h was 41.8% (45.3% vs. 38.3% for the two subgroups described above).

Table 11.4.3.2 Summary of Pulmonary Retention of Radiolabelled Liposomes

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

A report on the scintigraphy sub-study of TR02-112 was not available (see above).

### Excretion

Amikacin: After IV administration, amikacin is excreted unchanged in urine, primarily by glomerular filtration. After inhalation of LAI the POPPK estimate of CL<sub>r</sub> for the combined CF and NTM dataset was 2.7 L/h (45 mL/min). This is below the normal GFR range, which suggests that reabsorption of urinary

amikacin at the proximal renal tubules may occur at low systemic exposures. The data are consistent with retention of amikacin in the proximal tubule epithelium via an active process, a phenomenon which has been reported to be common for all aminoglycosides [Nagai et al. 2004]. In addition, Contrepois *et al.* (1985) showed that amikacin exhibited tubular reabsorption at a low dose (1 mg/kg/h) and tubular secretion at a higher dose (4 mg/kg/h).

DPPC: DPPC occurs naturally in the lung as a monolayer at the air-water interface. The applicant re-calculated the amount of DPPC deposited in the lung after a dose of LAI during the procedure and reported a value of ~43 mg per dose administered once daily. The calculation of delivered lung dose of DPPC after 590 mg LAI assumed the following:

- 15.5% Deposition
  - 0.7:1 lipid to drug weight ratio
  - 2:1 DPPC to cholesterol weight ratio
- Leading to the calculation of  $590 \text{ mg} \times 0.155 \times 0.7 \times 0.67 = 42.9 \text{ mg}$

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

A literature search was conducted to find relevant publications on inhalation of DPPC. In summary, there was very limited information for the review of the relevant literature to assess possible problems with DPPC inhalation over several years. However, there were no reports of serious adverse events associated with DPPC.

#### Metabolism

Amikacin is not metabolised to a significant extent.

#### Other information

By the ultrafiltration technique, reports of serum protein binding of amikacin range from 0 to 11%. Due to the low systemic exposure to amikacin after inhalation as well as low protein binding and lack of metabolism, no adjustment of the LAI dose is proposed for patients with renal or hepatic impairment.

The applicant has not conducted any in-vitro or in-vivo studies relevant to the potential for drug-drug interactions to occur. During the procedure the applicant reviewed the literature and was unable to find evidence that amikacin interacts with the CYP system or with specific transporters.

#### Evaluation of amikacin concentrations in sputum

There was substantial variability observed in the sputum PK data, both within and between patients, regardless of dose, study or study day. In CF patients sputum concentrations tended to increase with increasing dose. Sputum concentrations were significantly higher than serum concentrations after LAI administration. For example, in CF patients the median 1-h post-dose concentrations across the first day of each cycle in TR02-108 were ~ 300 to 500-fold the maximum observed serum concentration of ~3.0 mg/L. The day 28 post-LAI concentrations in this study (pre-dose on day 57 and 113) showed that some patients had very substantial residual amikacin concentrations.



**Table 4-13.** Summary statistics for amikacin sputum concentrations (mcg/g) at individual sampling times stratified by study day for Study TR02-108

Cycle (Day)	Time	Amikacin sputum concentrations (mcg/g)		
		N	Mean (SD)	Median (min, max)
1 (Day 1)	Pre-dose	29	0 (0)	0 (0, 0)
	1 hr post-dose	28	1430 (1480)	982 (0, 6120)
2 (Day 57)	Pre-dose	26	89.1 (431)	1.2 (0, 2200)
	1 hr post-dose	28	3110 (4750)	1340 (3.47, 20200)
3 (Day 113)	Pre-dose	27	5.2 (11.9)	1.4 (0, 57.7)
	1 hr post-dose	29	3100 (3570)	1530 (0, 11000)

This issue is of importance since the pre-defined primary efficacy endpoint in TR02-112 was change in step on the SQS scale. As described under *Efficacy*, sputum culture conversion (SCC) was defined *post hoc* as three consecutive negative sputum cultures. Sputum amikacin levels were evaluated in 12 patients of the 16 patients who underwent PK sampling. Four were excluded for the following reasons:

- For three patients all positive pre-dose samples were collected while receiving placebo. All of these patients had a history of taking IV amikacin via a nebuliser prior to entry into the study.
- One seems to have had a mix up in pre- and post-dose samples but this cannot be confirmed.

The 12 patients provided 143 sputum samples (73 pre-dose samples and 70 post-dose samples) for amikacin PK. Overall 38/73 (52.1%) pre-dose sputum samples had amikacin concentrations BLQ compared to 26/70 (37.1%) of post-dose samples. It cannot be confirmed that samples that were BLQ came from patients while taking LAI (see the footnote to the table).

**Table 11-22 Summary Statistics of Amikacin Sputum Concentrations (µg/mL) for All Samples That Had Quantifiable Concentrations**

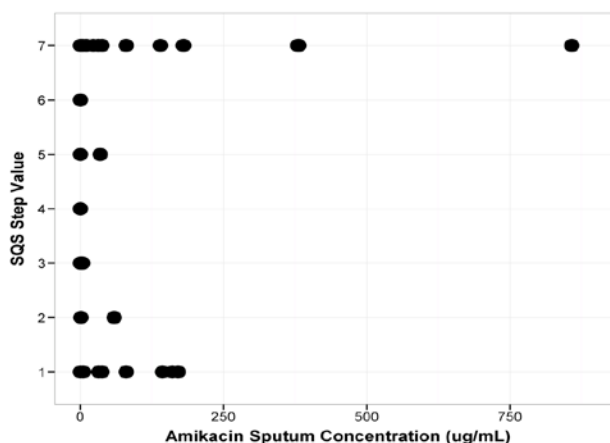
Timepoint	N	Mean (CV%)	Median	Minimum	Maximum
Predose	35 <sup>a</sup>	395 (314)	38.2	0.78	7080
Postdose	44 <sup>b</sup>	4808 (87.8)	3185	1.07	16,800

a This represents 47.9% of all pre-dose samples collected; 38 pre-dose samples were BLQ (< 0.6 µg/mL).

b This represents 62.9% of all post-dose samples collected; 26 post-dose samples were BLQ (< 0.6 µg/mL).

The CSR states that the SQS results were independent of the time-matched pre-dose amikacin concentrations ( $p = 0.570$ , Spearman's test of correlation) and that the distribution of measurable pre-dose sputum concentrations was similar at the extremes of the SQS distribution (SQS = step 1/culture negative and SQS = step 7/4+ growth).

**Figure 2b-1: Distribution of Quantifiable, Pre-dose Amikacin Sputum Concentrations by SQS Step in Study TR02-112**



Note: Three observations with amikacin sputum concentrations above 900 µg/mL were removed from the plot to aid in visualization. These were concentration values of 1670, 1870 and 7080 µg/mL and corresponding SQS Step values of 4, 7 and 1, respectively. (The patient with an amikacin concentration of 7080 µg/mL pre-dose had a concentration below quantifiable levels post-dose at the same time-point, indicating human error in labeling the pre- and post-dose samples but this was not the patient removed from the analysis).

**Table 11-23 Comparison of the Number of BLQ Samples by SQS Result**

SQS Result <sup>a</sup>	Number of Quantifiable Samples	Number of BLQ Samples
Step 1: Culture negative (confirmed with no growth in liquid medium)	8	2
Step 2: Growth in liquid medium only (liquid positive)	2	0
Step 3: Agar positive, 1-49 colonies (manual count on agar)	2	9
Step 4: 1+	1	1
Step 5: 2+	1	2
Step 6: 3+	0	3
Step 7: 4+	15	15

Three of the 16 patients for which sputum PK data were available had amikacin detected in pre-dose samples while receiving placebo. They had a history of treatment with nebulised amikacin (using the IV formulation) prior to study but nebulised antibacterial agents were to have been stopped during the screening period. The amikacin concentrations in sputum for these excluded patients at entry to the double-blind phase of the study were low (< 4 µg/g) and decreased further post-baseline while on placebo. Two of the three had isolated sputa with measurable amikacin in pre-dose sputum samples taken on Days 2, 28 and 56 whilst on placebo but they were close to the LLOQ.

### ***Comment on pharmacokinetics***

#### Systemic bioavailability of amikacin after LAI inhalation

The applicant has focussed on estimating the systemic exposure to amikacin after inhalation of LAI and comparing this to exposures typically observed during IV dosing of CF patients treated with 30 mg/kg IV. This has been accomplished by limited PK sampling and application of POPPK analyses.

In CF studies with daily dosing of LAI for 28-day cycles three studies showed evidence of accumulation in serum. These accumulations in serum would not be expected based on the short half-life of amikacin after parenteral administration and may reflect several factors, including slow release of amikacin from liposomes deposited in the airways. In addition, POPPK analyses indicated that renal clearance of amikacin is less than creatinine clearance in LAI-dosed patients. The literature reports that this is not observed during parenteral dosing and higher systemic exposures, suggesting saturable reabsorption in the proximal renal tubules.

The serum PK data from the 12 TR02-112 patients with recalcitrant NTM who participated in the PK sub-study had not yet been analysed at the time of submitting the application dossier. The updated POPPK estimates after including the NTM patient data gave even higher inter-individual variability estimates compared to the original analysis based on CF patients alone. Importantly, the revised analysis reports that the mean CL<sub>T</sub>/F was ~2.5-fold higher in patients with CF relative to patients with NTM. The finding is said to possibly represent the lower total clearance in non-CF vs. CF patients as well as a difference in absorption. Therefore estimates that are based on integrated data from CF and non-CF patients are potentially misleading.

Based on very limited PK data from non-CF patients with NTM, it becomes very clear that plasma exposures to amikacin after LAI treatment are considerably higher than in CF patients, including CF patients with NTM. However, more data are needed to be able to evaluate the highest possible



exposures that could occur in non-CF NTM patients and it is hoped that such data will come from the ongoing Phase 3 study. Meanwhile it is not agreed that the margin of safety vs. IV dosing is necessarily as great as the applicant claims based on comparisons between the non-CF NTM population and literature reported exposures in CF patients who received 30 mg/kg IV amikacin. The applicant should confirm whether PK data are being obtained during the Phase 3 study and explain the sampling schema.

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

In TR02-112, amikacin sputum concentrations were measured as µg/g but the PK report incorrectly reported concentrations in µg/mL. In the discussions of possible effects of residual amikacin in specimens on culture results the applicant assumed that 1 mL sputum weighs 1 g, which is unverified.

The SOP for the NTM study sputum samples states that some samples were induced using saline for collection. Samples could be left unrefrigerated for up to 1 h before shipping, although shipping was to be under refrigerated conditions. After receipt at the central laboratory there was digestion and decontamination using N-acetyl-L-cysteine, which involves vortex mixing. The timing of the digestion is critical since there is sodium hydroxide in the mixture to reduce/remove non-Mycobacterial organisms but over-exposure can also impact on Mycobacterial numbers. The SOP states that *M. gordonae* was used as the positive QC due to its relative sensitivity to the alkali. In light of variable sputum collection methods, airway disease and sputum composition between patients it is hardly surprising that there was very considerable variability in sputum concentrations of amikacin and even more so than observed for serum levels.

There are no data on amikacin persistence in sputa at the day 28 post-therapy visit in TR02-112, which was the last time point at which the protocol planned to assess culture results. In the CF study TR02-108 the mean sputum concentrations after patients had been off treatment for 28 days, were 89.1 (day 57) and 5.2 (day 113) µg/g with pre-dose medians of 1.2 and 1.4 µg/g.

In TR02-112 sputum concentrations were measured in only 16 patients but results from four were excluded. For the remaining 12, the 73 pre-dose samples showed concentrations that ranged from BLOQ (in about half) to a range from 0.78 to 7080 µg/mL in the samples with quantifiable levels. The applicant reports that the very high value of 7080 µg/mL also came from a patient with a sample mix up and proposes that the median is the more reliable value to assess residual amikacin.

Based on this subset an analysis of 61 samples for which there were “time-matched” concentration and culture results concluded that the SQS results were independent of the pre-dose amikacin concentrations.

It should be noted that the samples that were used for PK were not the same samples used for culture since the latter were processed and made unsuitable for PK studies. “Time-matched” samples presumably represent separate expectorations with a short time interval, which can influence both the apparent sputum concentration and the numbers of organisms.

In a 2013 publication from the applicant’s central laboratory for TR02-112 ~50% of 462 *M. avium* complex (MAC) strains had amikacin MICs of 8 µg/mL, and 86% <16 µg/mL. The MICs of amikacin for the mycobacterial isolates obtained during TR02-112 ranged from 8 to >64 µg/mL, with the majority being ≥ 16 µg/mL. Based on the day 28 post-therapy concentrations in TR02-108 and the MICs of amikacin for organisms obtained from NTM patients, the applicant proposes that the culture results obtained from the NTM patients at the day 28 post-therapy visit are reliable. The assessor is not able to agree with this conclusion based on the data presented. In addition, the measurements of step change on the SQS scale during therapy and up to day 28 post-therapy have to be viewed with caution.

As stated in the discussion of efficacy, the only acceptable primary endpoint for the NTM study would be sustained SCC (defined as three consecutive visits with wholly negative cultures) conducted at an appropriate time post-therapy. A further discussion is included under *Efficacy*.

#### Lung distribution

Unfortunately the lung distribution study in healthy subjects did not include a control group that received non-liposomal amikacin, which could have shed some light on the possible benefit of producing a liposomal formulation as opposed to inhaling amikacin intended for IV use. Only the amikacin was radiolabelled. The report repeatedly refers to radiolabelled liposome deposition and clearance but such statements assume that the radiolabelled amikacin remained associated with the liposomal material. This assumption conflicts with the proposed leakage of the active from the liposomes.

The study actually showed that the radiolabel in lungs decreased rapidly initially (3 h) and then slowly over 48 h (beyond which accurate determinations are not possible due to the short half-life of the radioisotope) at which time the table indicates that 42% of the deposited dose was retained in the lung. Whilst it is not entirely clear how this fraction was calculated (the CSR being very unclear on several matters and with lack of clarity regarding exactly which fraction of what is referred to) the table and figure suggest that there is some initial rapid clearance by mechanical means and/or systemic absorption and then a slow clearance of amikacin. The pattern of decay described fits with the data on persistence of residual amikacin in pre-dose sputa. Unfortunately this study did not assay radiolabel in blood, which would have assisted in confirming the estimates of systemic bioavailability. The only information available from the scintigraphy sub-study in NTM patients is the applicant's report of the amount estimated to be deposited in the lung, which was higher than in the healthy subject study. It is unclear whether this difference relates only to the different nebulisation system or whether there is a real difference between study populations.

#### Conclusion

There is a need for a careful appraisal of the worst case systemic exposures that may occur during treatment of the revised target population (non-CF patients with MAC lung disease) with LAI. This assessment cannot be conducted with confidence based on available data. Phase 3 data are awaited.

The possibility that residual amikacin in sputa interfered with culture results seems likely but the extent to which this may have influenced the applicant's conclusions on efficacy cannot be gauged.

#### **Pharmacodynamics**

The primary mechanism of action of amikacin is the same as that for all aminoglycosides, i.e. it binds to bacterial 30S ribosomal subunits and interferes with mRNA binding and tRNA acceptor sites. This leads to disruption of normal protein synthesis and production of non-functional or toxic peptides. Other actions have been postulated for drugs of this class. It is not known whether additional mechanisms of action may apply at the very high concentrations that can be achieved at least temporarily in sputum after inhalational dosing. Thus, it is not known whether the PK-PD index is the same as that applicable to IV dosing.

The effects of inhaled LAI on numbers of non-tuberculous mycobacteria in sputum are described in the section on efficacy. In support of the clinical data the applicant conducted in-vitro and in-vivo nonclinical studies. Two *M. avium* studies were conducted by Oregon State University as follows:

#### In-vitro study

Human mononuclear macrophages (THP-1) were infected with three strains of *M. avium* and exposed to LAI (1, 2, 4, 8 and 10 µg/mL) once daily for 4 days. Untreated macrophages and macrophages

exposed to empty liposomes (lipid concentration 6.4 µg/mL) were used as the negative controls and 10 µg/mL amikacin was the positive control. On day 5 the cells were lysed and colony counts were performed.

- Empty liposomes gave counts very similar to those for untreated cells.
- LAI at 4-10 µg/mL amikacin killed or inhibited growth of the three strains and was more bactericidal against each strain (1.5-fold, 2.1-fold and 5.7-fold) than free amikacin at 10 µg/mL. LAI did not demonstrate cytotoxicity at 10 µg/mL.

### In-vivo study

Six groups of 12 female mice were infected nasally with *M. avium* strain 104 (~2x10<sup>7</sup> CFU) on day 0. After 3 weeks the control mice lungs were harvested, homogenised and plated on agar to determine the mean CFU (~0.7 x 10<sup>5</sup>) after which dosing of remaining mice was as follows:

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

On Day 50 lungs were harvested from Groups 1-5.

LAI 76 mg/kg QD for 28 days significantly ( $p = 0.0002$ ) reduced the *M. avium* burden in the lungs vs. controls in Group 1. There were also significant reductions vs. controls in *M. avium*/lung ( $p < 0.0001$ ) in mice treated with inhalation either every other day for 28 days or for 14 consecutive days. All LAI groups had a numerically greater reduction in mean CFU/lung vs. Group 5 (intraperitoneal amikacin). The rate of complete eradication of *M. avium* was the highest in Group 4 (42%) and lowest in Group 5 (25%).

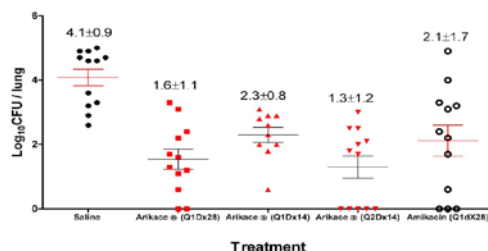


Figure 1. Significant Reduction in the Log<sub>10</sub>CFU of *M. avium* / lungs of mice after Inhalation of Arikace and Intraperitoneal Injections of Amikacin. The symbols represent the Log<sub>10</sub>CFU/lungs of each mouse 50 days after the instillation of *M. avium*. The horizontal lines and vertical lines represent the means and standard deviations that were calculated using Excel software by Microsoft. The numerical means and standard deviations are above each group's symbols.

### PK-PD analyses

The applicant commissioned several POPPK and PK-PD analyses of data from CF clinical studies from an outside contractor. There was no PK/PD analysis of the data from TR02-112 in which only 14/89 patients with serum samples and 12/89 with sputum samples were included in PK analyses.

### ***Comment on clinical pharmacology***

The applicant has conducted very few studies to document the possible advantages of using liposomal LAI rather than inhaling amikacin itself. Since amikacin is proposed to leak out from liposomes and since the carryover effects apply similarly to assays of concentrations in nonclinical and clinical samples, the evidence for a clinical benefit for providing amikacin in liposomes is somewhat weak. Nevertheless, additional nonclinical studies are not likely to help and are not requested at this stage of development.

For inhaled therapy the MIC of amikacin is of no known relevance to the clinical response. Nevertheless, pathogens are not treated via the inhalation route with antibacterial agents to which they are known to be *inherently resistant*. Whether or not *acquired resistance* to an antibacterial agent in normally susceptible species (based on breakpoints applicable to systemic use) can be overcome by very high local concentrations potentially achievable after inhalation remains unclear although there is evidence from CF patients to indicate that PFTs can be maintained or even improved when patients are colonised with *P. aeruginosa* strains that would be considered resistant to the agent under test based on parenteral dosing breakpoints.

Whether or not the same would apply to treatment of NTM is not known. Very high MICs of amikacin have been documented for some NTM or, at least, for a subset of strains within specific species. For example, very high MICs have been linked to 16S RNA mutations (A1408G) in *M. abscessus* and *M. avium* complex and to cellular impermeability coupled with AME production in *M. abscessus*. The bactericidal activity of amikacin has also been reported to vary between slow-growing and rapidly-growing species, with lowest MICs for the latter, and is generally reported to be greater for *M. tuberculosis* vs. all other mycobacterial species.

The applicant has not provided an assessment of the in-vitro activity of amikacin against NTM strains with the exception of the study against intracellular MAC. In addition, the only in-vivo nonclinical data concerned MAC. However, MAC predominates among NTM lung infections in N. America, where TR02-112 was conducted. In addition, following the comments made on the data presented in the initial dossier, the applicant modified the proposed indication such that it is now confined to non-CF patients with MAC lung disease (all of whom were also HIV negative).

A PK-PD analysis of TR02-112 is not possible due to insufficient PK data. It is hoped that this deficiency can be addressed using the data generated from the ongoing Phase 3 study, which is confined to non-CF patients with MAC lung disease and which compared addition of LAI to SOC vs. SOC alone.

### **Clinical efficacy**

The application for use in CF patients chronically colonised with *P. aeruginosa* was withdrawn. The revised indication requested is based on a subset of patients enrolled in the Phase 2 study in NTM patients TR02-112.

#### **TR02-112**

This Phase 2 randomised, double-blind, placebo-controlled study evaluated the use of LAI in patients with *recalcitrant* non-tuberculous mycobacterial (NTM) lung disease.

- The double-blind phase compared LAI 590 mg QD vs. placebo (empty liposomes) for 84 days in patients with treatment-refractory NTM lung infection on a stable multi-drug regimen. Randomisation (1:1) was stratified based on presence/absence of CF and MAC vs. *M. abscessus* lung infection.
- Patients who consented to continue in the open-label phase received LAI 590 mg QD for 84 days. Patients who interrupted or discontinued study drug in the randomised, double-blind phase due to use of an inhaled antibacterial agent or parenteral aminoglycoside were allowed to receive LAI in the open-label phase.
- There were to be safety follow-up visits at 28 days and at 12 and 24 months after the end of treatment visit. Sputum culture was planned for the day 28 follow-up visit.
- There were planned PK and scintigraphy sub-studies.

Eligible patients were adults aged from 18 to 85 years with NTM lung disease diagnosed in accordance with the 2007 ATS/IDSA criteria with evidence of nodular bronchiectasis and/or fibrocavitary disease by chest CT.

- Chronic NTM infection was defined as  $\geq 2$  positive cultures in the prior 2 years, including  $\geq 1$  obtained in the 6 months prior to screening. Cultures were to show either MAC or *M. abscessus* or mixed infection with both species. NTM contaminants (*M. goodii*, *M. haemophilum*, *M.*

*mucogenicum*, *M. nonchromogenicum* and *M. terrae* complex) were allowed as long as MAC and/or *M. abscessus* were predominant.

- All patients were to have a positive sputum culture obtained during the screening period with either MAC or *M. abscessus* or mixed infection (as above) with 1 dominant species.
- Patients were to be receiving ATS/IDSA guidelines-based treatment regimens and adherent to a multi-drug regimen for at least 6 months prior to screening.
- Patients with CF or primary ciliary dyskinesia were eligible.

Important exclusions included FEV1 < 30% predicted at screening, and any change in chronic NTM multi-drug regimen within 28 days prior to study Day 1. Inhaled antibacterial therapy was not allowed within 28 day prior to day 1 (baseline).

On days 1-84 patients received LAI 590 mg QD or matching placebo QD, each administered via a PARI Investigational eFlow nebuliser. The placebo comprised the same lipid carriers at a total lipid concentration of 2.25 mg/mL in 1.5% sodium chloride. In the open-label phase all patients received LAI 590 mg QD from day 85 through day 168. On days 1, 28, 56 and 84 in the double-blind phase and on days 85, 112, 140 and 168 the study drug was administered at the clinical site.

The background NTM regimen was not to change during the study except for safety concerns or in case of need for rescue anti-mycobacterial therapy. Efforts were to be made not to change other concomitant medications (including anti-inflammatory medications) or other treatment modalities. Bronchodilator therapy was allowed as long as it was used consistently for the duration of the study.

For the double-blind phase all efficacy analyses were performed using the mITT population (all-treated). In the open-label phase all efficacy analyses were performed using the open-label mITT (OLmITT) population, i.e. all who received at least 1 dose of LAI in the open-label phase. The PP population included patients who completed at least 70/84 doses, did not miss > 4 consecutive doses during the double-blind phase and those who did not meet these criteria because they needed to receive an aminoglycoside for an acute exacerbation.

#### Microbiological processing of sputum samples

Pre-dose expectorated or induced sputum specimens with a minimum volume of 3.0 mL were required for semi-quantitative evaluation of NTM at each study visit. Patients were to collect 2 (or preferably 3) sputum samples at home (preferably early morning and on consecutive days) prior to study visits on days 1, 28, 56, 84, 112, 140, 168 and the 28-day follow-up visit.

The SOP allowed for samples to be induced using saline for collection. Samples could be left unrefrigerated for up to 1 h before shipping, although shipping was to be under refrigerated conditions within 2 days of collection by the patient or study site. Central laboratory processing involved diluting the sputum sample in a ratio of 1:1 with NaOH and then adding the same volume (1:1) of phosphoric acid. The timing of the digestion is critical since there is sodium hydroxide in the mixture to reduce/remove non-Mycobacterial organisms but over-exposure can also impact on Mycobacterial numbers. *M. goodii* was used as the positive QC due to its relative sensitivity to the processing method.

The sample was then centrifuged so that a 'pellet' containing the mycobacterium was formed. This pellet was separated from the supernatant and cultured in both liquid and solid media. In accordance with the ATS/IDSA 2007 and the CLSI 2008 guidelines there was semi-quantitative reporting of NTM colony counts on solid media. Sputum specimens were cultured in liquid media in addition to solid media (agar). If the result was negative on agar, the liquid media culture was held for 6 weeks before reporting as culture negative.

#### Primary efficacy endpoint

This was the change from baseline on the SQS for mycobacterial culture for the LAI vs. placebo group at Day 84. The endpoint used the semi-quantitative mycobacterial culture reporting method, expressed on a 7-step scale as shown in the categorical result column below. The result for a given visit was the highest mycobacterial load among the samples available for testing for that visit. Handling of contaminated samples was not pre-specified in the Statistical Analysis Plan. Initially the applicant assigned them to SQS 2. Subsequently the CSR was revised so that contaminated samples for which no mycobacteria were found in the liquid media cultures even after DNA probing (for MAC) and all additional sputum samples obtained at the same time point were negative for mycobacteria were considered to be negative (SQS 1). This re-assignment affected 38 sputum samples (~2%).

**Table 9-4 Semiquantitative Mycobacterial Culture Reporting Method**

Step	Solid Media Result	Liquid Medium Result	Categorical Result
1	0 colonies	Negative	Culture negative (confirmed with no growth in liquid medium)
2	0 colonies	Positive	Growth in liquid medium only (liquid positive)
3	1-49 colonies (manual count on agar)	Positive	Agar positive
4	50-100 colonies	Positive	1+
5	> 100-200 colonies	Positive	2+
6	> 200-500 colonies	Positive	3+
7	> 500 colonies	Positive	4+

Of note, as indicated in the first column above, movement from row to row within the table above constitutes "steps".

#### Major secondary endpoints

According to section 9.5.2 of the CSR NTM culture conversion to negative was defined as 1 culture negative sputum sample. Although not a pre-defined endpoint, subsequently the applicant applied a *post hoc* definition of sputum culture conversion (SCC) that required three consecutive visits with negative sputum cultures. The applicant counted those with negative sputum cultures at day 1 (baseline) in the totals considered to meet the initial and/or *post hoc* definitions of culture conversion.

#### Primary efficacy analysis

This was conducted in the mITT population using a stratified Wilcoxon rank sum test (i.e. van Elteren test), adjusting for the randomisation strata, to compare treatments at a 2-sided significance level of 0.05. If death occurred on or before day 84 the patient was counted as a failure, i.e. as a unique outcome of 7 steps on the change from baseline scale (which otherwise would have ranged from -6 to +6 steps). The analysis was designed to assess the entire range of changes on the SQS. A secondary analysis of the primary efficacy endpoint employed a Wilcoxon rank sum test of treatment arm.

Methods for imputation of missing data were pre-specified in the statistical analysis plan, as follows:

- If a subject had missing sputum culture data for the Primary Endpoint analysis, and this was due to inadequate sputum even after an adequate attempt for induction, the subject's missing data were counted as a negative culture (i.e. Step 1 on the SQS), as this was considered to reflect symptom resolution associated with negative sputum cultures. In these cases, the Change from Baseline was calculated using Step 1 as the result for Day 84.

All other reasons for missing data were to be handled via missing equals failure as follows:

- If a post Baseline value is missing and the Baseline value is non-missing, then the change value will be imputed as (Step) 7 – Baseline value, where the 7 represents the highest of Steps 1 through 7 on the SQS, i.e. change of + 4 if the Baseline value were Step 3, then the change value would be  $7 - 3 = +4$ .

- If the Baseline value is missing and a post Baseline value is non-missing, then the change value will be imputed using an imputed value of Step 1 at Baseline, whereby Step 1 represents the lowest of Steps 1 through 7 (e.g., if a post-Baseline value was Step 4, then the change in value would be  $4 - 1 = +3$ ).
- If both the Baseline and post Baseline values are missing, then the change value will be imputed as +6 (as Step 7 is imputed for the post Baseline value and Step 1 for the Baseline value:  $7 - 1 = +6$ ). If death occurred, the primary analysis applied a 'unique' change in Steps of +7. This was an extremely conservative imputation as the largest possible change on the SQS is +6, and the largest possible change for a patient who met inclusion criteria (i.e. positive sputum culture at screening) would be +5 (Step 2 to Step 7 [liquid media positive to 4+ growth on solid media]).

## Results of TR02-112

The study enrolled 90 patients at 18 sites in the United States (1-15 each) and 1 site in Canada (2).

In the double-blind phase 1/90 patients randomised was not treated, so 89 were included in the mITT population of which 9/44 (20.5%) in the LAI group vs. 0/45 in the placebo group did not complete dosing in the double-blind phase mostly (7/9) due to AEs.

Patient baseline demographics and disease characteristics were comparable between treatment groups for the mITT population.

- Most were Caucasian (92.1%) and female (87.6%) with a mean age of 58.5 years (range 18-85 years).
- There were some differences between treatment groups in lung function parameters at baseline.
- Three patients in each group had negative sputum cultures at baseline (on day 1).
- Approximately 19% had CF, 2/3 had predominately MAC lung infection and 1/3 had predominately *M. abscessus*.
- There was an imbalance in baseline mycobacterial loads. Based on the original assignment of samples on the SQS a greater proportion of LAI vs. placebo patients were at Step 1 (1-49 colonies) and a greater proportion of placebo vs. LAI patients were at Step 7 (>500). The re-assigned SQS stages still showed this imbalance.



**Table 11-2 Demographics and Baseline Characteristics (mITT Population)**

	LAI 590 mg QD (N = 44)	Placebo (N = 45)	Total (N = 89)
<b>Baseline FEV<sub>1</sub> (L)</b>			
Mean (standard deviation)	1.730 (0.6910)	1.637 (0.5168)	1.683 (0.6075)
Median	1.530	1.560	1.560
Minimum, Maximum	0.66, 3.71	0.77, 3.17	0.66, 3.71
<b>Baseline FEV<sub>1</sub> % predicted</b>			
Mean (standard deviation)	63.56 (21.339)	62.56 (17.168)	63.06 (19.239)
Median	61.25	61.00	61.00
Minimum, Maximum	30.2, 114.9	34.4, 101.6	30.2, 114.9
<b>Baseline FEV<sub>1</sub> % predicted by stratum, n (%)</b>			
25%-50%	14 (31.8)	11 (24.4)	25 (28.1)
> 50%-75%	18 (40.9)	25 (55.6)	43 (48.3)
> 75%	12 (27.3)	9 (20.0)	21 (23.6)
<b>Baseline mycobacterial load</b>			
Culture negative (confirmed with no growth in liquid medium)	3 (6.8)	3 (6.7)	6 (6.7)
Growth in liquid medium only (liquid positive)	3 (6.8)	3 (6.7)	6 (6.7)
1-49 colonies (manual count on agar) (agar positive)	17 (38.6)	10 (22.2)	27 (30.3)
1+ (50-100 colonies)	2 (4.5)	4 (8.9)	6 (6.7)
2+ (> 100-200 colonies)	2 (4.5)	2 (4.4)	4 (4.5)
3+ (> 200-500 colonies)	3 (6.8)	4 (8.9)	7 (7.9)
4+ (> 500 colonies)	14 (31.8)	19 (42.2)	33 (37.1)

Most patients (60/89, 67.4%) were treated with at least 3 antibacterial agents prior to study baseline.

#### Number of antibacterial agents for NTM in patients prior to Baseline (Day 1) in TR02-112

Number of antibacterial agents used for NTM	All Patients (n)	Patients in the LAI Treatment Group (n)	Patients in the Placebo Treatment Group (n)
2	29	18	11
3	47	22	25
4	11	3	8
5	2	1	1

In accordance with the fact that 88/90 patients were enrolled in the US the treatment history reflected ATS/IDSA guidelines, which recommend a macrolide, ethambutol and rifampicin/rifabutin. Thus, the most common regimen was a combination of macrolide, ethambutol and rifampicin/rifabutin (36/89, 40.4%). The most common class used was macrolide (72/89, 87.6%), followed by rifampicin/rifabutin (53/89, 59.6%) and ethambutol (52/89, 58.4%). Five had been treated with IV amikacin and 33 with inhaled amikacin.

Approximately 84% (75/89) of patients were diagnosed >24 months prior to enrolment while 75% (33/44) in the LAI group and 93% (42/45) in the placebo group had a diagnosis of NTM >24 months prior to the study. Approximately 80% (71/89) of patients were treated with a standard multi-drug regimen for NTM for ≥ 12 months prior to randomisation into the study and 49% (41/89) were treated for ≥ 24 months.

#### Results based on SOS as pre-specified in the protocol

Most patients (20/44; 45.5% LAI and 20/45; 44.4% placebo) had no change in step at day 84. There were 18 LAI vs. 13 placebo patients (p = 0.148) with at least a 1-step reduction and therefore the study failed based on the pre-defined primary endpoint. The table below shows that for the 18 LAI and



13 placebo patients with a reduction this was by -1 step in 9/18 and 6/13 and by -1 or -2 steps for 13/18 and 12/13 in respective groups. Thus, very few patients in either group had more than a 2-step reduction. A sensitivity analysis in the mITT population in which the patient who died was not imputed as Step 7 gave a p value of 0.044.

**Table 11-11 Change from Baseline on the Full SQS for Mycobacterial Culture (TR02-112; mITT)**

Categorical Result	LAI 590 (N = 44) n (%)	Placebo (N = 45) n (%)	Total (N = 89) n (%)
<b>Baseline</b>			
Culture negative (confirmed with no growth in liquid medium)	3 (6.8)	3 (6.7)	6 (6.7)
Growth in liquid medium only (liquid positive)	3 (6.8)	3 (6.7)	6 (6.7)
Agar positive (1-49 colonies, manual count on agar)	17 (38.6)	10 (22.2)	27 (30.3)
1+ (50-100 colonies)	2 (4.5)	4 (8.9)	6 (6.7)
2+ (>100-200 colonies)	2 (4.5)	2 (4.4)	4 (4.5)
3+ (>200-500 colonies)	3 (6.8)	4 (8.9)	7 (7.9)
4+ (>500 colonies)	14 (31.8)	19 (42.2)	33 (37.1)
<b>Day 84</b>			
-6	1 (2.3)	0	1 (1.1)
-5	0	0	0
-4	1 (2.3)	0	1 (1.1)
-3	3 (6.8)	1 (2.2)	4 (4.5)
-2	4 (9.1)	6 (13.3)	10 (11.2)
-1	9 (20.5)	6 (13.3)	15 (16.9)
0	20 (45.5)	20 (44.4)	40 (44.9)
+1	3 (6.8)	7 (15.6)	10 (11.2)
+2	0	3 (6.7)	3 (3.4)
+3	1 (2.3)	0	1 (1.1)
+4	1 (2.3)	2 (4.4)	3 (3.4)
+5	0	0	0
+6	0	0	0
+7 (Death)	1 (2.3)	0	1 (1.1)
p-value for stratified Wilcoxon rank sum test of treatment arm adjusting for the randomization strata			0.148
p-value for unstratified Wilcoxon rank sum test of treatment arm			0.118

Note: If a patient had a missing endpoint due to inadequate sputum even upon attempted induction, then the patient's missing data were counted as a success. All other reasons for missing data, including death, were handled as missing equals failure.

There were 16 LAI and 5 placebo patients eliminated from the PP population, leaving 28 vs. 41. The reasons for exclusion from the PP population were not provided in the CSR. However, the results in the PP population paralleled those for the mITT population. No statistically significant differences between the LAI and placebo groups were noted in sensitivity analyses when applied to the mITT or PP populations.

The analysis of change in SQS using logistic regression without taking into account baseline step in the logistic regression model gave a p-value of 0.092. After adding the Baseline step as a covariate in the logistic regression model, the p-value was 0.042 i.e. statistically significant at the nominal alpha of 0.05.

At day 84 a statistically significantly greater proportion of patients in the LAI group (14 of 41; 34.1%; note the denominator) achieved a negative NTM culture (i.e. a negative culture regardless of prior or subsequent results) compared with patients in the placebo group (4 of 45; 8.9%) ( $p = 0.003$ ). Re-analysis taking into account baseline Step in the logistic regression model gave a p-value of 0.010 for the treatment comparison at Day 84 using the stratified CMH test. The logistic regression model with the Baseline step as a covariate and treatment arm as a fixed effect gave a p-value of 0.037.

Of the 80 patients who completed dosing in the double-blind phase, 78 enrolled in the open label phase (i.e. were in the OLmITT population) but 19/78 (24%; 12/43 from the initial placebo group and 7/35 from the original LAI group) did not complete dosing (i.e. 59/78 completed dosing to day 168). Most patients (11/12 and 5/7, respectively) who discontinued study drug did so due to an AE.

In the open-label phase the baseline was on day 85, at which time a greater proportion of prior LAI-treated patients were culture negative (11 vs. 3) and a greater proportion of prior placebo-treated

patients (17 vs. 7 prior LAI) were at step 7 (4+, > 500 colonies). At day 168, 57.7% (45/78) of patients had no change on the SQS for mycobacterial culture. Some reduction on the scale was observed for 8 prior LAI vs. 12 prior placebo patients.

#### Results based on the revised SQS

As shown below, after re-assignment of SQS step for some contaminated samples the primary endpoint analysis (mITT at day 84) approached statistical significance ( $p=0.072$ ) but it remained the case that the majority in both groups had no change.

#### **Change from Baseline on the Full SQS for Mycobacterial Culture (mITT)**

<b>Day 84</b>	<b>LAI Group (N=44) N (%)</b>	<b>Placebo Group (N= 45) N (%)</b>
-6	1 (2.3)	0 (0.0)
-5	0 (0.0)	0 (0.0)
-4	1 (2.3)	0 (0.0)
-3	3 (6.8)	0 (0.0)
-2	6 (13.6)	6 (13.3)
-1	5 (11.4)	5 (11.1)
0	23 (52.3)	23 (51.1)
+1	2 (4.5)	5 (11.1)
+2	0 (0.0)	3 (6.7)
+3	1 (2.3)	0 (0.0)
+4	1 (2.3)	2 (4.4)
+5	0 (0.0)	1 (2.2)
+6	0 (0.0)	0 (0.0)
+7(Death)	1 (2.3)	0 (0.0)

$p = 0.072$  for the stratified Wilcoxon rank sum (van Elteren) test of treatment arm adjusting for the randomisation strata

Regardless of duration of previous NTM treatment, patients treated with LAI showed a mean decrease from baseline to Day 84 in their SQS step, while patients who were treated with placebo showed a mean increase.

#### **Mean Change from Baseline to Day 84 in SQS Based on Duration of Previous NTM Treatment**

<b>Duration of NTM treatment Prior to Baseline (Day 1) (Months)</b>	<b>Mean change from Baseline to Day 84 in SQS Step LAI Treatment Group</b>	<b>Mean change from Baseline to Day 84 in SQS Step Placebo Treatment Group</b>
6 – 12	-0.50	0.14
>12 – 24	-0.65	0.23
>24	-0.23	0.12

After correcting the SQS assignment and adding the Baseline step as a covariate, the logistic regression model there was a nominally statistically significant treatment effect ( $p=0.031$ ) in favour of LAI compared with the p-value of 0.077 without the Baseline step as a covariate.

#### **Change from Baseline on the SQS for Mycobacterial Culture at Day 84 (mITT Population)**

<b>Day 84</b>	<b>LAI (N = 44)</b>	<b>Placebo (N = 45)</b>	<b>Total (N = 89)</b>
Improvement (a decrease of one step or more)	16/41 (39.0)	11/45 (24.4)	27/86 (31.4)
No change	20/41 (48.8)	23/45 (51.1)	43/86 (50.0)
Worsening (an increase of one step or more) or Death	5/41 (12.2)	11/45 (24.4)	16/86 (18.6)
p-value for treatment effect in ordinal logistic regression model <sup>a</sup>			0.077
<b>p-value for treatment effect in ordinal logistic regression model<sup>b</sup></b>			<b>0.031</b>

mITT = modified intent-to-treat, QD = dosed every day

<sup>a</sup> The ordinal logistic regression model has an effect for treatment arm, with testing at a two-sided significance level of 0.05.

<sup>b</sup> The ordinal logistic regression model with baseline step as a covariate and treatment arm as a fixed effect.

For NTM conversion (i.e. not using the post hoc definition of SCC) the logistic regression model with the Baseline step as a covariate produces a p-value of 0.012 showing a nominally statistically significant treatment effect in favour of LAI.

#### Proportion of Patients with NTM Culture Conversion to Negative (mITT Population)

	Number (%) of Patients			P-value
	LAI (N = 44)	Placebo (N = 45)	Overall (N = 89)	
<b>Baseline</b>	5/44 (11.4)	5/45 (11.1)	10/89 (11.2)	
Day 28	10/42 (23.8)	5/45 (11.1)	15/87 (17.2)	0.100 <sup>a</sup>
Day 56	11/42 (26.2)	4/45 (8.9)	15/87 (17.2)	0.038 <sup>a</sup>
Day 84	14/41 (34.1)	4/45 (8.9)	18/86 (20.9)	0.003 <sup>a</sup>
<b>Day 84</b>	<b>14/41 (34.1)</b>	<b>4/45 (8.9)</b>	<b>18/86 (20.9)</b>	<b>0.012<sup>b</sup></b>

mITT = modified intent-to-treat, QD = dosed every day

Note: Missing values were excluded under the assumption of missing at random, for which missing baseline or post baseline values are excluded but all non-missing data were included (ie, exclusion was not at patient level, but rather at time point level).

a P-value for stratified Cochran-Mantel-Haenszel test of treatment arm adjusting for the randomization strata.

b P-value from a logistic regression model with baseline step as a covariate and treatment arm as a fixed effect.

The Baseline SQS and change from Baseline per treatment group for patients with non-CF underlying lung disease and MAC infection each demonstrated statistical significance ( $p=0.036$  for the non-CF sub-group;  $p=0.045$  for the MAC sub-group).

Patients who achieved SCC (post hoc definition) had greater mean reductions from Baseline on their SQS than the overall patient population. All converters had a Baseline SQS step of 1 to 4.

#### SCC at 28-day and 12-Month post therapy visits (see the table below)

Using the revised SQS assignment of samples and including those with negative cultures at day 1 (baseline) in the numbers, the applicant counted 23 patients who demonstrated SCC (defined *post hoc* as 3 consecutive negative sputum cultures) by the 28-day follow up visit. As shown in the table, 19/23 had non-CF underlying disease and were infected with MAC. Of the 23, 20 patients achieved SCC while receiving LAI added to their multidrug regimen, either during the double-blind phase or in the open-label phase of the study.

Of the 23 patients with SCC:

- 17 patients attended the 12 month follow up visit (14 non-CF MAC; 2 non-CF Mab; 1 CF Mab)
- 1 patient died prior to the visit (non-CF MAC)
- 5 did not sign consent to enter the 12 month follow up

Thus, 14 of the 17 patients who attended the 12 month follow up visit had non-CF MAC:

- 3/14 could not produce sputum despite reasonable attempts (these 3 patients were not taking any medications to treat their NTM at the time of the visit)
- 9/14 were culture negative (1/9 remained on medications to treat their NTM)
- 2/14 were broth positive (neither patient remained on medication to treat their NTM)

**Patients who demonstrated Conversion (defined as 3 consecutive monthly negative sputum cultures) during  
Study TR02-112 (post hoc analysis)**

Treatment Arm DBL Phase	CF Status	NTM Organism at screening	Length of prior NTM Tx (Months)	Screening SQS	Amikacin MIC at Baseline	Day 1	Day 28	Day 56	Day 84	Day 112	Day 140	Day 168	28 Day Follow-Up	12 Month Follow-Up
LAI	Non-CF	MAC	>12 - 24	3	No growth	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	No Visit
LAI	Non-CF	MAC	6 - 12	3	No growth	Negative	Negative	Negative	Negative	Negative	Negative	2	Negative	Negative
LAI	Non-CF	MAC	>24	5	32/ND	4	Negative	Negative	Negative	Negative	Negative	Negative	Negative	No Visit
LAI	Non-CF	MAC	>24	2	16/WT	2	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
LAI	Non-CF	MAC	>12 - 24	3	8/ND	3	Negative	Negative	Negative	Negative	Negative	Negative	Negative	2
LAI	Non-CF	MAC	6 - 12	3	16/WT	3	Negative	Negative	Negative	Negative	Negative	Negative	2	No Visit
LAI	CF	<i>M abscessus</i>	6 - 12	6	16/WT	3	Negative	Negative	Negative	Negative	Negative	Negative	Negative	No Visit
LAI	Non-CF	MAC	>24	6	16/ND	3	2	Negative	Negative	Negative	Negative	Negative	Negative	Negative
LAI	Non-CF	MAC	6 - 12	2	No growth	Negative	2	Negative	Negative	Negative	Negative	Negative	Negative	Negative
LAI	Non-CF	MAC	6 - 12	3	No growth	Negative	3	Negative	Negative	Negative	Negative	Negative	Negative	Negative
LAI	Non-CF	MAC	>24	2	64/WT	3	3	3	Negative	Negative	Negative	Negative	Negative	Negative
LAI	Non-CF	MAC	>12 - 24	2	No growth	Negative	Negative	3	Negative	Negative	Negative	Negative	Negative	Negative
LAI	Non-CF	MAC	>24	5	16/WT	3	2	3	2	Negative	Negative	Negative	Negative	Unable to Obtain Sputum
PBO	Non-CF	MAC	>24	3	No growth	Negative	Negative	Negative	Negative	2	Negative	Negative	Negative	Negative
PBO	Non-CF	MAC	6 - 12	2	No growth	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Unable to Obtain Sputum
PBO	Non-CF	MAC	>12 - 24	3	16/WT	3	Negative	Negative	Negative	Negative	Negative	Negative	Negative	No Visit
PBO	CF	<i>M abscessus</i>	>12 - 24	3	No growth	Negative	Negative	3	Negative	Negative	Negative	Negative	No Visit	Negative
PBO	Non-CF	<i>M abscessus</i>	>24	3	16/WT	3	Negative	Negative	3	Negative	Negative	Negative	Negative	Negative
PBO	Non-CF	MAC	>24	4	16/WT	4	3	3	3	Negative	Negative	Negative	Negative	Negative
PBO	Non-CF	MAC	>24	7	32/ND	4	4	3	5	Negative	Negative	Negative	No Visit	No Visit
PBO	Non-CF	<i>M abscessus</i>	>24	2	8/WT	3	3	2	3	3	Negative	Negative	Negative	2
PBO	Non-CF	MAC	>24	3	8/MIX	3	6	3	4	2	Negative	Negative	Negative	Unable to Obtain Sputum
PBO	Non-CF	MAC	>12 - 24	3	No growth	Negative	3	2	6	2	Negative	Negative	Negative	2

CF = cystic fibrosis; DBL = Double-blind phase; LAI = liposomal amikacin for inhalation; *M. abscessus* = *Mycobacterium abscessus*; MAC = *Mycobacterium avium* Complex; MIC = minimum inhibitory concentration; ND = not done; NTM = non-tuberculosis mycobacterium; PBO = placebo; SQS = semi-quantitative scale; Tx = treatment; WT = wild-type;

The two non-CF Mab patients were culture negative; both remained on medication to treat their NTM.

The CF Mab patient was broth positive and remained on medication to treat NTM

Of the patients who did not achieve SCC but attended the month 12 visit, sputum culture results were available for 28 patients and only one could not produce sputum despite reasonable attempts. [The assessor assumes then that 29 attended. Together with the 17 that did have SCC as above, 46 in total attended; 4 could not produce sputum so 42 samples were obtained]. Of the 28 patients who produced sputum, six were NTM culture negative (6/28; 21.4%) of which 3/6 (50%) remained on medication to treat their NTM at this time point. Of the other 22 patients, 10 (45.5%) remained on medication to treat their NTM.

The applicant counts 11/14 (79%) patients with prior SCC who were negative at month 12 follow-up (10 were not on medication) while 6/28 (21%) non-converters had a negative sputum culture. [The assessor's count does not agree with this figure; see the comment on efficacy]. During the observation period between the 28-day follow up and the 12-month follow-up, a total of 7 patient deaths were reported. Of these, 6 patients were non-converters.

#### MIC results for amikacin

In patients with non-CF MAC MICs of amikacin for their MAC isolates ranged from 8 to 64 µg/mL at baseline and the majority was  $\geq 16$  µg/mL. In the Double-blind phase, patients in the LAI group had a greater reduction in SQS compared with the placebo group, regardless of baseline MIC. When patients in the placebo group were treated with LAI added to their multidrug regimen during the open-label phase, a reduction in the mean SQS step was demonstrated. Regardless of baseline MIC, treatment with LAI added to a multidrug regimen resulted in a decrease in mean SQS step for both converters and non-converters.

#### Acute pulmonary exacerbation

- No statistically significant difference was observed between the treatment groups for time to treatment for acute pulmonary exacerbation in CF patients ( $p = 0.0939$ ).
- In the non-CF patients, a statistically significant difference was observed in favour of placebo ( $p = 0.0171$ ), with a hazard ratio of 2.95 (95% CI: 1.21, 7.19).

#### Protocol-defined pulmonary exacerbation

There were 32 events in the LAI group and 26 in the placebo group. A statistically significant difference ( $p = 0.0216$ ) in favour of placebo was observed during the double-blind phase for time to first protocol-defined pulmonary exacerbation (hazard ratio [LAI/placebo]: 1.84; 95% CI: 1.09, 3.11).

#### Investigator-defined exacerbations

There were 21 events in the LAI group and 10 in the placebo group. The time from baseline to first investigator-defined pulmonary exacerbation was statistically significant in favour of placebo ( $p = 0.0058$ ; hazard ratio [LAI/placebo]: 2.91; 95% CI: 1.36, 6.21).

#### Time to anti-mycobacterial or other drug use

There was a statistically significant difference between the LAI and placebo groups for time to first use of any rescue drug (censoring at date of last contact or at initiation of open-label LAI treatment) during the double-blind phase. More LAI than placebo patients required rescue (21 vs. 11) and the time to rescue was shorter. In the open-label phase 37 patients required rescue therapy, including 17 patients from the prior LAI group and 20 from the prior placebo group.

### Relative and absolute change in PFTs

There was no clinically meaningful change in PFTs from study baseline to day 168.

### Change in RSSQ

In the double-blind phase up to day 84 there was no appreciable difference between treatments in the mean change from baseline in the composite RSSQ score (-0.8 for LAI and -0.6 for placebo; decrease signifies improvement). In the total OLMITT population the mean composite RSSQ score decreased overall and at day 168 there was a larger difference in those who previously received LAI (-1.01 vs. -0.49).

### Change in GRH

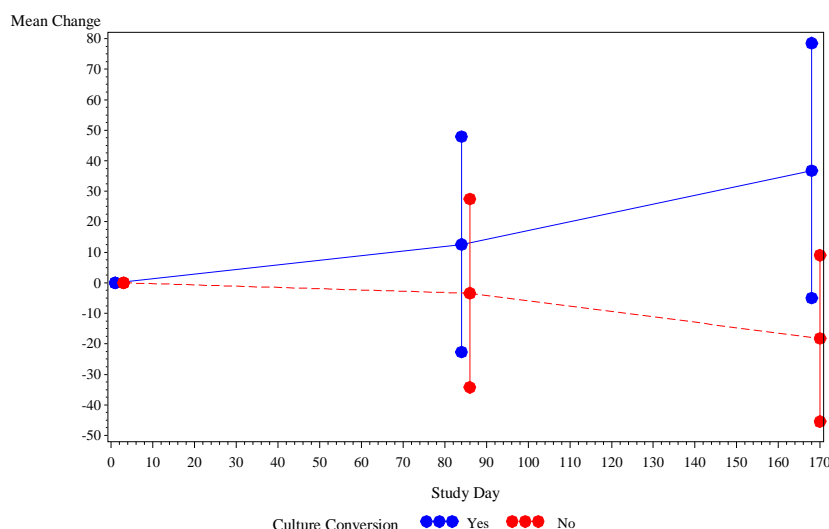
Most patients (55.7%) rated their health as "good" at baseline but slightly more in the LAI group rated their health as "excellent" (11.6% vs. 4.4%) or "poor" (7.0% vs. 2.2%). There was no observable trend throughout the double-blind phase in the patients' rating of health and at day 84 most patients (65.5%) had no change from baseline. Similarly, most patients (76.7%) had no change from day 85 in their rating of health at day 168 and there was no statistically significant difference between the previous LAI and placebo groups.

### 6-minute walk assessment

At study entry the 6-minute walk distance was 441.6 m for LAI patients and 441.8 m for placebo patients. At day 84 in the mITT population the LAI group had a mean increase of 23.6 m and the placebo group had a mean decrease of 25 m. The difference was significant using the Wilcoxon rank sum analysis ( $p = 0.0134$ ) and using ANCOVA ( $p = 0.0090$ ). These results were confirmed in the sensitivity analyses. At day 168, patients in the previous LAI group had a mean increase from day 85 of 22.5 m while patients previously treated with placebo had a mean decrease of 8.7 m. This difference was not significant.

The applicant presented a post hoc analysis of 6MWT that compared patients who did and did not achieve SCC. The applicant states that those with SCC had a greater mean improvement in the 6MWT distance from Baseline to Day 168 ( $p=0.0734$ ). A further analysis of the 6MWT was confined to non-CF MAC patients with and without SCC and reported  $p=0.0323$ . The denominators are not stated (i.e. it is not known if numbers include those with negative cultures at baseline), the statistical test applied is not stated (which is important; see above), it is not known what the bars on the figure show and there are no details of any imputation. The revised CSR and appended additional tables do not provide the answers.

**TR02-112 Mean Change from Baseline in 6MWT Distance - LOCF**  
 Converters vs. non-Converters  
 mITT Population - MAC and non-CF Patients



### Comment on clinical efficacy

#### Treatment regimen for NTM

The applicant has assumed that the same dose of LAI used in CF patients should apply to patients with NTM but on a daily rather than cyclical basis. There is no justification provided for this assumption and there are several reasons why a different dose could be appropriate (e.g. differences in pathogens, sputum and type of lung damage due to chronic infection). In TR02-112, which compared LAI with empty liposomes, LAI at the chosen daily dose was associated with higher rates of discontinuations due to AEs, suggesting that amikacin *per se* is an irritant in the bronchial tree.

ATS/IDSA guidelines recommend 12 months of continuous treatment while sputum cultures remain negative (i.e. after SCC). For those without SCC treatment often continues for >2 years. There was no justification for a comparison with placebo over only 84 days in TR02-112. There are no safety data for LAI beyond 168 consecutive days and only 59 patients achieved this duration of exposure. The available data provide no useful basis for guiding physicians and it is not appropriate to ignore the fact that the applicant is promulgating continued use way beyond that supported by the safety database.

#### Observations on the population and organisms treated

In N. America, where TR02-112 was conducted, most cases of NTM pulmonary disease are due to *M. avium* complex (MAC), followed by *M. abscessus*. In TR02-112 cultures were to show either MAC or *M. abscessus* or mixed infection with both species. *M. gordonae*, *M. haemophilum*, *M. mucogenicum*, *M. nonchromogenicum* and *M. terrae* complex were regarded as contaminants in the protocol but their presence in cultures was allowed provided that MAC and/or *M. abscessus* predominated. Not surprisingly, in an HIV uninfected population, about 2/3 of patients enrolled had MAC and 1/3 had *M. abscessus*, with a predominant population of older females. Also about 1/5 had CF with a strong association between non-CF status and MAC but a mixed CF status for those with *M. abscessus*. The applicant now confines the indication to non-CF patients with MAC. It should be noted that they must also be HIV uninfected.

The NTM species considered to be causative for NTM pulmonary disease vary worldwide. In a UK report the commonest associated with lung disease was MAC, with proportions increasing during the last 50



years to about 2/3 of all NTM cases. This may be related in part to the association with HIV. However, in COPD patients *M. malmoense* was commonest and *M. xenopi* and *M. kansasii* also featured in the non-HIV-infected population. The commonest NTM species affecting EU CF patients is *M. abscessus* followed by MAC. Several case reports suggest that *M. abscessus* follows a more fulminant course and is associated with a less good outcome. *M. abscessus* is universally resistant to standard anti-tuberculous agents and no regimen based on in-vitro susceptibilities has been shown to produce long-term sputum conversion. In the UK intravenous amikacin is part of the first-line regimen recommended for *M. abscessus*. It is no surprise then that all but one of the patients who achieved SCC were non-CF patients with MAC lung disease.

#### *Summary of reasons for the Major Objection at D120*

- TR02-112 was a Phase 2 which initially evaluated the use of LAI vs. placebo over 84 days (12 weeks) in 89 treated patients with *recalcitrant* non-tuberculous mycobacterial (NTM) lung disease. After Day 84 78/80 patients who completed the double-blind phase (35 LAI and 43 placebo; the imbalance was due to withdrawals from LAI, mostly for AEs but none from placebo) elected to continue into the open label phase to receive LAI for up to 84 days. Of these 78 patients, 59 completed day 168 on study while 7/35 and 12/43 withdrew, mainly (16/19) due to AEs.
- The study was not discussed with EU Regulators until it was effectively completed and was not planned *ab initio* to support MAA.
- With a 2-sided significance level of 0.05, 50 patients per arm were believed to provide 80% power to detect a difference between the treatment arms of at least 0.94 steps on the SQS. Such a change on this scale is of no known clinical importance. There were 18 LAI vs. 13 placebo patients ( $p = 0.148$ ) with at least a 1-step reduction on the SQS from baseline so the study failed the pre-defined primary analysis.
- The conclusion drawn by the assessors based on a *post hoc* definition of sputum culture conversion [SCC] in this hypothesis-generating study was that, if there is any efficacy at all, which remains to be proven, it is probably confined to a subset of non-CF and HIV uninfected patients with a low sputum burden of MAC at baseline. However, there was concern that baseline imbalances in bacterial load and residual amikacin in sputum samples influenced the SCC rates and there were several other issues that required further explanation.
- The applicant's answer to this Major Objection and the answers to several of the related Other Concerns focus on supporting a revised indication based on SCC rates in 54 non-CF patients with MAC, half (27/54) of whom received LAI and half placebo in the double-blind phase.
- There is no comparison vs. placebo beyond day 84. The maximum possible duration of therapy was 168 days. There was no plan to follow-up patients for efficacy beyond 28 days post-treatment. The 12 months follow-up was planned to capture safety data; no data were reported from this visit.
- The study was not suitable to support an indication for treatment of NTM or for treatment of the non-CF HIV-negative MAC-infected subset in which this study suggested there might be some benefit.
- The applicant has since commenced a Phase 3 study. Unfortunately, this is not placebo-controlled.

#### *Revised proposed indication*

The applicant now proposes to claim an indication for treatment of MAC lung disease in adults who have not achieved SCC after treatment with "first line therapy". There are no antibacterial agents approved for this use so "first line therapy" reflects various guidance documents. In particular, the IDSA/ATS guidance, repeatedly referred to by the applicant, recommends that MAC affecting only the lung should be treated until culture negative on therapy for 1 year. In the Phase 2 study, the comparison with placebo was for 84 days. After that, all patients were offered 84 days LAI and then it was stopped.

Patients remained on their background NTM regimen in accordance with IDSA/ATS guidance (this being a US/Canada study) but there was no plan to follow them up for efficacy after 28 days post-study therapy. The planned visit at 12 months post-study therapy was to be for safety but during the procedure the applicant provided some culture results from this visit.



The patients enrolled into TR02-112 were HIV uninfected, which is an important issue, and the majority (71/89) had received > 12 months prior therapy for MAC without achievement of SCC. In this HIV-negative population almost all patients were female (78/89 enrolled) with a mean age of 58.5 years. This reflects the type of non-CF patient afflicted with non-HIV-associated MAC lung disease.

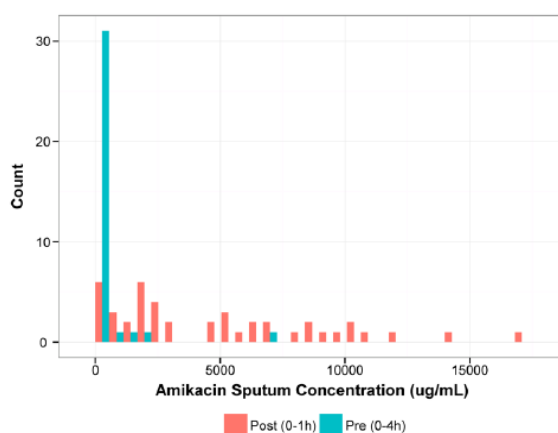
Despite the time elapsed since diagnosis and the duration of prior therapy without SCC, most (55.7%) of the total 89 patients (i.e. not just the non-CF MAC sub-population) rated their health as “good” at baseline, 8% as excellent (11.6% LAI vs. 4.4% Placebo) and 31.8% as fair. Only 4% said their health was poor (7.0% vs. 2.2%). The mean FEV1% predicted was 63 and 64/89 had >50%. In addition, at baseline the mean 6-minute walk distance was 441.6 m for LAI patients and 441.8 m for placebo patients. Therefore, the study population was apparently in reasonable health at baseline.

It is important the wording of any final indication and the content of the SmPC adequately reflects the population studied. Nevertheless, at this time there are inadequate data to support the applicant’s proposed indication. The results of the Phase 3 study, which compares addition of LAI to SOC vs. SOC alone, would be needed before any decision could be reached.

#### *Sputum concentrations of amikacin*

The sputum concentration data presented in the responses were already provided and fully described in the D80 report. Sputum amikacin levels were analysed for 12/16 patients in the PK sub-study. Overall 52.1% (38/73) of the pre-dose sputum samples had amikacin concentrations BLQ compared to 37.1% (26/70) of the post-dose samples. However, it is currently unclear whether all these BLQ samples were actually obtained from patients while taking LAI and this requires clarification. Thus the mean and median values are based on 35 pre-dose and 44 post-dose samples. Both datasets showed a very wide spread of concentrations (see the figure below).

**Figure 11-2** Distribution of Amikacin Sputum Concentrations by Nominal Sampling Time



Although one PK sub-study data point from one patient was already eliminated due to apparent likely mix-up of samples, the applicant now states that the pre-dose levels are affected by a single outlier who also seems likely to have had a sample mix-up yet was not removed from the analysis presented previously (as above). The applicant proposes that the median is the more accurate representation of central tendency for the concentration of amikacin in sputum. Even if the newly-identified outlier is discarded, the range of concentrations in this subset of sputa with quantifiable amikacin taken from 12 patients (it is not explained if they were among those with non-CF MAC and SCC) indicate that it is

likely at least some values fall above the MIC of amikacin for the patients' individual strains even after taking into account the description of sputum processing and the dilution steps (1/4) before culture.

There was a subset of 61 samples for which there were "time-matched" concentration and culture results, which concluded that the SQS results were independent of the pre-dose amikacin concentrations. It should be noted that the samples that were used for PK were not the same samples used for culture since the latter were processed and made unsuitable for PK studies.

"Time-matched" samples presumably represent separate expectorations with a short time interval, which can influence both the apparent sputum concentration and the numbers of organisms. In addition, due to lack of sputum homogeneity, if amikacin levels had been measured in more than one sample obtained on the same day at pre-dose it is possible that these could be quite different. Added to all of this is the inherent variability in the numbers of organisms that can be retrieved from any one specimen taking into account that some organisms exposed to amikacin within the airways are alive when expectorated but cannot sufficiently recover from aminoglycoside exposure to grow on artificial media (broth or solid) in the laboratory.

Since non-PK samples were processed for culture the applicant is not able to retrieve samples from all patients and retrospectively measure amikacin levels. Reporting the sputum amikacin levels in CF patient sputa obtained up to 4 weeks post-treatment in another study does not help and only serves to show that in some sputa amikacin persisted for a remarkably long time after dosing with LAI.

Overall it is not a surprise that no correlation can be detected between apparent residual amikacin concentrations and organism numbers. The only reliable way to assess the effect of treatment with LAI is to document sustained SCC at a time point long after cessation of inhaled therapy. Sustained SCC should be the primary endpoint in any study intended to support approval for treatment of NTM. Sustained SCC was not a primary or secondary endpoint in TR02-112 and no assessment of sputum culture was planned beyond 28 days post-study treatment. The secondary endpoint of conversion to negative culture was defined in the protocol as negativity *at a single time point*. Only in the retrospective *post hoc* analysis was SCC defined as negative cultures at 3 consecutive time points.

#### *Re-analysis of the SQS data*

The applicant provided a revised CSR during the procedure that included re-analysis of the primary and several secondary endpoints after re-assigning 38 contaminated samples previously counted as Step 2 to Step 1 (i.e. negative on liquid and solid media) after negative DNA probing for MAC. This DNA probing seems to have used an in-house method described in the CSR appendices for which no assay performance or validation data are provided. Re-assignment of 2% of the total samples leads the applicant to report that 23 patients demonstrated SCC by the 28-day follow-up visit of which 20 achieved SCC while receiving LAI (see the table of serial culture results and discussion of these numbers below).

The counting of contaminated specimens as negative if they were MAC PCR negative could be agreed subject to adequate data to support the assay that was applied. However, the applicant should also show the sequential culture data up to the month 12 follow-up visit based on the original protocol-specified counting of contaminated specimens. This should be done tabulating all patients who had a negative culture at some time point and separately for the subset that had 3 consecutive negative cultures. In this way, if the information received on the assay is not reassuring, there will be an alternative presentation available that includes the additional month 12 follow-up data that were reported during the procedure.

Using the applicant's revised assignment of contaminated specimens, there remains an imbalance in baseline loads favouring LAI. The re-analysis of shifts on the SQS scale does not assist in evaluation of the application because an apparent shift on this scale of any magnitude at a single time point cannot be correlated with a clinical benefit for LAI vs. placebo. Therefore claiming that this re-analysis now gives a study that just met its pre-defined primary endpoint is not of importance. It was already communicated to the applicant that the pre-defined primary endpoint for this study was inappropriate and the CHMP has since recommended an appropriate primary endpoint for the ongoing Phase 3 study based on confirmed SCC rates. Specifically, the CHMP notified the Company in the scientific advice on the ongoing Phase 3 study (INS-212) that achieving 3 negative cultures while on LAI was not an acceptable primary efficacy endpoint. Specifically:

The CHMP does not agree with the proposed primary endpoint in INS-212. Sputum culture conversion on treatment is not regarded as a reliable endpoint nor does it have any known predictive capacity for eradication of MAC (i.e. to predict sustained negativity after stopping all treatment). The Applicant is advised that the primary endpoint for any future EU submission should be sustained SCC, which should be determined when at least 3 months have elapsed after stopping all anti-MAC treatment. If necessary, the Applicant should prepare a separate statistical analysis plan to support the required primary analysis for the EU.

#### *Re-analysis of SCC rates, including available month 12 follow-up*

The re-analysis of SCC is based on the revised SQS assignment as described above and on the post hoc definition of SCC that required negative cultures at three consecutive visits. This was not a pre-defined endpoint in the protocol or statistical analysis plan.

The protocol did not plan to assess efficacy at the month 12 follow-up visit. From the applicant's response the assessor counts 42 sputum culture results available from 46 patients (17 with prior SCC on or off LAI and 29 with no prior SCC) who attended the 12-month follow-up visit. These numbers indicate that 17/23 with SCC at some time and therefore 29/66 without SCC attended the visit, which demonstrates a bias in favour of attendance at the month 12 follow-up visit by the patients with prior SCC. However, the safety addendum to the CSR reports that 57 patients actually attended the month 12 follow-up visit. The discrepancy vs. 46 counted from the applicant's response is not understood.

The applicant states that of the 29 who attended this visit who had not had SCC by the end of the 28-day off LAI visit, sputum culture results were available for 28 patients. Of these, six were NTM culture negative (6/28; 21.4%) of which 3/6 (50%) remained on routine medication to treat their NTM at this time point. Ten of the other 22 patients (45.5%) also remained on medication to treat their NTM, which means that 12 still culture positive were not on any treatment.

#### Outcomes at the 12 month follow-up visit in non-CF MAC patients

Based on the updated SQS analysis (see above) the assessor counts the following patients and outcomes relevant to the new target population (non-CF MAC):

- 54 patients with non-CF MAC lung disease were randomised and treated.
- In the double-blind phase 27 received LAI and 27 received placebo (noting that overall 9/44 LAI vs. 0/45 placebo patients discontinued the double-blind phase, 7/9 due to AEs)
- In the open-label phase (OLP) 22/27 from the LAI group and all 27 from the placebo group received LAI (noting that overall another 7 from the initial LAI and 12 from the initial placebo group discontinued, 6 and 12 due to AEs).
- Therefore 54 non-CF MAC patients started on LAI on day 1 or on entering the OLP and had the opportunity to receive between 84 and 168 days treatment if they did not discontinue.

From the table that shows the 23 patients the applicant states had SCC, including 20 stated to have had SCC on LAI, the assessor counts the following:

- 19/23 were non-CF MAC patients, 12 from the initial LAI group and 7 from the initial placebo group.
- 5/12 from the initial LAI group had negative cultures on day 1. One of these never had a positive culture at any visit. The other four each had a single visit with a positive culture (all were step 2 or 3). Two were positive at day 28, one at day 168 and one at the day 28 follow-up. There were negative cultures at all other visits. The results from these patients are strange and raise additional questions that cannot be answered regarding sample mix-ups and the sensitivity of the laboratory culture methods. With negative cultures at day 1 and single positives on therapy it is not possible to conclude that these patients really had SCC on LAI.
- Thus 7/12 from the initial LAI group were positive on day 1 and at some time had 3 consecutive visits with negative cultures (i.e. met the *post hoc* definition of SCC). Of these 7:
  - 1 was positive at the day 28 follow-up and had no M12 follow-up visit
  - 1 was positive at M12 follow-up
  - 1 was negative up to the day 28 follow-up but had no M12 visit
  - 1 was negative from day 112 to the day 28 follow-up but had no sputum at the M12 visit
  - 3 were negative from first SCC time point to M12 follow-up
- 3/7 from the initial placebo group had negative cultures on day 1. One never had a positive culture and one had a single positive result (step 2 on day 112). These two patients cannot be included in the analysis of SCC on LAI (see also above). The third was positive from day 28-112 and is counted below in the SCC rates.
- Thus 5/7 from the initial placebo group (4 positive on day 1 and the patient described above who was negative on day 1 but positive from day 28-112) could be assessed for possible SCC:
  - 1 had SCC on placebo and remained negative at the day 28 follow-up but had no M12 visit
  - 4 had SCC at some time after switching to LAI. Of these 4:
    - 1 was negative at M12
    - 1 was positive at M12
    - 2 have no result at M12 (one had no day 28 or M12 follow-up and one had no sputum)
- Based on assuming contaminated cultures to be negative, that the month 12 follow-up is based on 3 consecutive sputa (to be clarified) and that any missing samples have not been assumed to be negative, these data show that 47/54 non-CF MAC patients enrolled and treated with LAI had positive baseline cultures and can be assessed for SCC.
- Based on this denominator of 47 there were 4 with a confirmed SCC that persisted at the M12 follow-up visit, which gives a SCC rate of **4/47 (= 8.5%)**. **This is the only reliable SCC rate.**
- If the two patients who attended M12 but had no sputum are assumed to be negative then the SCC rate is **6/47 (= 12.8%)**.
- If the other two patients who were negative at the day 28 follow-up but did not attend the M12 visit are assumed to be negative then **the most optimistic SCC rate is 8/47 (= 17%)**.

However, 54 non-CF MAC patients had a positive screening sample before randomisation and this FAS is more representative of a population that might be selected for LAI treatment. Based on this denominator:

- The confirmed SCC rate (persisted at M12 follow-up) is 4/54 (**7.4%**).
- Counting the two with no sputum at M12 the rate is 6/54 (**11%**).
- Counting the two negative at day 28 follow-up without a M12 visit the most optimistic rate is 8/54 (**14.8%**).

The applicant's count of SCC includes the 5 LAI and 2 placebo group patients with non-CF MAC who were negative on day 1 and which the assessor rejects from the analysis. In these 7 patients:

- 2 never had a positive at any time and cannot be regarded as having SCC during the study
- 1 was negative at both follow-up visits but was positive at D168 so does not meet the *post hoc* SCC definition (3 consecutive negative cultures)

4 had SCC while on LAI after single positive visits and were negative at both follow-up visits. If these 4 are counted then 8/54 would have confirmed SCC at the month 12 visit (**SCC rate of 14.8%**).

These numbers and the confirmed sustained SCC rates are not a sufficient basis for approval.

The applicant also points to the day 28 post-therapy visit results, based on claims that there was not sufficient amikacin left in sputa at that time point to have caused false negative cultures. This claim is based on day 28 post-LAI sputum concentrations in CF patients, which gave means of 89 and 5 µg/g with ranges from 0-2200 and from 0-57.7 µg/g after cycles 1 and 2, respectively. If concerns regarding interference with culture results were to be wholly dismissed, the assessor's count of outcomes at the day 28 post-therapy visit for the 47 non-CF MAC patients described above as culture positive on day 1 is as follows:

- o Of the 7 from the initial LAI group:
  - 1 was positive at the day 28 follow-up after 6 prior negative visits
  - 6 were negative at the day 28 follow-up after between 3 and 6 prior negative visits but one of these was positive at month 12 so it is not reasonable to assign this patient to SCC at day 28 follow-up
  - Therefore 5 could be regarded as negative at day 28 follow-up based on available data
- o Of the 5 from the initial placebo group, 4 had SCC at some time after switching to LAI. Of these 4:
  - 1 had no post-therapy visit
  - 3 were negative but one was positive at month 12 follow-up so it is not reasonable to assign this patient to SCC at the day 28 follow-up
  - Therefore 2 were negative at the day 28 follow-up (but after only 2 or 3 prior negative visits)

This count gives a maximum of 7/47 patients who have some evidence of SCC on MAC who were still negative at the day 28 follow-up visit (**SCC rate of 14.9%**). Based on the FAS the rate is 7/54 (**13%**).

If the 4 baseline negative patients with single post-baseline positives are counted then the SCC rate is 11/54, which is 20%. This is the most optimistic estimate possible from the available data but it is not reliable.

These numbers and the confirmed sustained SCC rates are not a sufficient basis for approval.

The applicant's response also points to recent decisions taken for two agents approved for treatment of tuberculosis, suggesting a lack of consistency in approach. In this regard it is important to distinguish lung MAC infections in HIV uninfected non-CF populations from infections due to *M. tuberculosis*. The applicant's assertion that sputum concentrations of active agents were not taken into consideration is incorrect. It also must be remembered that, as repeatedly pointed out by the applicant, the whole point of inhaled therapy is to achieve very high local concentrations within the airways.

The data indicate that there is persistence of LAI in the airways and a slow amikacin release phenomenon. Therefore there are additional concerns for the validity of any on-treatment culture results for inhaled vs. oral formulations.

There also has to be considerable concern that there was bias in attendance at the month 12 visit by those with prior SCC. The applicant states that between the 28-day follow-up and the month 12 follow-up visits 7 patients died (6 non-converters) but it is not known how many were actually followed up and have clear documentation of status.

#### *Other endpoints*

The applicant proposes that the 6MWT results support a benefit for LAI. At day 84 there was a significant difference between groups due to a mean increase of 23.6 m for LAI vs. a mean decrease of

25 m for placebo. The applicant now compares change from baseline to D168 for non-CF MAC patients who did and did not have SCC (applicant's counting of SCC cases) and claims there is a significant difference that supports the reliability of the negative culture results. This test points to a correlation between culture results and walking distance (although there are several issues surrounding the analysis that need to be clarified) but it does not help to clarify which patients had a true SCC. Furthermore, this is not a comparison of randomised groups and there may be other factors affecting the difference observed.

It should be noted that the CSR reported on several other endpoints for LAI vs. placebo up to D84 as follows:

- There were 32 protocol-defined pulmonary exacerbations in the LAI group and 26 in the placebo group with a statistically significant difference in time to exacerbation favouring placebo.
- There were 21 investigator-defined exacerbations in the LAI group and 10 in the placebo group and the time to first investigator-defined pulmonary exacerbation was statistically significant in favour of placebo.
- There was a statistically significant difference for time to first use of any rescue drug such that more LAI than placebo patients required rescue and the time to rescue was shorter.
- There was no appreciable difference in the mean change from baseline in the composite RSSQ score.

TR02-112 compared LAI with empty liposomes. The discontinuation rates and the rates of "exacerbations" actually suggest that amikacin *per se* is an irritant within the airways.

### Conclusion

The revised indication is based on subset of 54 patients from a Phase 2 study that has several deficiencies of design and on a *post hoc* primary endpoint that gives a sustained SCC rate at month 12 follow-up of 8.5% in 47 non-CF MAC patients with positive baseline cultures. Approval is not possible even based on the most optimistic rate of 17%, which is reached only by assuming that patients who could not produce sputum or did not attend the month 12 follow-up visit had sustained SCC (which cannot be verified). Basing the conclusion on efficacy on the day 28 follow-up visit does not improve on this most optimistic rate.

The study provides some preliminary evidence that there might be a benefit in patients who can actually tolerate inhaled LAI, i.e. do not discontinue because of airway intolerance. However, LAI appears to be an irritant in the respiratory tract based on the discontinuation rates for AEs and on the exacerbation rates (which may well reflect a response to LAI in the airways). It should be remembered that in TR02-112 the placebo was *empty liposomes*, which points to airway irritation by amikacin. This may be the net result of free amikacin in the inhaled product and amikacin released from the liposomes within the airways. The applicant has since commenced a Phase 3 study in the non-CF MAC-infected population. Unfortunately this is not a placebo-controlled study but it does compare LAI + SOC with SOC alone. Based on the results of the CHMP-recommended primary endpoint of SCC this study may suffice to support a future application provided that any quality and nonclinical concerns can be addressed.

### Clinical safety

Across all clinical studies LAI has been administered to 519 individuals, including 6 healthy subjects, 383 patients with CF, 43 patients with bronchiectasis and 89 patients with NTM lung disease.

### Number of Patients Exposed in Cystic Fibrosis Studies

	LAI 70 mg QD	LAI 140 mg QD	LAI 280 mg QD	LAI 560 mg QD	LAI 590 mg QD	TOBI 300 mg BID	Placebo
<b>Active-controlled Phase 3 Study</b>							
TR02-108	—	—	—	—	148	146	—
<b>Ongoing Open-label Phase 3 Study</b>							
TR02-110	—	—	—	—	206	—	—
<b>Placebo-controlled Phase 2a Studies</b>							
TR02-105	—	—	21	21	—	—	22
TR02-106	7	5	—	15	—	—	14
<b>Open-label Phase 2a Extension Study</b>							
TR02-105-Extension	—	—	—	49	—	—	—
<b>Total CF Patients</b>	<b>7</b>	<b>5</b>	<b>21</b>	<b>85</b>	<b>354</b>	<b>146</b>	<b>36</b>

*NB: some patients in the table are counted twice if they received LAI in core and extension phases).*

In the Phase 3 CF study and extension (TR02-108 and 110) using 28 days on/off-treatment cycles, the mean exposure sum was similar for the LAI-LAI (39.0 weeks) and TOBI-LAI (36.1 weeks) groups and was similar for the LAI and TOBI patients in TR02-108 only (9.9 vs. 9.7 weeks). In TR02-112 there was non-cyclical exposure for a maximum of up to 168 days.

The focus of the safety analysis is on three studies in paediatric and adult CF patients with *P. aeruginosa* lung infection (TR02-105 + extension, 106 and 108 + extension 110) and on the NTM study TR02-112.

#### TR02-108/110

Among patients who were only enrolled in TR02-108:

- The percentages with  $\geq 1$  TEAE were greater in the LAI group (94.6%) vs. the TOBI group (81.3%).
- The crude incidence and the exposure-adjusted incidence of treatment-related TEAEs were much higher in the LAI group (53.6%; 208.8) vs. the TOBI group (25.0%; 69.9).

For those who participated in TR02-108 and 110 the crude and exposure-adjusted incidences of treatment-related TEAEs were similar between LAI-LAI (34.8%; 31.1) and TOBI-LAI groups (30.7%; 26.2).



### Overview of Adverse Events in TR02-108 and TR02-110 - crude incidence rate (Safety Population)

Parameter	LAI-LAI (N= 92) n (%)	TOBI-LAI (N= 114) n (%)	LAI (N= 56) n (%)	TOBI (N= 32) n (%)
≥ 1 TEAE	81 (88.0)	103 (90.4)	53 (94.6)	26 (81.3)
Number of TEAEs	800	898	314	113
≥ 1 SAE	28 (30.4)	47 (41.2)	14 (25.0)	8 (25.0)
≥ 1 SAE related to study medication	2 (2.2)	3 (2.6)	1 (1.8)	0
≥ 1 SAE related to study procedure	1 (1.1)	0	0	0
≥ 1 SAE leading to hospitalization	28 (30.4)	47 (41.2)	14 (25.0)	8 (25.0)
≥ 1 TEAE leading to drug discontinuation	7 (7.6)	16 (14.0)	13 (23.2)	3 (9.4)
≥ At least 1 TEAE related to study drug	32 (34.8)	35 (30.7)	30 (53.6)	8 (25.0)
≥ At least 1 TEAE related to study procedure	17 (18.5)	15 (13.2)	14 (25.0)	3 (9.4)
Patient died (CTCAE grade = 5)	1 (1.1)	0	0	0
≥ 1 TEAE in acute renal failure	1 (1.1)	0	0	0
≥ 1 TEAE in asthma bronchospasm	2 (2.2)	7 (6.1)	3 (5.4)	1 (3.1)
≥ 1 TEAE in hearing impairment	3 (3.3)	1 (0.9)	3 (5.4)	1 (3.1)

TEAEs were most frequently associated with the SOC of infections and infestations. The most common individual TEAEs were infective pulmonary exacerbation of CF, nasopharyngitis, haemoptysis, URTI, dysphonia and cough. The exposure-adjusted incidence of the most common TEAEs was generally higher in the LAI group. Most TEAEs were CTCAE Grade 1 or 2.

### TEAEs in ≥ 10% of patients in TR02-108 and TR02-110 (Safety Population)

Parameter MedDRA Preferred Term Version 15.0	LAI-LAI (N=92)			TOBI-LAI (N=114)			LAI (N=56)			TOBI (N=32)		
	No. Subjects	(%)	No. Events	No. Subjects	(%)	No. Events	No. Subjects	(%)	No. Events	No. Subjects	(%)	No. Events
At least 1 TEAE	81	(88.0)	800	103	(90.4)	898	53	(94.6)	314	26	(81.3)	113
Infective pulmonary exacerbation of cystic fibrosis	60	(65.2)	205	82	(71.9)	272	41	(73.2)	71	19	(59.4)	32
Nasopharyngitis	30	(32.6)	41	41	(36.0)	75	11	(19.6)	15	5	(15.6)	7
Haemoptysis	21	(22.8)	67	14	(12.3)	39	9	(16.1)	23	4	(12.5)	8
Upper respiratory tract infection	20	(21.7)	41	19	(16.7)	33	4	(7.1)	5	2	(6.3)	3
Cough	17	(18.5)	32	15	(13.2)	36	8	(14.3)	11	2	(6.3)	3
Rhinitis	13	(14.1)	15	10	(8.8)	11	3	(5.4)	4	3	(9.4)	3
Dysphonia	11	(12.0)	23	21	(18.4)	32	11	(19.6)	17	1	(3.1)	2
Diarrhoea	10	(10.9)	13	7	(6.1)	8	5	(8.9)	7	1	(3.1)	1
Sinusitis	10	(10.9)	16	7	(6.1)	7	4	(7.1)	4	1	(3.1)	1
Headache	9	(9.8)	14	10	(8.8)	15	7	(12.5)	16	1	(3.1)	1
Oropharyngeal pain	8	(8.7)	12	9	(7.9)	16	6	(10.7)	7	3	(9.4)	4

The most frequently reported treatment-related TEAEs were associated with the respiratory tract. The exposure-adjusted incidence was mostly highest in the LAI group.

### Treatment-related TEAEs in TR02-108 and TR02-110 - Safety Population

MedDRA PT Version 15.0	LAI-LAI (N=92)			TOBI-LAI (N=114)			LAI (N=56)			TOBI (N=32)		
	Patients	(%) <sup>a</sup>	Events	Patients	(%) <sup>a</sup>	Events	Patients	(%) <sup>a</sup>	Events	Patients	(%) <sup>a</sup>	Events
At least 1 TEAE related to study medication <sup>b,c</sup>	32	(34.8)	120	35	(30.7)	111	30	(53.6)	77	8	(25.0)	13
Cardiac disorders	2	(2.2)	2	0	(0)	0	1	(1.8)	1	0	(0)	0
Palpitations	0	(0)	0	0	(0)	0	1	(1.8)	1	0	(0)	0
Tachycardia	2	(2.2)	2	0	(0)	0	0	(0)	0	0	(0)	0
Ear and labyrinth disorders	1	(1.1)	1	1	(0.9)	1	3	(5.4)	3	1	(3.1)	2
Deafness	1	(1.1)	1	0	(0)	0	1	(1.8)	1	0	(0)	0
Deafness bilateral	0	(0)	0	0	(0)	0	1	(1.8)	1	0	(0)	0
Deafness unilateral	0	(0)	0	0	(0)	0	1	(1.8)	1	0	(0)	0
Hypacusis	0	(0)	0	0	(0)	0	0	(0)	0	1	(3.1)	1
Tinnitus	0	(0)	0	0	(0)	0	0	(0)	0	1	(3.1)	1
Vertigo	0	(0)	0	1	(0.9)	1	0	(0)	0	0	(0)	0
Eye disorders	1	(1.1)	1	1	(0.9)	1	0	(0)	0	0	(0)	0
Dry eye	1	(1.1)	1	0	(0)	0	0	(0)	0	0	(0)	0
Eye pruritus	0	(0)	0	1	(0.9)	1	0	(0)	0	0	(0)	0
Gastrointestinal disorders	4	(4.3)	4	2	(1.8)	3	2	(3.6)	4	1	(3.1)	1
Abdominal pain upper	1	(1.1)	1	0	(0)	0	0	(0)	0	0	(0)	0
Diarrhoea	2	(2.2)	2	0	(0)	0	1	(1.8)	3	0	(0)	0
Dry mouth	0	(0)	0	0	(0)	0	0	(0)	0	1	(3.1)	1
Gastro-oesophageal reflux disease	1	(1.1)	1	0	(0)	0	0	(0)	0	0	(0)	0
Nausea	0	(0)	0	1	(0.9)	1	1	(1.8)	1	0	(0)	0
Swollen tongue	0	(0)	0	1	(0.9)	1	0	(0)	0	0	(0)	0
Vomiting	0	(0)	0	1	(0.9)	1	0	(0)	0	0	(0)	0
General disorders and administration site conditions	3	(3.3)	3	1	(0.9)	1	1	(1.8)	1	1	(3.1)	1
Chest discomfort	1	(1.1)	1	1	(0.9)	1	0	(0)	0	1	(3.1)	1
Fatigue	1	(1.1)	1	0	(0)	0	1	(1.8)	1	0	(0)	0
Pyrexia	1	(1.1)	1	0	(0)	0	0	(0)	0	0	(0)	0
Infections and infestations	8	(8.7)	16	5	(4.4)	13	6	(10.7)	7	1	(3.1)	1
Aspergillosis	1	(1.1)	1	0	(0)	0	0	(0)	0	0	(0)	0
Bronchopulmonary aspergillosis	1	(1.1)	1	0	(0)	0	0	(0)	0	0	(0)	0
Infective pulmonary exacerbation of CF	4	(4.3)	4	5	(4.4)	5	6	(10.7)	6	1	(3.1)	1
Oral candidiasis	1	(1.1)	1	1	(0.9)	1	0	(0)	0	0	(0)	0
Pseudomonas infection	1	(1.1)	2	0	(0)	0	0	(0)	0	0	(0)	0
Staphylococcal infection	1	(1.1)	1	0	(0)	0	0	(0)	0	0	(0)	0
Vaginal infection	1	(1.1)	1	0	(0)	0	0	(0)	0	0	(0)	0
Viral upper respiratory tract infection	1	(1.1)	1	0	(0)	0	0	(0)	0	0	(0)	0
Investigations	3	(3.3)	3	1	(0.9)	1	2	(3.6)	2	1	(3.1)	1
Blood alkaline phosphatase increased	1	(1.1)	1	0	(0)	0	0	(0)	0	0	(0)	0
Breath sounds abnormal	0	(0)	0	0	(0)	0	0	(0)	0	1	(3.1)	1
Forced expiratory volume decreased	1	(1.1)	1	0	(0)	0	1	(1.8)	1	0	(0)	0
Pulmonary function test decreased	1	(1.1)	1	1	(0.9)	1	1	(1.8)	1	0	(0)	0

MedDRA PT Version 15.0	LAI-LAI (N=92)			TOBI-LAI (N=114)			LAI (N=56)			TOBI (N=32)		
	Patients	(%) <sup>a</sup>	Events	Patients	(%) <sup>a</sup>	Events	Patients	(%) <sup>a</sup>	Events	Patients	(%) <sup>a</sup>	Events
Musculoskeletal and connective tissue disorders	1	(1.1)	2	1	(0.9)	1	0	(0)	0	0	(0)	0
Back pain	0	(0)	0	1	(0.9)	1	0	(0)	0	0	(0)	0
Musculoskeletal pain	1	(1.1)	1	0	(0)	0	0	(0)	0	0	(0)	0
Myalgia	1	(1.1)	1	0	(0)	0	0	(0)	0	0	(0)	0
Nervous system disorders	2	(2.2)	2	2	(1.8)	2	1	(1.8)	1	0	(0)	0
Aphonia	0	(0)	0	1	(0.9)	1	0	(0)	0	0	(0)	0
Dizziness	0	(0)	0	0	(0)	0	1	(1.8)	1	0	(0)	0
Headache	0	(0)	0	1	(0.9)	1	0	(0)	0	0	(0)	0
Sinus headache	2	(2.2)	2	0	(0)	0	0	(0)	0	0	(0)	0
Respiratory, thoracic and mediastinal disorders	21	(22.8)	86	30	(26.3)	88	21	(37.5)	54	5	(15.6)	7
Asthma	1	(1.1)	1	1	(0.9)	1	0	(0)	0	0	(0)	0
Bronchospasm	0	(0)	0	5	(4.4)	5	3	(5.4)	3	1	(3.1)	1
Cough	9	(9.8)	20	10	(8.8)	15	7	(12.5)	9	0	(0)	0
Dry throat	2	(2.2)	3	0	(0)	0	0	(0)	0	0	(0)	0
Dysphonia	9	(9.8)	19	15	(13.2)	23	10	(17.9)	15	1	(3.1)	2
Dyspnoea	2	(2.2)	4	3	(2.6)	5	3	(5.4)	5	0	(0)	0
Epistaxis	0	(0)	0	1	(0.9)	1	1	(1.8)	1	0	(0)	0
Haemoptysis	10	(10.9)	28	5	(4.4)	11	4	(7.1)	10	2	(6.3)	2
Nasal discharge discolouration	0	(0)	0	0	(0)	0	1	(1.8)	1	0	(0)	0
Oropharyngeal pain	2	(2.2)	4	5	(4.4)	12	2	(3.6)	2	0	(0)	0
Pharyngeal erythema	1	(1.1)	2	1	(0.9)	1	0	(0)	0	0	(0)	0
Pulmonary congestion	1	(1.1)	1	1	(0.9)	2	1	(1.8)	2	0	(0)	0
Respiratory tract congestion	0	(0)	0	0	(0)	0	0	(0)	0	1	(3.1)	1
Sputum increased	0	(0)	0	1	(0.9)	1	1	(1.8)	1	0	(0)	0
Throat irritation	4	(4.3)	4	2	(1.8)	2	2	(3.6)	3	1	(3.1)	1
Upper respiratory tract irritation	0	(0)	0	0	(0)	0	1	(1.8)	1	0	(0)	0
Wheezing	0	(0)	0	2	(1.8)	9	1	(1.8)	1	0	(0)	0
Skin and subcutaneous tissue disorders	0	(0)	0	0	(0)	0	2	(3.6)	4	0	(0)	0
Photosensitivity reaction	0	(0)	0	0	(0)	0	1	(1.8)	1	0	(0)	0
Rash	0	(0)	0	0	(0)	0	1	(1.8)	2	0	(0)	0
Urticaria	0	(0)	0	0	(0)	0	1	(1.8)	1	0	(0)	0

#### AEs of special interest (AESIs)

- Acute renal failure was reported for one LAI-LAI patient who died.
- Asthma bronchospasm was reported less frequently in the LAI-LAI group (2.2%) vs. the TOBI-LAI group (6.1%) and LAI group (5.4%). The respective exposure-adjusted incidences were 1.47 per 100 patient years vs. 4.37 and 13.81, with a rate of 7.59 in the TOBI group. None was serious.
- Audiology testing was performed during the screening period and at Day 168 or at an earlier discontinuation visit. Hearing impairment was reported most frequently in the LAI group (5.4% vs. LAI-LAI: 3.3%, TOBI-LAI: 0.9%, TOBI: 3.1%). The exposure-adjusted incidences were 13.1 per 100 patient years, 2.2, 0.6 and 7.7. None of these events was serious.
- Haemoptysis was reported in 16.8% of all patients exposed to LAI in TR02-108 and TR02-110. Most cases were mild to moderate in severity.

## TR02-112

During the double-blind phase the majority of the patients in both treatment groups (LAI: 93.2%, placebo: 88.9%) experienced  $\geq 1$  TEAE. Note that placebo was empty liposomes in this study.

### TEAEs in $\geq 5.0\%$ of patients in the double-blind phase of TR02-112 (Safety Population)

SOC MedDRA Preferred Term Version 15.0	LAI 590 mg QD (N=44)			Placebo (N=45)		
	n	%	events	n	%	events
Number (%) with at least 1 TEAE	41	(93.2)	240	40	(88.9)	140
Respiratory, thoracic and mediastinal disorders	35	(79.5)	85	23	(51.1)	36
Dysphonia	19	(43.2)	25	4	(8.9)	4
Cough	14	(31.8)	17	6	(13.3)	6
Haemoptysis	5	(11.4)	5	5	(11.1)	6
Oropharyngeal pain	9	(20.5)	9	1	(2.2)	1
Wheezing	4	(9.1)	4	1	(2.2)	1
Dyspnoea	3	(6.8)	4	1	(2.2)	2
Nasal congestion	3	(6.8)	3	0	0	0
Infections and infestations	32	(72.7)	50	18	(40.0)	30
Infective exacerbation of bronchiectasis	17	(38.6)	23	9	(20.0)	10
Pneumonia	3	(6.8)	3	3	(6.7)	5
Infective pulmonary exacerbation of cystic fibrosis	4	(9.1)	4	1	(2.2)	1
Laryngitis	3	(6.8)	3	1	(2.2)	1
Nasopharyngitis	3	(6.8)	3	0	0	0
General disorders and administration site conditions	15	(34.1)	20	9	(20.0)	13
Fatigue	7	(15.9)	8	4	(8.9)	4
Pyrexia	4	(9.1)	5	3	(6.7)	6
SOC MedDRA Preferred Term Version 15.0	LAI 590 mg QD (N=44)			Placebo (N=45)		
	n	%	events	n	%	events
Chest discomfort	5	(11.4)	5	0	0	0
Gastrointestinal disorders	10	(22.7)	17	11	(24.4)	14
Nausea	5	(11.4)	5	4	(8.9)	4
Abdominal discomfort	3	(6.8)	3	0	0	0
Diarrhoea	0	0	0	3	(6.7)	3
Nervous system disorders	10	(22.7)	13	4	(8.9)	8
Headache	3	(6.8)	4	3	(6.7)	7
Psychiatric disorders	5	(11.4)	5	2	(4.4)	2
Insomnia	3	(6.8)	3	0	0	0
Ear and labyrinth disorders	6	(13.6)	9	4	(8.9)	4
Ear pain	3	(6.8)	3	0	0	0

In this double-blind phase a greater proportion of LAI patients had treatment-related TEAEs (72.7% vs. 37.8%). The difference particularly reflected dysphonia, cough, oropharyngeal pain and infective exacerbation of bronchiectasis.

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

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

In the open-label phase in which all patients received LAI, almost all had TEAEs. Rates for individual AEs and treatment-related TEAEs were mostly higher for those patients first exposed to LAI in the open-label phase (i.e. the “placebo” group in the table below).

**Treatment-related TEAEs (≥ 2 patients) in the open-label phase of TR02-112 (Safety Population)**

System Organ Class MedDRA Preferred Term Version 15.0	LAI 590 mg QD (N=35)			Placebo (N=43)		
	n	%	events	n	%	events
Number (%) of patients with at least 1 treatment-emergent adverse event related to study drug	17	( 48.6)	37	26	( 60.5)	67
Respiratory, thoracic and mediastinal disorders	10	( 28.6)	17	16	( 37.2)	33
Dysphonia	3	( 8.6)	3	11	( 25.6)	11
Cough	2	( 5.7)	2	6	( 14.0)	8
Haemoptysis	4	( 11.4)	4	3	( 7.0)	3
Oropharyngeal pain	3	( 8.6)	6	3	( 7.0)	3
Productive cough	1	( 2.9)	1	2	( 4.7)	2
Dyspnoea	0		0	2	( 4.7)	2
Infections and infestations	5	( 14.3)	5	13	( 30.2)	13
Infective exacerbation of bronchiectasis	2	( 5.7)	2	4	( 9.3)	4
Laryngitis	0		0	4	( 9.3)	4
Infective pulmonary exacerbation of cystic fibrosis	2	( 5.7)	2	1	( 2.3)	1
Bronchitis	0		0	2	( 4.7)	2
Oral candidiasis	0		0	2	( 4.7)	2
Nervous system disorders	3	( 8.6)	3	4	( 9.3)	6
Aphonia	2	( 5.7)	2	2	( 4.7)	2
General disorders and administration site conditions	2	( 5.7)	2	4	( 9.3)	4
Chills	0		0	2	( 4.7)	2
Gastrointestinal disorders	2	( 5.7)	3	3	( 7.0)	4
Nausea	1	( 2.9)	1	2	( 4.7)	2
Ear and labyrinth disorders	3	( 8.6)	4	0		0
Ear discomfort	3	( 8.6)	4	0		0
Musculoskeletal and connective tissue disorders	1	( 2.9)	1	2	( 4.7)	2

**Bronchial reactivity vs. true hypersensitivity**

All preferred terms (PTs) that possibly represent hypersensitivity were compiled under the standardised MedDRA queries (SMQ) topic of “hypersensitivity”. These PTs were then analysed against the safety database of all TEAEs that occurred in the LAI programme.

**Summary of TEAEs possibly representing hypersensitivity in the LAI development programme**

Body System	Preferred Term	LAI n (%) event				Comparator n (%) event	
		70 mg N=7	280 mg N=45	560 mg N=71	590 mg N=349	TOBI N=146	Placebo N=110
Gastrointestinal Disorders	Swollen Tongue				1 (0.3%) 1		
Immune System Disorders	Drug Hypersensitivity				3 (0.9%) 4		
	Hypersensitivity				2 (0.6%) 2		
Infections And Infestations	Rash Pustular				1 (0.3%) 1		
Respiratory, Thoracic And Mediastinal Disorders	Respiratory Distress				1 (0.3%) 1		
	Rhinitis Allergic		2 (4.4%) 2	1 (1.4%) 2	4 (1.1%) 4		
	Sneezing	1 (14.3%) 1					2 (1.8%) 3
	Throat Tightness			3 (4.2%) 24			
Skin And Subcutaneous Tissue Disorders	Dermatitis				1 (0.3%) 1		1 (0.9%) 1
	Dermatitis Allergic				2 (0.6%) 2	1 (0.7%) 1	
	Erythema			1 (1.4%) 1			
	Erythema Multiforme			1 (1.4%) 1			
	Rash			1 (1.4%) 1	8 (2.3%) 9	1 (0.7%) 1	1 (0.9%) 1

There were very low occurrences of possible hypersensitivity reactions. Low rates of hypersensitivity (respiratory and dermatological) occurred. Non-respiratory hypersensitivity events predominantly involved the skin including rash, erythema and dermatitis in a total of 15 patients exposed to LAI. Five patients experienced hypersensitivity including drug hypersensitivity. All hypersensitivity events were considered not related to study drug. One patient experienced an 'allergic reaction to antibiotics' while off LAI for 20 days; two patients experienced 'reaction to meropenem' (2 AEs were reported for the same patient for the same event); one patient experienced an allergic reaction to nuts; and one patient experienced an unknown allergic reaction while off LAI.

There were also two SAEs in TR02-112 reported as 'Pneumonitis' and 'Hypersensitivity Lung Reaction', which are described below.

#### Deaths

None of the deaths reported during the main phases of trials was considered by the investigator to be related to the study drug.

- In TR02-110 one patient died due to cardiac failure. The patient was a 13-year-old female who had received LAI in TR02-108 and who died after being on-study for ~1 year. She had TEAEs of renal failure and infective pulmonary exacerbation of CF not considered related to study treatment by the investigator. She was hospitalised due to these events and due to Grade 5 cardiac failure, also not related to treatment, and discontinued LAI and study. She died shortly afterwards.

#### In TR02-112

- In the double-blind phase one patient, a 63-year-old female, had fatal SAEs of pneumonia and acute respiratory distress syndrome.
- In the open-label phase one patient, a 69-year-old female, had fatal SAEs of multi-organ failure, intestinal ischaemia and urosepsis.

At the time of responding to the questions the applicant provided an update on TR02-112 up to month 12, reporting that 7 patients were stated to have died in the interim. However, since only 46/89 patients appear to have attended the month 12 follow-up it is not known how the applicant obtained information on the deaths and, more importantly, whether these data are complete and whether all had received LAI at some stage.

#### SAEs in TR02-108 and 110

Rates of SAEs were similar between in the LAI and TOBI groups (both 25%). The most frequently reported SAE was hospitalisation due to pulmonary exacerbation. Treatment-related SAEs were reported for two in the LAI-LAI group (infective pulmonary exacerbation of CF and staphylococcal infection), three in the TOBI-LAI group (all with infective pulmonary exacerbation of CF) and one in the LAI group (FEV1 decreased).

**SAEs in CF studies TR02-108 and TR02-110; Crude incidence rate (Safety Population)**

MedDRA SOC PT Preferred Term Version 15.0	LAI-LAI (N=92)			TOBI-LAI (N=114)			LAI (N=56)			TOBI (N=32)		
	N	(%)	SAEs	N	(%)	SAEs	N	(%)	SAEs	N	(%)	SAEs
<b>At least 1 SAE</b>	<b>28</b>	<b>(30.4)</b>	<b>62</b>	<b>47</b>	<b>(41.2)</b>	<b>103</b>	<b>14</b>	<b>(25.0)</b>	<b>20</b>	<b>8</b>	<b>(25.0)</b>	<b>9</b>
Cardiac disorders	1	(1.1)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Cardiac failure	1	(1.1)	1	0	(0)	0	0	(0)	0	0	(0)	0
Gastrointestinal disorders	2	(2.2)	3	4	(3.5)	4	0	(0.0)	0	1	(3.1)	1
Distal intestinal obstruction	2	(2.2)	2	1	(0.9)	1	0	(0)	0	0	(0)	0
Dyspepsia	1	(1.1)	1	1	(0.9)	1	0	(0)	0	0	(0)	0
Haematochezia	0	(0)	0	0	(0)	0	0	(0)	0	1	(3.1)	1
Intestinal obstruction	0	(0)	0	1	(0.9)	1	0	(0)	0	0	(0)	0
Rectal haemorrhage	0	(0)	0	1	(0.9)	1	0	(0)	0	0	(0)	0
General disorders and administration site conditions	1	(1.1)	1	1	(0.9)	1	0	(0.0)	0	0	(0.0)	0
Chest pain	0	(0)	0	1	(0.9)	1	0	(0)	0	0	(0)	0
Non-cardiac chest pain	1	(1.1)	1	0	(0)	0	0	(0)	0	0	(0)	0
Infections and infestations	26	(28.3)	51	42	(36.8)	87	13	(23.2)	18	7	(21.9)	8
Appendicitis	0	(0)	0	1	(0.9)	1	0	(0)	0	0	(0)	0
Bronchitis	1	(1.1)	1	1	(0.9)	1	0	(0)	0	0	(0)	0
Bronchopulmonary aspergillosis	0	(0)	0	1	(0.9)	1	0	(0)	0	0	(0)	0
Bronchopulmonary aspergillosis allergic	0	(0)	0	0	(0)	0	1	(1.8)	1	0	(0)	0
Chronic sinusitis	1	(1.1)	1	0	(0)	0	0	(0)	0	0	(0)	0
Infective pulmonary exacerbation of CF	23	(25.0)	44	41	(36.0)	80	13	(23.2)	17	7	(21.9)	8
Lung infection pseudomonal	1	(1.1)	1	0	(0)	0	0	(0)	0	0	(0)	0
Measles	0	(0)	0	1	(0.9)	1	0	(0)	0	0	(0)	0
Pneumonia	0	(0)	0	3	(2.6)	3	0	(0)	0	0	(0)	0
Respiratory tract infection	1	(1.1)	1	0	(0)	0	0	(0)	0	0	(0)	0
Respiratory tract infection viral	1	(1.1)	1	0	(0)	0	0	(0)	0	0	(0)	0
Staphylococcal infection	1	(1.1)	1	0	(0)	0	0	(0)	0	0	(0)	0
Urosepsis	1	(1.1)	1	0	(0)	0	0	(0)	0	0	(0)	0
Investigations	1	(1.1)	1	1	(0.9)	1	1	(1.8)	1	0	(0.0)	0
FEV decreased	0	(0)	0	0	(0)	0	1	(1.8)	1	0	(0)	0
PFT decreased	1	(1.1)	1	1	(0.9)	1	0	(0)	0	0	(0)	0
Metabolism and nutrition disorders	0	(0.0)	0	1	(0.9)	1	0	(0.0)	0	0	(0.0)	0
Malnutrition	0	(0)	0	1	(0.9)	1	0	(0)	0	0	(0)	0
Renal and urinary disorders	1	(1.1)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Renal failure	1	(1.1)	1	0	(0)	0	0	(0)	0	0	(0)	0
Respiratory, thoracic and mediastinal disorders	3	(3.3)	3	6	(5.3)	9	1	(1.8)	1	0	(0.0)	0
Atelectasis	0	(0)	0	1	(0.9)	1	0	(0)	0	0	(0)	0
Bronchial secretion retention	0	(0)	0	0	(0)	0	1	(1.8)	1	0	(0)	0
Bronchiectasis	1	(1.1)	1	0	(0)	0	0	(0)	0	0	(0)	0
Dyspnoea	0	(0)	0	1	(0.9)	1	0	(0)	0	0	(0)	0
Haemoptysis	1	(1.1)	1	1	(0.9)	3	0	(0)	0	0	(0)	0
Nasal polyps	0	(0)	0	1	(0.9)	1	0	(0)	0	0	(0)	0



MedDRA SOC PT Preferred Term Version 15.0	LAI-LAI (N=92)			TOBI-LAI (N=114)			LAI (N=56)			TOBI (N=32)		
	N	(%)	SAEs	N	(%)	SAEs	N	(%)	SAEs	N	(%)	SAEs
Pneumothorax	1	(1.1)	1	2	(1.8)	3	0	(0)	0	0	(0)	0
Vascular disorders	1	(1.1)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Aneurysm	1	(1.1)	1	0	(0)	0	0	(0)	0	0	(0)	0

#### TR02-105 and TR02-106

Across the two studies 13 patients had SAEs, including 8 who received LAI (1 at 140 mg and 7 at 560 mg) and 5 who received placebo. SAEs in the LAI group were pulmonary exacerbation (8 patients) and haemoptysis. None was considered treatment-related and all patients recovered. In the TR02-105 extension study 15 patients had SAEs, mostly due to exacerbations considered not to be treatment-related.

#### TR02-112

In the double-blind phase SAEs were reported by a greater proportion in the LAI group (18.2% vs. 8.9% placebo). The most frequently reported were infective exacerbation of bronchiectasis and pneumonia. Three SAEs in the LAI group were considered treatment-related (exacerbation of bronchiectasis in 2 and respiratory disorder in 1 patient).

In the open-label phase SAEs were reported by (14.3% prior LAI and 11.6% prior placebo group patients). The most frequently reported SAEs were infective exacerbation of CF and pneumonitis, two of which were considered treatment-related.

Two patients experienced events that were reported as 'Pneumonitis' and 'Hypersensitivity Lung Reaction', which were coded to the preferred terms of 'Pneumonitis' and 'Respiratory Disorder', respectively. These were SUSARs. The applicant determined that they were very similar and should be considered cumulative rather than singular.

Both cases occurred in female patients in their early 70s with non-CF MAC lung infection. They had high MAC burdens at baseline (SQS steps 6 and 7). One received LAI and one placebo followed by LAI. Both developed non-specific and generalised symptoms including fever, aches and pains as well as increasing respiratory distress within the first 2 weeks after starting treatment with LAI, which led to decreased oxygenation and hospitalisation. Study drug was discontinued and a diagnostic work-up was done for each patient with the only new finding on High Resolution Chest CT scan being 'ground-glass opacities' for one patient and 'hazy ground glass mosaic attenuation' for the other patient. A course of high-dose corticosteroids was started leading to improved dyspnoea and oxygenation.

The applicant considers these events as important potential risks and included them in the RMP and SmPC, where they were described as 'allergic alveolitis' as this was considered the most relevant terminology for this type of event based on the MedDRA dictionary. No other events similar to these two cases have been reported to date. The applicant points out that it is debated whether NTM pulmonary disease syndrome with presentation similar to hypersensitive lung disease ('hot tub lung') is related to MAC. One other possibility is a Herxheimer-like reaction, as these patients had high organism burdens followed by a marked reduction in burden in one patient who provided sputum at her subsequent visit (to Step 3).

Finally, the events may be due to amikacin *per se* within the liposomal formulation, although this particular constellation of signs and symptoms was not seen in the CF programme. A causal link has not been established.

### Other Studies of LAI

There were 3 SAEs reported in LAI patients in the other studies. None was considered treatment-related.

### Laboratory findings

The applicant stated that there were no *unexpected findings* in haematology or clinical chemistry parameters in patients who received LAI. However, the presentations of the data in CSRs were very limited. Tables of the maximal changes or pre-defined clinically significant changes were not provided. On request the applicant provided shift tables for laboratory parameters were analysed for TR02-108, TR02-110, and TR02-112. In TR02-112, laboratory value shifts were comparable between treatment arms.

Clinically significant findings, defined as shifts reported as AEs by investigators, were non-serious and reported in 7 patients in TR02-108 (4 LAI; 3 TIS), 8 in TR02-110 and 5 in TR02-112 (3 LAI; 2 PLB).

One patient in TR02-110 developed liver transaminase increase with lab values just over 3x ULN with resolution 28 days later (next visit).

### Discontinuation due to AEs

In TR02-108 TEAEs leading to study drug discontinuation occurred in 10.1% LAI and 4.8% TOBI patients. The most commonly reported TEAE leading to study drug discontinuation was infective pulmonary exacerbation of CF (6.1% and 3.4%, respectively).

In TR02-110 21/206 (10.2%) discontinued study drug due to a TEAE with rates of 5.4% for the prior LAI group and 14% for the LAI-naïve group. Again, the most common of these TEAEs was infective pulmonary exacerbation of CF (5.8%).

In TR02-112 in the double-blind phase 8 LAI patients (18.2%) and no placebo patients had TEAEs leading to study drug discontinuation. The most common of these TEAEs were infective exacerbation of bronchiectasis (3) and dyspnoea (2) while others occurred in single patients (cough, oropharyngeal pain, respiratory disorder and pneumonia). In the open-label phase TEAEs leading to study drug discontinuation occurred in 6 prior LAI patients (17.1%) and 12 prior placebo patients (27.9%).

### ***Comment on clinical safety***

The safety database relevant to the final proposed daily dose includes 519 patient exposed to 560 mg or 590 mg QD. TR02-105 and 106 provide a comparison with saline, TR02-112 provided a comparison with empty liposomes and TR02-108 compared LAI to TOBI in a population in which the majority had received TOBI previously. In each comparison made LAI was associated with higher airway reactivity, higher rates of treatment-related AEs and higher rates of discontinuations due to AEs.

Based on the entire population in TR02-108 rather than the subset that only participated in the comparative phase (as shown in the tables in the summary of safety) the differences between LAI and TOBI become even more marked. For example, treatment-related TEAEs occurred in 38.5% LAI vs. 14.4% TOBI patients. The most notable differences in treatment-related TEAEs were dysphonia (10.8% vs. 2.7%), cough (8.8% vs. 2.1%), haemoptysis (7.4% vs. 3.4%) and infective pulmonary exacerbation of CF (6.8% vs. 2.1%). Rates of severe and serious TEAEs were also higher with LAI.

The tables of TEAEs in TR02-108/110 in the applicant's summary show total TEAEs from baseline for the LAI/LAI and LAI/TOBI groups, which do not allow for an assessment of the effect of switching. Based on the safety data obtained only after switching from TOBI to LAI in study TR02-110 (as presented in the CSR for the extension study) it is clear that there were lesser differences between

those who had previously received LAI or TOBI compared to the post-switch period in TR02-112. The AEs by serial cycle do not show a consistent trend of lesser numbers of TEAEs with continued exposures but these data need to be viewed with caution due to the diminishing numbers over time.

The data from the NTM study TR02-112 indicated that amikacin per se is mainly responsible for the respiratory effects of LAI since there was a clear difference between LAI vs. empty liposomes. In the double-blind phase of TR02-112 notable differences were observed between the LAI and empty liposomes for dysphonia (43.2% vs. 8.9%), infective exacerbation of bronchiectasis (38.6% vs. 20.0%), cough (31.8% vs. 13.3%), oropharyngeal pain (20.5% vs. 2.2%), fatigue (15.9% vs. 8.9%), chest discomfort (11.5% vs. 0%), wheezing (9.1% vs. 2.2%) and infective pulmonary exacerbation of CF (9.1% vs. 2.2%). TR02-112 also showed very clearly that treatment-related TEAEs were much more common with LAI vs. empty liposomes (72.7% vs. 37.8% of patients) and that the difference was mainly driven by respiratory tract disorders.

The TEAEs observed in the open-label phase of this study underline the role of amikacin since patients who switched from empty liposomes to LAI experienced higher rates of TEAEs than those who had already persisted with LAI for 84 days and chose to continue.

There have been some other differences of note. In TR02-108 LAI was associated with higher rates of diarrhoea (6.8% vs. 3.4%) and headache (8.1% vs. 3.4%) compared to TOBI although this pattern was not observed in TR02-112. The fact that swallowed amikacin is not absorbed that leads to a potentially enhanced risk of CDAD. Diarrhoea that was considered to be treatment-related by investigators occurred commonly in clinical trials. Although the revised indication will refer only to non-CF MAC patients, section 4.8 of the SmPC should take into account the entire safety database.

According to the Common Terminology Criteria for Adverse Events (CTCAE), hearing impairment of Grade 1 is defined as a threshold shift of 15 – 25 decibels (dB) averaged at 2 contiguous test frequencies in at least one ear. In TR02-108 audiology did not detect a change of Grades 1-4 in sensorineural hearing loss from baseline in any patient even though 6 LAI and no TOBI patients had TEAEs associated with changes in audiology. Review of the cases indicates small changes at specific frequencies.

Upon evaluating all patients in TR02-110 at Day 337 (End of Year 1) all except two patients who had complete data reported 'no change or minimal change' in sensorineural hearing from Baseline. These two patients each reported a Grade 1 hearing loss. One was exposed to cyclical LAI for 12 months (TR02-110 only) and the other was exposed for 18 months (TR02-108 and TR02-110). At Day 672 (End of Year 2), 6 patients who had complete data reported Grade 1 changes in sensorineural hearing from Baseline and 1 patient reported a Grade 3 change in sensorineural hearing from Baseline. In TR02-112 there was no excess of audiology TEAEs in the LAI group.

In summary, LAI is clearly less well tolerated than empty liposomes and less well tolerated than TOBI in a population with a reasonably high rate to prior exposure to TOBI. The comparison with empty liposomes indicates that amikacin is per se an irritant. These issues do not merit a Major Objection on safety grounds since, if there was convincing efficacy the safety profile observed would not preclude an approval. However, since efficacy is not currently supported in either indication the comparative safety profile of LAI adds to the overall conclusions on the lack of a favourable benefit-risk relationship. In light of the anticipated long duration of exposure to LAI it would be important to reflect the rate of Grade 1 hearing loss after 2 years exposure in the SmPC.

### ***Pharmacovigilance system***

The Rapporteur considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

### ***Risk management plan***

See the PRAC report.

## **4. Orphan medicinal products**

Arikayce has EU Orphan Drug Designation for:

- Treatment of cystic fibrosis patients with *Pseudomonas aeruginosa* lung infections (EU/3/06/387)
- Treatment of non-tuberculous mycobacterial lung infections (EU/3/14/1259).

## **5. Benefit risk assessment**

### ***Benefits***

#### ***Beneficial effects***

There is insufficient evidence of efficacy in non-CF patients with MAC lung disease to be able to determine any beneficial effects. It is not possible to draw any conclusions on the efficacy of LAI in non-CF patients with MAC lung disease based on TR02-112. The Phase 3 study compares LAI plus SOC with SOC alone. Results from this study based on the CHMP-recommended primary endpoint are needed before any conclusion on benefit can be reached.

#### ***Uncertainty in the knowledge about the beneficial effects***

The use of Arikayce to treat NTM is based on a single Phase 2 study in which 54 non-CF patients with MAC lung disease received anything up to 168 days of LAI. The study had an inappropriate pre-defined primary endpoint (at least a one-step change on the SQS). The results for post-therapy sputum culture conversion (SCC, defined post hoc only), which is the only acceptable primary efficacy endpoint, are confined to those patients who attended the day 28 and month 12 post-therapy (post-Arikayce) visits.

The results of sustained SCC rates in non-CF MAC patients are non-comparative since the study compared LAI with placebo for only 84 days. Of the 89 total NTM patients enrolled, 54 patients had non-CF MAC lung disease of which 27 were randomised to LAI and 27 to placebo. In the OLP 22/27 from the LAI group and all 27 from the placebo group elected to receive LAI. Therefore 54 non-CF MAC patients started on LAI on day 1 or on entering the OLP and had the opportunity to receive between 84 and 168 days treatment if they did not discontinue.

The protocol did not plan to assess efficacy at the month 12 follow-up visit. Of the total 89 enrolled, it appears that 17/23 stated by the applicant to have had prior SCC on or off LAI and 29/66 with no prior SCC attended the 12-month follow-up visit, which demonstrates a bias in favour of attendance at the month 12 follow-up visit by the patients with prior SCC. Based on the updated SQS analysis in which contaminated cultures that were MAC DNA negative were assigned to Step 1 (wholly negative) the assessor has counted outcomes at month 12 follow-up in 19 non-CF MAC patients considered by the applicant to have had prior SCC.

Among the 19, 12 came from the initial LAI group and 7 from the initial placebo group but 5/12 and 2/7 had negative cultures on day 1 and no or single positives post-baseline. Among the remaining 12 (7/12 + 5/7) there were 4/47 (8.5%) non-CF MAC patients who were positive on day 1 of the study and had a confirmed SCC that persisted at the M12 follow-up visit (SCC rate of 7.4%). If the two patients who attended M12 but had no sputum are assumed to be negative then the rate is 6/47 (SCC rate of 12.8%). If the other two patients who were negative at the day 28 follow-up but did not attend the M12 visit are assumed to be negative then the rate is 8/47 (SCC rate of 17%).

If the 7 patients with non-CF MAC who were negative on day 1 are also taken into account, two never had a positive at any time so did not have SCC during the study. One was negative at both follow-up visits but was positive at D168 so does not meet the *post hoc* SCC definition. The other 4 had SCC while on LAI after single positive visits and were negative at follow-up visits. If these 4 are counted then 8/47 would have confirmed SCC at the month 12 visit (SCC rate of 17%).

If the SCC rates are based on the day 28 post-therapy visit results, despite remaining concerns that for some patients there could have been sufficient amikacin left in sputa to affect results, then there is a maximum of 7/47 patients positive at baseline who have some evidence of SCC on MAC who were still negative at the day 28 follow-up visit (SCC rate of 14.9%). If the 4 baseline negative patients with single post-baseline positives are counted then the SCC rate is 11/54, which is 20%. This is the most optimistic estimate possible from the available data but it is not reliable. These numbers and the confirmed sustained SCC rates are not a sufficient basis for approval. In addition, the entire study was an hypothesis-generating Phase 2 study and it is not of an appropriate design to be regarded as pivotal.

There are other findings in this study that should also be considered. Whilst the applicant proposes that the 6MWT results support a benefit for LAI based on it is not possible to verify this claim. It is not known which test of significance was applied (different p-values were obtained at D84 using ANOVA vs. Wilcoxon rank test) nor are the numbers of patients in the analysis stated. Furthermore, it is not known what the bars on the figure represent and how missing data were imputed.

In addition, taking into account that in the double-blind phase 7 LAI and no placebo group patients discontinued due to AEs whilst another 16 discontinued LAI due to AEs in the OLP, the CSR reported on several other endpoints for LAI vs. placebo up to D84 as follows:

- There were 32 protocol-defined pulmonary exacerbations in the LAI group and 26 in the placebo group with a statistically significant difference for time to exacerbation favouring placebo.
- There were 21 investigator-defined exacerbations in the LAI group and 10 in the placebo group and the time to first investigator-defined pulmonary exacerbation was statistically significant in favour of placebo.
- There was a statistically significant difference for time to first use of any rescue drug such that more LAI than placebo patients required rescue and the time to rescue was shorter.
- There was no appreciable difference in the mean change from baseline in the composite RSSQ score.

## **Risks**

### **Unfavourable effects**

Arikayce is clearly associated with greater airway hyper-reactivity than saline in CF patients or empty liposomes in NTM patients, leading to more discontinuations due to AEs compared to control groups. TR02-112 compared LAI with empty liposomes and the discontinuation rates and rates of “exacerbations” actually suggest that amikacin *per se* is an irritant within the airways. There have been two cases of apparent allergic alveolitis in NTM patients while taking LAI.

It appears from the CF data that long term cyclical exposure to amikacin is associated with at least Grade 1 hearing loss.

### ***Uncertainty in the knowledge about the unfavourable effects***

There are currently Major Objections regarding the quality of Arikayce on the drug product, along with a list of other concerns. Until such time as these may be resolved there must be uncertainty with regard to risks posed by the clinical use of Arikayce.

The applicant provided some evidence that the nonclinical findings of concern in the carcinogenicity/repeat dose toxicology rat studies were species-specific and that 1) the cause could be due to lung burden and 2) a threshold effect could exist. The possible relevance of the rodent data to humans remains unknown. If the future Phase 3 study results should support an approval then appropriate guidance on duration of therapy will be considered based on the evidence, which will take into account the non-clinical data as well as the clinical safety data over a longer period of exposure.

It is not possible at present to obtain an accurate measure of worst case systemic exposure in NTM patients. During the procedure the applicant provided the plasma amikacin data from 14 patients in the PK sub-study of TR02-112, 12 without and 2 with CF, and compared POPPK-predicted exposures with those in younger CF patients. The population in TR02-112 was very predominantly female and older (mean age 55.8 years) with lower CLcr values (mean 87.7 mL/min) compared to all CF study populations sampled. Most NTM patients had only one serum sample and the maximum was 3. It was clear that projected AUC on day 1 was 4-fold higher than those in the non-CF NTM patients and 2.5-6-fold higher at steady state. The mean steady-state AUC<sub>(0-24)</sub> in the patients with non-CF NTM was >10 times lower than the mean AUC<sub>(0-24)</sub> reported in the literature by Byl *et al.* for patients with CF given amikacin 30 mg/kg IV once daily (20.8 µg•h/mL compared with 235 µg•h/mL, respectively).

There was a clear relationship between indication (CF vs. NTM) and apparent clearance (CLt/F) such that the population mean CLt/F was estimated to be approximately 2.5-fold higher in patients with CF relative to patients with NTM. The report stated that it is not possible to draw definitive conclusions on the mechanism behind these differences but it is probable that increased absorption from the lungs in NTM patients may explain some of the observed differences. The report concluded that NTM patients exhibited lower apparent oral amikacin clearance after LAI administration. This lower clearance translated into slightly higher predicted exposures in NTM patients. Patient age was not a significant covariate, suggesting that the observed difference is an inherent PK difference such that diagnosis is not masking some other difference in the populations. Nevertheless, these conclusions are based on 12 non-CF NTM patients and there was high IIV. More PK data are needed from the ongoing Phase 3 NTM study.

During the procedure the applicant also reported preliminary data from the scintigraphy sub-study from TR02-112, which demonstrated that approximately 43% of the loaded dose using the PARI eflow Electronic Nebuliser (using the electronic vibrating mesh) was deposited in the lung compared to only 15% in the initial scintigraphy study in healthy subjects using a different nebulisation system. This finding indicates the possibility that systemic exposure at least in part reflects absorption via the lung following a higher delivered dose. It is also possible that the ADRs in the respiratory tract at least in part reflect the lung deposition load.

### ***Balance***

### ***Importance of favourable and unfavourable effects***

There is no adequate demonstration of efficacy and the safety profile of LAI is inferior to that of empty liposomes in the revised target population for use. More data on safety and efficacy will come from the

ongoing Phase 3 study in non-CF MAC patients, noting that LAI plus SOC is being compared to SOC alone so the study is open label. This may impact on the discontinuation rates and could introduce bias but it is not clear at present which way the bias may operate. The quality of Arikayce is currently unsatisfactory, which has unknown clinical implications.

### ***Benefit-risk balance***

The evidence is insufficient to conclude on efficacy in the target population and LAI demonstrates safety issues especially regarding tolerance in the bronchial tree. Therefore the balance is not in favour of LAI based on current evidence.

## ***5.1. Conclusions***

The overall B/R of LAI (Arikayce) is negative for the revised proposed indication.