Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2432

amikacin liposomal nebuliser dispersion 590mg (Arikayce®)

Insmed Limited

05 November 2021

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a resubmission considered under the orphan medicine process

amikacin liposomal nebuliser dispersion (Arikayce®) is accepted for use within NHSScotland.

Indication under review: Treatment of non-tuberculous mycobacterial (NTM) lung infections caused by Mycobacterium avium Complex (MAC) in adults with limited treatment options who do not have cystic fibrosis. Consideration should be given to official guidance on the appropriate use of antibacterial agents.

The addition of amikacin liposomal nebuliser dispersion to standard oral guideline-based therapy for MAC NTM lung infections significantly increased the proportion of patients achieving sputum culture conversion at 6 months and post-treatment at 3 months.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of views from a Patient and Clinician Engagement (PACE) meeting.

Chairman
Scottish Medicines Consortium

Indication

Treatment of non-tuberculous mycobacterial (NTM) lung infections caused by Mycobacterium avium Complex (MAC) in adults with limited treatment options who do not have cystic fibrosis. Consideration should be given to official guidance on the appropriate use of antibacterial agents.[1]

Dosing Information

One vial (590 mg) administered once daily, by oral inhalation via the Lamira® Nebuliser System. It must not be administered by any other route or using any other type of inhalation delivery system. Treatment, as part of a combination antibacterial regimen, should be continued for 12 months after sputum culture conversion (SCC). Treatment should not continue beyond a maximum of 6 months if SCC has not been confirmed by then. Maximum duration of treatment should not exceed 18 months.

Amikacin liposomal nebuliser dispersion (Arikayce®) should be initiated and managed by physicians experienced in the treatment of NTM due to MAC. It should be used in conjunction with other antibacterial agents active against MAC lung infections.[1]

Product availability date

1 December 2020.
Amikacin liposomal nebuliser dispersion (Arikayce®) meets SMC orphan criteria.

Summary of evidence on comparative efficacy

Amikacin liposomal nebuliser dispersion (ALIS; Arikayce®) consists of amikacin encapsulated in liposomes. Amikacin is an as an aminoglycoside antibiotic that binds to the 30S subunit of bacterial ribosomes and interferes with an initiation complex between messenger RNA and the 30S subunit resulting in inhibition of protein synthesis.[1,2]

An open-label phase III study (CONVERT) recruited adults with active MAC lung disease, defined as MAC-positive sputum or bronchoscopy cultures despite guideline based therapy (GBT) for at least six months. Randomisation was stratified by current smoking status and prior GBT (on treatment versus off treatment for 3 to 12 months) and patients were assigned in a 2:1 ratio to GBT plus ALIS (Arikayce®) 590mg via PARI eFlow nebuliser daily, except for two days before a study visit, or GBT alone. The primary outcome was the proportion of patients achieving SCC, defined as three negative consecutive monthly sputum culture, after six months treatment. The European Medicines Agency (EMA) considered sustained SCC at 3 months post-treatment to be the main efficacy outcome and this was defined as no positive agar cultures and no more than 3 consecutive positive monthly broth cultures at any time after conversion. Analyses were also presented for sustained SCC at 12 months post-treatment. These were assessed in the intention-to-treat population, which comprised all randomised patients.[2,3]

Both SCC at 6 months and sustained SCC at 3 months post-treatment were achieved by significantly more patients in the ALIS (Arikayce®) group compared with the control group, as detailed in Table 1. A hierarchical statistical testing strategy was used for secondary outcomes in the following order: change from baseline to 6 months in 6-minute-walk test (6MWT), time to conversion and change from baseline to 6 months in St George's Respiratory Questionnaire (SGRQ). For the first of these, 6MWT, there was no significant difference between groups. Median time to SCC could not be calculated but the hazard ratio (HR) of 3.92 (95% confidence interval [CI]: 2.08 to 8.57) suggested an increased likelihood of achieving this outcome by month 6 with ALIS (Arikayce®). There was generally little change from baseline to month 6 in health related quality of life outcomes, SGRQ and EQ-5D-3L, and no differences between treatment groups.[2-4]

Table 1: Primary and secondary outcomes of CONVERT study.[2,3]

Sputum culture conversion	**ALIS + GBT (N=224)**	**GBT (N=112)**	**Odds ratio (95% confidence interval)**
At 6 months	65 (29%)	10 (8.9%)	4.22 (2.08 to 8.57)
At 3 months post-treatment	36 (16%)*	0	NE (NE to NE)
At 12 months post-treatment	30 (13%)*	0	NE (NE to NE)

ALIS = amikacin liposome inhalation suspension (Arikayce®); GBT = guideline-based therapy; * in additional analyses that that excluded patients with negative cultures at baseline and counted any agar or broth cultures after SCC as failure, sustained SCC with ALIS was 13% (30/224) and 11% (25/224) at 3 and 12 months post-treatment, respectively.

Patients who failed to achieve SCC or had relapse or recurrence by month 6, could enrol in an open-label extension study (INS-312). This included 73 and 90 patients from the ALIS (Arikayce®) and control groups of the CONVERT study. They all continued their oral GBT and received ALIS (Arikayce®) 590mg once daily by PARI eFlow nebuliser once daily for up to 12 months. At month 6, SCC was achieved by 9.6% (7/73) and 27% (24/90) of patients in the respective groups and at month 12 by 14% (10/73) and 33% (30/90) of patients.[2]

A double-blind phase II study (TRO-112) recruited adults (18 to 85 years) with refractory NTM due to MAC or mycobacterium abscessus, with positive cultures despite at least 6 months GBT. Randomisation was stratified by concomitant cystic fibrosis and predominant bacteria (MAC versus mycobacterium abscessus) and patients were assigned equally to ALIS (Arikayce®) 590mg once daily by PARI eFlow nebuliser or matching placebo for 84 days, then all patients could receive open-label ALIS (Arikayce®) for a further 84 days. All patients continued their GBT. The primary outcome, between group difference in change from baseline to day 84 on a semi-quantitative scale for mycobacterial growth, did not achieve statistical significance and all other analyses were descriptive. In the ALIS (Arikayce®) and placebo groups SCC at day 84 was achieved by 32% (14/44) and 9% (4/45) of patients, respectively. The subgroup of 54 patients with MAC and without cystic fibrosis was representative of the licensed indication. In post-hoc analyses, SCC was achieved by 7 patients in the group initially assigned to ALIS (Arikayce®) and by 5 patients in the group initially assigned to placebo, with all but one of the latter achieved some time after converting to open-label treatment with ALIS (Arikayce®).[2,5]

Summary of evidence on comparative safety

The EMA safety review concluded that there are several concerns regarding pulmonary adverse events (especially allergic alveolitis) and systemic toxicities (especially nephrotoxicity, ototoxicity and effects on neuromuscular conditions) that may be associated with chronic use of amikacin. However, it noted that ALIS (Arikayce®) would be administered via specialised centres and the safety profile appears manageable if patients are adequately supervised by specialists.[2]

In the CONVERT study at data cut-off for the primary outcome at 6 months (7 July 2017), within the ALIS (Arikayce®) and control groups 98% (219/223) and 91% (102/112) of patients had an adverse event, which were serious in 20% and 18% of patients, respectively. Adverse events led to discontinuation of ALIS (Arikayce®) alone in 18% of patients and ALIS (Arikayce®) plus GBT in 1.8% of patients. GBT alone was discontinued due to adverse events in 4.0% and 2.7% of patients in the respective groups.[3] In the ALIS (Arikayce®) group 83% (185/224) of patients had treatment-related adverse events. During the double-blind phase of the TRO-112 study, within the ALIS (Arikayce®) and placebo (empty liposome) groups 93% (41/44) and 89% (40/45) of patients reported adverse events. In the ALIS (Arikayce®) group, compared with placebo, there were higher rates of adverse events which were treatment-related (73% versus 38%), serious (18% versus 8.9%) and led to discontinuation of study drug (16% versus 0).[5]

In the CONVERT study, within the ALIS (Arikayce®), compared with the control group, there were higher rates of respiratory adverse events (88% versus 51%), including dysphonia (46% versus 0.9%), cough (37% versus 15%), dyspnoea (22% versus 8.9%), upper airway inflammation (18% versus 1.8%), haemoptysis (18% versus 12%), oropharyngeal pain (11% versus 1.8%) and COPD exacerbation (8.5% versus 3.6%).[3] Similarly, in the double-blind phase of the TRO-112 study there were higher rates of respiratory adverse events in the ALIS (Arikayce®) group compared with placebo including: dysphonia (43% versus 8.9%), bronchiectasis exacerbation (39% versus 20%), cough (32% versus 13%), oropharyngeal pain (20% versus 2.2%), chest discomfort (11% versus 0), wheezing (9.1% versus 2.2%) and infective pulmonary exacerbation of cystic fibrosis (9.1% versus 2.2%).[5] The EMA review noted that the latter study indicated that amikacin itself is a bronchial irritant.[2,3,6]

The EMA review noted that current evidence points to a conclusion that chronic exposure (up to 20 months) to relatively low serum levels of amikacin constitutes a risk for developing aminoglycoside-related toxicities affecting the ear, kidney and neuromuscular system.[2]

Summary of clinical effectiveness issues

Mycobacterium avium and M. intracellulare (which belong to MAC), are the predominant infective species in NTM pulmonary disease worldwide. NTM lung disease due to MAC is often associated with productive cough, shortness of breath and fatigue. Dyspnoea, fever, haemoptysis and weight loss can occur, usually with advanced disease. Patients experience a decline in lung function and have increased mortality. There are no other treatments licensed specifically for NTM lung disease

in the UK. It is managed primarily with a 12 to 18 month multi-drug regimen, with the aim of achieving 12 months of negative sputum cultures while on treatment.[2] The 2017 British Thoracic Society (BTS) guidelines on NTM recommend an intermittent (3 times per week) or daily oral regimen of rifampicin, ethambutol and clarithromycin or azithromycin for clarithromycin-sensitive MAC pulmonary disease and, for clarithromycin-resistant disease, the latter medicines should be replaced by isoniazid or a quinolone. An injectable aminoglycoside (amikacin or streptomycin) should be considered in patients with severe MAC-pulmonary disease. Off-label use of nebulised amikacin injection may be considered in place of an injectable aminoglycoside when parenteral administration is impractical, contraindicated or longer term use is required. Antibiotic treatment should continue for a year after culture conversion.[7] There are similar recommendations in the 2020 guideline from the American Thoracic Society (ATS), European Respiratory Society (ERS), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), and Infectious Diseases Society of America (IDSA), which also advises that ALIS (Arikayce®) be added to the treatment regimen in patients with MAC pulmonary disease who have failed therapy after at least 6 months of GBT.[8]

Clinical experts consulted by SMC advised that amikacin can be associated with adverse effects such as ototoxicity, especially with chronic administration and currently patients are treated with off-label amikacin injection parenterally or via nebuliser. They consider there is an unmet need for a licensed nebuliser formulation of amikacin that has an improved safety profile relative to amikacin injection administered parenterally or via nebuliser.

Amikacin liposome inhalation dispersion (ALIS; Arikayce®) is the first medicine licensed for treatment of NTM due to MAC and it is the first nebulised formulation of amikacin. It meets SMC orphan criteria in this indication.

In the phase III CONVERT study, the addition of ALIS (Arikayce®) to GBT increased SCC at 6 months by about 20%. Similar results were observed in patients from the control group who received ALIS (Arikayce®) in an open-label extension study and in the placebo-controlled phase II study. The EMA preferred sustained SCC at 3 months post-treatment as the main outcome, supported by results at 12 months post-treatment. ALIS (Arikayce®) was associated with rates of 16% and 13%, respectively, for these outcomes [2]

An expert group convened during the EMA review noted that the magnitude of effect with ALIS (Arikayce®) was limited. However, it may be clinically relevant in a selected population, for example, those with intractable disease and limited treatment options. Identifying the best target population is challenging due to lack of data. The experts also considered that attaining SCC on treatment, which is not continued post-therapy, may have clinical benefit in reducing bacterial load and short-term symptom amelioration for patients with limited options. However, this should be weighed against potential increases in drug-resistance and adverse events.[2]

There was no evidence of improvements in health-related quality of life during treatment with ALIS (Arikayce®) and no long-term outcomes such as mortality. Data from the phase III CONVERT study did not support conclusions on efficacy within subgroups. There were no comparative efficacy or safety data versus amikacin injection administered parenterally or via nebuliser.

The CONVERT study was open-label and this may affect discontinuation rates and the assessment of subjective outcomes such as adverse event rates and quality of life. Within the ALIS (Arikayce®) group, compared with the control group, more patients discontinued treatment in the CONVERT study (35% versus 11%), with differences in rates of discontinuation due to adverse events (19% versus 0.9%) and withdrawal by the patients (9.8% versus 5.4%), respectively.[2] There were similar rates of discontinuation due to adverse events with ALIS (Arikayce®) compared with placebo in the double-blind phase of the TRO-112 study, 16% versus 0.[5]

The CONVERT study had no measures to optimise oral GBT at baseline. It recruited patients with positive cultures who had received at least 6 months' treatment for MAC. This consisted of two medicines (as opposed to three recommended in guidelines) in 18% and 12% of patients in the ALIS (Arikayce®) and control groups, respectively, and had been stopped for 3 to 12 months before screening in 10% of patients in both groups. It is possible that in addition to treatment-resistant patients, the study population could also have included some inadequately treated patients.[2] However, the licence does not restrict ALIS (Arikayce®) to patients who remain culture positive despite 6 months standard BGT.[1] In the CONVERT study within the ALIS (Arikayce®) and control groups, median duration of multi-drug regimen treatment was 4.3 and 3.2 years, respectively.[3] In practice if ALIS (Arikayce®) was used when patients have failed 6 months of GBT, patients may have had a shorter exposure to GBT alone.

The introduction of ALIS (Arikayce®) would provide a licensed alternative to the off-label use of nebulised amikacin injection. However, it must only be used with the PARI Pharma's Lamira® nebuliser system and this may have service implications.[1]

Clinical experts consulted by SMC advise that ALIS (Arikayce®) in the treatment of adults with NTM lung infections caused by MAC who have limited treatment options is a therapeutic advance as it provides an improved method of administering amikacin to the lungs. They consider that it would be used in practice to replace off-label use of nebulised amikacin injection. They advise that there may be service implications associated with the need to administer ALIS (Arikayce®) via the Lamira® nebuliser system, which is not currently in routine use within NHS Scotland. These may relate to financial and staff resources.

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of ALIS (Arikayce®), as an orphan medicine, in the context of treatments currently available in NHSScotland.

- NTM due to MAC is a chronic, progressive lung infection associated with debilitating symptoms, lung damage and decreased life expectancy. Current first-line treatment with a prolonged oral multi-drug antibiotic regimen is not always effective in achieving sputum clearance and can be associated with substantial adverse events, which further reduce the patient's quality of life.

- Amikacin is a key treatment that can be added to oral multi-drug antibiotics to improve sputum clearance, but prolonged systemic use can lead to ototoxicity and renal adverse events. It can be given by IV injection or via nebuliser, with ALIS (Arikayce®) the first licensed nebuliser formulation.
- Nebulised amikacin is associated with fewer systemic adverse events than IV amikacin. Administration via nebuliser at home may be more convenient for the patient and their family or carers than a course of IV injections (usually as a hospital outpatient) and it would negate the risks associated with prolonged vascular access.
- Amikacin liposomal nebuliser dispersion (ALIS; Arikayce®) can be associated with local upper airway and lung adverse events such as altered voice, sore throat and cough. However, in view of the severity of the condition and difficulties treating it, patients are prepared to tolerate some side effects for better control of their lung disease and reduction of the associated symptoms. They are also happy to undergoing training in the use of the Lamira® nebuliser required to administer ALIS (Arikayce®).
- There is an agreement in place with a large chain of community pharmacies to provide a homecare service with the nebuliser. This would provide additional patient support and may improve adherence.

Additional Patient and Carer Involvement

We received a patient group submission from NTM Patient Care UK, which is a registered charity. NTM Patient Care UK has received 100% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from NTM Patient Care UK participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The submitting company originally presented a cost utility analysis comparing ALIS (Arikayce®) plus GBT versus GBT alone (SMC2369), for the treatment of MAC lung disease (MAC-LD) adults who have failed to response to previous GBT (for at least 6 months) and who do not suffer from cystic fibrosis. GBT is a multi-drug regimen which included IV amikacin as per recommended guidelines, included in the model for 11.52% of the comparator arm GBT patients, derived from a UK survey. The economic analysis therefore considered ALIS (Arikayce®) as an additional treatment for all patients, that is, ALIS (Arikayce®) would be an additional treatment for 88.48% of the patients, and replace IV amikacin in 11.52% of the patients. However, SMC clinical experts advised that in the Scottish setting ALIS (Arikayce®) would be used as a replacement for IV amikacin. Therefore the treatment arm in the base case economic analysis did not align with likely Scottish practice. A revised analysis with ALIS (Arikayce®) only as a replacement for IV amikacin was provided and was the focus of the economic analysis in this resubmission. It should be noted that in order to estimate the outcomes for this comparison, the submitting company assumed that the benefits of

ALIS (Arikayce®) versus IV amikacin were assumed to be the equal to those of ALIS (Arikayce®) versus GBT alone from their original modelling, as described below.

A 5 health state-transition model was built and an individual patient microsimulation was undertaken to analyse the model. The 5 health states include MAC positive, MAC negative, microbiological cure, surgery, and death. Patients start in MAC positive state and are treated with either ALIS (Arikayce®) plus GBT or GBT alone. Patients can transition to MAC negative (culture conversion) or remain MAC positive. Once a patient has been MAC negative for a year, they achieve microbiological cure. Patients can experience a recurrence to the MAC positive state from the MAC negative and cure states.

The model is run for a lifetime horizon, which is appropriate given ALIS (Arikayce®) has potential to achieve sustained culture conversion and cure in a proportion of patients. However, it may over-estimate the benefits of ALIS (Arikayce®). A 10-year time horizon is considered in scenario analyses.

The CONVERT phase III study was the key source of data to inform the parameters in the economic analysis. Treatment effect in the model is based upon culture conversion at 6 months, the primary endpoint in CONVERT. Time-to-event (TTE) analysis was undertaken on the 6 month culture conversion data and informed transition from MAC positive to MAC negative in the model, stratified by treatment arm. Four parametric distributions (Weibull, Gompertz, log-normal, and log-logistic) were fitted to the Kaplan-Meier curves from the CONVERT study, and the optimal distributions for each arm were selected based on statistical fit criteria (AIC and BIC criterion), visual inspection and clinical plausibility. For ALIS (Arikayce®) plus GBT the log-normal and for GBT alone the Gompertz distributions were used in the base case. No extrapolation beyond the 6 months CONVERT data was needed as after this time point patients who have not converted to MAC negative were considered to be non-responders and stop treatment with ALIS (Arikayce®).

The model is primarily driven by higher negative culture conversion rates in the ALIS (Arikayce®) plus GBT arm. However, additional beneficial impacts are implemented through (i) a much lower probability of recurrence from the MAC negative to MAC positive state and (ii) a greater probability of achieving microbiological cure (sustained culture conversion for 12 months) than the GBT alone arm. Recurrence to MAC positive from the MAC negative state is applied as a constant annual risk stratified by treatment arm, derived from a CONVERT post hoc analysis. The sample sizes used to derive these values were very small (n= 8/65 ALIS plus GBT) and (n=4/10 GBT alone) and is subject to uncertainty. All-cause mortality for the general population (UK age and sex adjusted lifetables) was adjusted by a disease-specific mortality risk for MAC-LD patients (derived from a Danish study with MAC-LD survival data). A risk reduction to account for reduced mortality in the microbiological cure state was applied from a published source. An alternative approach to modelling mortality was explored in scenario analysis.

A stopping rule was applied to the ALIS (Arikayce®) plus GBT arm, if culture conversion (MAC negative) is not achieved after 6 months of treatment. No stopping rule was applied for GBT alone arm, patients failing to achieve sustained culture conversion remain on GBT and this applies to both treatment arms. A discontinuation rule for ALIS was applied (46.4% annual risk based on CONVERT), for the first 6 months of treatment. It is assumed this rate includes AE related

discontinuation. Adherence (in both arms) was set to 86% in the base case based on real world data from the submitting company of ALIS medication shipping to patients over a 12 month treatment period.

Utilities were derived from a CONVERT study post hoc analysis of EQ-5D-3L data. A combined weighted average of monthly utilities for converters and non-converters was calculated to derive utility values for the MAC positive and MAC negative states in the model, stratified by treatment arm. The cure state in the model applies a constant utility value, derived from CONVERT post hoc analysis and was not age-adjusted.

Four types of adverse events were accounted for (dysphonia, cough, dyspnoea, and pulmonary exacerbations), using the incidence rates for each arm in CONVERT. AEs only impact for the first 6 months of treatment, and only impact costs. IV aminoglycoside-related permanent AEs are set to 0% in the model base case due to lack of published data, and have not been explored in sensitivity analyses.

The analysis included cost of medications and delivery of the treatment regimen (ALIS and associated control unit, GBT oral multidrug regimen and delivery of IV aminoglycosides), direct medical costs, and management of adverse events (cost per event for ALIS related AEs). The ALIS (Arikayce®) device related cost (nebuliser system and handset) was set to zero as these will be provided by the company in Scotland. SMC clinical experts advised that ALIS (Arikayce®) patients would require education and training on how to use the equipment and take medication - either at home or in an outpatient setting. The costs of this were not accounted for.

This resubmission has been assessed under the fast track resubmission process. A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price. The results at PAS price are shown in table 2 for the resubmission base case i.e. comparison of ALIS (Arikayce®) as replacement for IV amikacin only (ALIS [Arikayce®] + GBT 100% versus GBT + IV amikacin 100%).

Table 2: Base case results with PAS

	Incremental life years gained	Cost per quality adjusted life year (QALY) gained
ALIS (Arikayce® plus GBT versus IV amikacin	0.15	£32,650

The submitting company was asked to provide some sensitivity analysis around the base case incremental cost-effectiveness ratio (ICER) versus IV amikacin to test uncertainties associated with longer term benefits and the utility values, as shown in table 3 below.

Table 3: selected scenario analysis, with PAS

	Scenario	ICER
0	Base Case: Comparison ALIS (Arikayce®) as replacement for IV amikacin only (Amikacin + GBT 100% versus GBT + IV amikacin 100%)	£32,650
1	base case +10 year time horizon	£64,181
2	base case + age- adjusted utilities in long term cure state	£42,077
3	base case + no treatment- specific utility differences	£42,784
4	base case + 10 year horizon, age- adjusted utilities in cure state and no treatment-specific utilities	£86,363

A number of weaknesses were identified with the analysis;

- As noted above, the benefits of ALIS (Arikayce®) versus IV amikacin were assumed to be the equal to those of ALIS (Arikayce®) versus GBT alone, with a concern that this may overestimate the incremental effect, and thus under-estimate the cost-effectiveness ratio. The company asserted that the levels of incremental effect over IV amikacin were likely to be similar to those modelled in the original base case versus GBT alone on the basis that the population in the CONVERT trial were heavily pre-treated and many (one-third) had been pre-treated with this regimen and it was found not to be effective.
- The lifetime horizon is a potential limitation, possibly overestimating quality of life gains for patients in the amikacin arm who spend a much greater proportion of time in the cure state. The New Drugs Committee (NDC) at the time of the initial submission considered a 10-year time horizon may be more relevant (scenario 1, table 3), reflecting on the patient population but it is noted that this shorter time horizon could curtail some benefits for patients who achieve a cure.
- Recurrence to MAC positive from the MAC negative state was applied as a constant risk stratified by treatment arm until microbiological cure can be achieved. The risk is derived from the CONVERT post hoc analysis, which has a very small sample size and therefore is subject to considerable uncertainty: (n= 8/65 ALIS plus GBT) and (n=4/10 GBT alone). Additionally in terms of recurrence rates, the recurrence from microbiological cure to MAC positive was set as constant in the base case model and is associated with uncertainty. The company explained that recurrence is influenced by a host of factors, and as no data are available as to how it would change over time is was set as constant.
- Utilities in the model are derived from a combined weighted average from CONVERT study monthly utilities for converters/non converters to obtain utility values for the MAC positive and MAC negative states, stratified by treatment arm. This approach does not account for the baseline difference in utilities between arms from the CONVERT trial, and potentially further

biases the model by assuming that once MAC negative state is achieved, quality of life would still vary by treatment arm.

- The utility value for the cure state in the model (value from CONVERT post hoc analysis - 0.92) is applied as a constant rate. This value has some uncertainty given the small sample size and is not reflective of published UK age adjusted population utility values. Given the cure state has longevity in the lifetime model, UK population age adjusted utility values are more appropriate (scenario 2, table 3).

- There is some conflicting information regarding EQ-5D data, analysis and methodology used to derive utility weights used in the model. The clinical report from CONVERT notes no evidence of improvements in health-related quality of life during treatment with ALIS. However, the post hoc analysis of EQ-5D data from CONVERT used in the model shows utility benefits for converters with ALIS compared to converters with GBT. Therefore, scenario 3 in table 3 above which applies utility based on state (MAC positive/MAC negative) not treatment arm, is a more appropriate base case analysis. The company suggest that a utility regression model would not appropriately capture the dynamic nature of the health state populations in CONVERT and also highlight the psychometric validation of the EQ-5D-3L data which demonstrated that the EQ-5D-3L data had poor responsiveness to clinically meaningful changes in patients with MAC-LD.

- Adverse events experienced by ALIS (Arikayce®) patients may be underplayed in the model, which only includes 4 AEs, which impact on cost parameters only. The submission notes that including additional disutility for early treatment related side-effects and adverse events could incur double counting. However, it is unclear that the combined weighted utilities derived from the CONVERT post-hoc analysis are a true reflection. The submitting company did not include any scenario analyses to explore impact of adverse events on quality of life and when requested to do so reiterated that the treatment-specific utilities used in the model already account for disutilities due to AEs. The company however noted that the £32k ICER would not capture any quality of life advantages of ALIS (Arikayce®) over IV amikacin, such as reduced otoxicity.

- SMC clinical experts advised that ALIS (Arikayce®) patients would require education and training on how to use the equipment and take medication - either at home or in an outpatient setting. The NHS related costs of this were not accounted for. It should be noted that while this could be an important service impact, including these costs would be unlikely to affect the ICERs given the high medicine acquisition cost which influences the ICER.

It was also noted that there may be differences in costs and outcomes for a comparison to the use of nebulised amikacin injection and IV amikacin and this had not been explored in the presented results.

The Committee considered the benefits of ALIS (Arikayce®) in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as ALIS (Arikayce®) is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted ALIS (Arikayce®) for use in NHSScotland.

*Other data were also assessed but remain confidential.**

Additional information: guidelines and protocols

In 2017 the British Thoracic Society (BTS) published 'BTS guidelines for the management of non-tuberculosis mycobacterial pulmonary disease'. For clarithromycin-sensitive MAC pulmonary disease this recommends rifampicin, ethambutol and clarithromycin or azithromycin using an intermittent (3 times per week) or daily oral regimen. The choice of regimen should be based on the severity of disease and treatment tolerance. An intermittent (3 times per week) oral antibiotic regimen should not be used in patients with severe MAC-pulmonary disease or in patients with a history of treatment failure. An injectable aminoglycoside (amikacin or streptomycin) should be considered in patients with severe MAC-pulmonary disease. Clarithromycin-resistant MAC-pulmonary disease should be treated with rifampicin, ethambutol and isoniazid or a quinolone, and consider an injectable aminoglycoside (amikacin or streptomycin). Nebulised amikacin may be considered in place of an injectable aminoglycoside when intravenous/intramuscular administration is impractical, contraindicated or longer term treatment with an aminoglycoside is required for the treatment of MAC-pulmonary disease. Macrolide monotherapy or macrolide/quinolone dual therapy regimens should not be used for the treatment of MAC-pulmonary disease. Antibiotic treatment for MAC-pulmonary disease should continue for a minimum of 12 months after culture conversion.[8]

In 2020 the American Thoracic Society (ATS), European Respiratory Society (ERS), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), and Infectious Diseases Society of America (IDSA) published 'Treatment of Nontuberculous Mycobacterial Pulmonary Disease: An Official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline'. In patients with MAC pulmonary disease, this recommends susceptibility-based treatment for macrolides and amikacin over empiric therapy. In patients with macrolide-susceptible MAC pulmonary disease, it recommends a 3-drug regimen that includes a macrolide over a 3-drug regimen without a macrolide. In patients with macrolide-susceptible MAC pulmonary disease it suggests azithromycin-based treatment regimens rather than clarithromycin-based regimens. For patients with cavitary or advanced/severe bronchiectatic or macrolide-resistant MAC pulmonary disease, it suggests that parenteral amikacin or streptomycin be included in the initial treatment regimen. In patients with newly diagnosed MAC pulmonary disease, it suggests neither inhaled amikacin (parenteral formulation) nor amikacin liposome inhalation suspension (ALIS) be used as part of the initial treatment regimen. In patients with MAC pulmonary disease who have failed therapy after at least 6 months of guideline-based therapy, it recommends addition of ALIS to the treatment regimen rather than a standard oral regimen, only. In patients with macrolide-susceptible MAC pulmonary disease, it suggests a treatment regimen with at least 3 drugs (including a macrolide and ethambutol) over a regimen with 2 drugs (a macrolide and ethambutol alone). In patients with non-cavitary nodular/bronchiectatic macrolide-susceptible MAC pulmonary disease, it suggests a 3 times per week macrolide-based regimen rather than a daily macrolide-based regimen. In patients

with cavitary or severe/advanced nondular bronchiectatic macrolide-susceptible MAC pulmonary disease it suggests a daily macrolide-based regimen rather than 3 times per week macrolide-based regimen. It suggests that patients with macrolide-susceptible MAC pulmonary disease receive treatment for at least 12 months after culture conversion.[9]

Additional information: comparators

Standard oral GBT; off-label use of amikacin injection administered IV or by nebuliser.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per course (£)
Amikacin liposomal nebuliser dispersion (Arikayce®)	590mg once daily by nebuliser	£132,503 to £183,465*

*Costs from dm+d, accessed 28/07/21. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take patient access schemes into consideration. * costs based on 13 to 18 month courses, where a month = 30 days.*

Additional information: budget impact

The submitting company estimated there would be 29 patients eligible for treatment with ALIS in year 1, followed by 8 per annum in subsequent years to which confidential estimates of treatment uptake were applied.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

References

1. Insmed. Amikacin liposomal nebuliser dispersion (Arikayce®) Summary of product characteristics. Electronic Medicines Compendium www.medicines.org.uk/emc/ Last updated 19.2.21.

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3. Griffith DE, Eagle G, Thomson R, et al. Amikacin Liposome Inhalation Suspension for Treatment-Refractory Lung Disease Caused by *Mycobacterium avium* Complex (CONVERT). A Prospective, Open-Label, Randomized Study. Am J Respir Crit Care Med 2018; 198(12): 1559–69.

4. Insmed. Clinical study report for INS-212, 9.10.19.

5. Olivier KN, Griffith DE, Eagle G, et al. Randomized Trial of Liposomal Amikacin for Inhalation in Nontuberculous Mycobacterial Lung Disease. Am J Respir Crit Care Med 2017; 195(6): 814–23.

6. US Food and Drug Administration (FDA). Multi-discipline review for Amikacin liposomal nebuliser dispersion (Arikayce®), 207356Orig1s000.

7. Aliberti S, Sotgiu G, Castellotti P, Ferrarese M, Pancini L, Pasat A, et al. Real-life evaluation of clinical outcomes in patients undergoing treatment for non-tuberculous mycobacteria lung disease: A ten-year cohort study. Respiratory Medicine. 2020 Apr;164:105899.

8. Haworth CS, Banks J, Capstick T, et al. British Thoracic Society guidelines for the management of non-tuberculous mycobacterial pulmonary disease (NTM-PD). Thorax 2017; 72(Suppl 2): ii1–64.

9. Daley CL, Iaccarino JM, Lange C, et al. Treatment of Nontuberculous Mycobacterial Pulmonary Disease: An Official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline. Clin Infect Dis 2020; 71(4): e1–e36.

This assessment is based on data submitted by the applicant company up to and including 06 September 2021.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises

NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.