NHS England Evidence Review:

Nebulised liposomal amikacin in patients with non-tuberculous mycobacterial pulmonary disease caused by Mycobacterium avium complex with limited treatment options who do not have cystic fibrosis

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Nebulised liposomal amikacin in patients with non-tuberculous mycobacterial pulmonary disease caused by Mycobacterium avium complex with limited treatment options who do not have cystic fibrosis

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Prepared by Solutions for Public Health (SPH) on behalf of NHS England Specialised Commissioning

Contents

1. Introduction

This evidence review examines the clinical effectiveness, safety, and cost effectiveness of nebulised liposomal amikacin plus guideline-based therapy (GBT) compared to the current standard of care with GBT and no nebulised liposomal amikacin in patients with non-tuberculous mycobacterial pulmonary disease (NTM PD) caused by Mycobacterium avium complex (MAC) with limited treatment options who do not have cystic fibrosis.

NTM PD caused by MAC is a chronic, potentially debilitating lung condition associated with progressive structural lung damage, worsening symptoms, decreased quality of life and increased mortality.

Macrolide-resistant NTM PD caused by MAC is more difficult to treat. Amikacin is an aminoglycoside antibiotic; it has a liposomal formulation which has marketing authorisation for use in adults with NTM PD caused by MAC with limited treatment options who do not have cystic fibrosis. Limited treatment options include patients that have refractory disease, macrolide-resistant disease or patients with contraindications or intolerance to GBT. People are considered to be refractory to GBT if they have failed to culture convert after at least 6 months of treatment.

A recent international guideline made a ‘strong’ recommendation to add inhaled amikacin to the standard oral regimen for patients who have failed to culture convert after at least six months of GBT (Daley et al 2020). Clinicians wishing to treat a patient with inhaled amikacin currently use off-label non-liposomal IV amikacin formulation as a nebuliser solution.

2. Executive summary of the review

This report review examines the evidence for clinical effectiveness, safety, and cost effectiveness of adding Liposomal Amikacin for Inhalation (LAI) to guideline-based therapy (GBT) in patients with Non-tuberculous Mycobacterium pulmonary disease (NTM PD) caused by Mycobacterium avium complex (MAC). The searches for evidence were informed by the PICO document and were conducted on 30 July 2021 and identified 162 references. Titles and abstracts were screened for relevance against the criteria in the PICO document and 26 full text papers were obtained and assessed for relevance.

Four papers were identified for inclusion. These studies compared LAI with placebo or GBT alone in adult patients who had previously not responded to GBT alone. One phase II, double-blind randomised controlled trial (Olivier et al 2017) included 89 patients. The RCT by Griffith et al 2018 (CONVERT study) included 336 patients; while the two open-label follow-up studies followed up patients from the CONVERT trial – those who had culture conversion at six months (Griffith et al 2021, n=75) and those who did not (Winthrop et al 2021, n=163). The study by Olivier et al 2017 was carried out in 19 sites in North America, while the CONVERT study was conducted in 127 sites in North America, Europe, Australasia, and Asia. Patients in the Olivier et al 2017 and the Griffith et al 2018 study were followed up for six months; the two open follow-up studies followed patients up for up to 24 months in total.

In terms of clinical effectiveness:

- **Culture conversion (critical outcome)**. Two RCTs provided very low to high certainty evidence that LAI + GBT produces significantly higher culture conversion rates compared to placebo or GBT alone at 84 days to 6 months follow-up. Two open-label follow-up studies also provided low to moderate certainty evidence that the culture conversion continues beyond 6 months, is sustained at 12 months of treatment and persists at 3-month follow-up following discontinuation of treatment.
- **Health-related quality of life (critical outcome)**. Two RCTs provided low to moderate certainty evidence that LAI + GBT produced numerical improvements in SGRQ[1] score changes from baseline at 84 days and at six months. These were not statistically significant.
- **Mortality (critical outcome)**. No evidence was identified for this outcome.
- **6-minute walk test (important outcome).** Two RCTs provided very low to moderate certainty evidence on the effectiveness of adding LAI to GBT in terms of 6MWT improvements. However, the data are conflicting. The double-blind RCT reported a significant improvement in 6MWT at both 84 days and 168 days follow-up. However, the CONVERT RCT reported no improvement in 6MWT at six months and one open-label follow-up study provided very low certainty evidence for no significant difference between treatment arms in the change from baseline in the 6MWT distance at 6 months or at 3 months follow-up after 12 months of LAI treatment.
- **Lung function (important outcome).** One RCT provided moderate certainty evidence for small, clinically insignificant increases in the forced expiratory volume (FEV_1) per cent predicted in both the LAI and placebo groups.
- **Adherence to treatment (important outcome).** One open-label follow-up study provided low certainty evidence for high adherence rates among LAI + GBT patients who achieved

[1] The Saint George's Respiratory Questionnaire (SGRQ) is a self-reported disease specific, health-related quality of life (QOL) questionnaire. It was originally developed to measure the impact of Chronic Obstructive Pulmonary Disease (COPD) on a person's life but has also been studied and applied to non-COPD pulmonary populations.

conversion. Comparative adherence rates with GBT alone were not reported. No measures of statistical significance were reported.

- **Radiographic changes (important outcome).** No evidence was identified for this outcome.

In terms of safety:

- Two RCTs and two open-label follow-up studies provided very low to high certainty evidence on the safety of LAI + GBT compared with GBT alone. Treatment-emergent adverse events (TEAEs) and serious effects including those leading to discontinuation were more common in the LAI group and were mostly respiratory effects. No measures of statistical significance were reported. Renal adverse effects were minimal and the most common audiovestibular effects associated with LAI were tinnitus and dizziness.

In terms of cost-effectiveness:

- No evidence was identified for cost effectiveness.

In terms of subgroups:

- No evidence was identified regarding any subgroups of patients who might benefit from treatment with nebulised liposomal amikacin more than others.

Limitations

There were limitations to the studies that reduced the certainty of the results. Most of the results were of very low, low or moderate certainty. One double-blind RCT included a proportion of patients who did not meet the PICO criteria. This heterogeneity could have confounded the results. Another RCT was open-label as it lacked a masked comparison with an inhaled comparator after eight months. This could have biased the results but is unlikely to have exaggerated the benefit in the LAI arm as the investigator might have been more likely to intensify GBT measures in unwell patients in the control group. Results were unblinded in the open follow-up studies and randomisation was not preserved in the patients in the converter analysis. The level of imprecision was not calculable for most outcomes due to poor reporting of results and no measures of statistical significance.

Conclusion

The four studies identified for this review provided very low to high certainly evidence suggesting that adding LAI to GBT in individuals with NTM PD caused by MAC with limited treatment options increases the proportion of patients who achieve culture conversion up to six months and the effect is sustained for up to 12 months and endures three months after discontinuing full (at least 12 months) of treatment. There was conflicting very low to moderate certainty evidence for improvement in functional outcomes as measured by 6MWT. No significant improvement in Quality of Life, as measured by SGRQ QOL were observed in any of the studies.

No outcomes were reported for mortality (a critical outcome), radiographic changes or cost-effectiveness. No outcomes were reported on subgroups of patients that are more likely to benefit from LAI treatment.

Treatment-emergent adverse events (TEAEs) and serious effects including those leading to discontinuation were more common with LAI group and were mostly respiratory effects. Grade 3, 4 or 5 adverse events, serious adverse events, deaths, and adverse events leading to discontinuation were more common with LAI compared with GBT alone.

The limitations of the studies reduce the reliability of the conclusions about treatment effects and safety.

3. Methodology

Review questions

The review questions for this evidence review are:

1. In patients of all ages with non-tuberculous mycobacterial pulmonary disease (NTM PD) caused by mycobacterium avium complex (MAC) with limited treatment options[2] who do not have cystic fibrosis what is the clinical effectiveness of nebulised liposomal amikacin with guideline-based therapy (GBT) compared with no treatment with nebulised liposomal amikacin?
2. In patients of all ages with NTM PD caused by MAC with limited treatment options who do not have cystic fibrosis what is the safety of nebulised liposomal amikacin with GBT compared with no treatment with nebulised liposomal amikacin?
3. In patients of all ages with NTM PD caused by MAC with limited treatment options who do not have cystic fibrosis what is the cost-effectiveness of nebulised liposomal amikacin with GBT compared with no treatment with nebulised liposomal amikacin?
4. From the evidence selected, are there any data to suggest that there are particular subgroups of patients that would benefit from treatment with nebulised liposomal amikacin more than others?

See Appendix A for the full PICO document.

Review process

The methodology to undertake this review is specified by NHS England in its 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2020).

The searches for evidence were informed by the PICO document and were conducted on 30 July 2021.

See Appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO document. Full texts of potentially relevant studies were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See Appendix C for evidence selection details and Appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE profiles.

[2] Limited treatment options include patients that have refractory disease, macrolide-resistant disease or patients with contraindications or intolerance to guideline-based therapy.

4. Summary of included studies

Four papers reporting outcomes for patients with NTM PD caused by MAC with limited treatment options who do not have cystic fibrosis were identified for inclusion (Griffith et al 2018, Griffith et al 2021, Olivier et al 2017, Winthrop et al 2021). The first two papers were RCTs including 336 and 89 patients respectively, while the latter two were open-label follow-up studies involving two different groups of patients from the first RCT. Table 1 provides a summary of the included papers and full details are given in Appendix E.

Table 1: Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported
Griffith et al 2018 **A randomized, open-label, parallel, multicentre study** 18 countries in North America, Asia-Pacific region, and Europe; United States (141 patients) and Japan (48 patients) were the largest contributors	**N= 336 adults (18 years or older) with MAC-positive sputum or bronchoscopy cultures within 6 months before screening and at screening** LAI + GBT (n = 224) GBT alone (n = 112) Mean age of enrolled patients: 64.7 yrs (SD 9.8) Female: 69.3% Median duration of MAC lung disease (LAI + GBT vs GBT: 4.5 ± 5.5 yrs vs 3.3 ± 3.9 yrs) No subgroups reported	**Intervention** LAI 590 mg once daily, by inhalation aerosolized via eFlow nebulizer over approximately 14 minutes, in addition to GBT[3] (LAI+GBT) **Comparison** GBT alone (GBT)	**Critical outcomes** • Culture conversion • Health-related quality of life **Important Outcomes** • 6-minute walk test • Safety
Griffith et al 2021 **Follow-up to randomized, open-label, parallel, multicentre study** 127 sites in North America, Europe, Australasia, and Asia **Follow-up**	N=75 adults who met protocol-defined culture conversion by month 6 (i.e., three consecutive monthly negative sputum culture results for MAC) in the original CONVERT primary analysis. LAI + GBT, n = 65 GBT alone, n = 10 Median duration of NTM lung disease in the converter group was 4.0 yrs. (IQR 2.0 to 7.0) for patients treated with LAI + GBT and 3.0 years (IQR 1.8 to 6.0) for patients treated with GBT alone; 89.2% (n = 58/65) and 90.0% (n = 9/10) were receiving a multidrug regimen at baseline.	**Intervention** LAI + GBT (as above) **Comparison** **GBT alone (as above)**	**Critical outcomes** • Culture conversion **Important Outcomes** • 6-minute walk test • Safety
Olivier et al 2017 Phase 2 placebo-controlled double-blind RCT, followed by open-label extension study	**N=89 adults with PNTM disease as defined by ATS/IDSA with ongoing guideline–based multidrug treatment for at least 6 months prior to screening, and persistently positive cultures for**	**Intervention** *Double-blind phase:* LAI + GBT (as above) *Open-label phase:* LAI + GBT (as above)	**Critical outcomes** • Culture conversion • Health-related quality of life **Important Outcomes**

[3] already prescribed anti-mycobacterial regimen based on the 2007 ATS/IDSA Guidelines

Study	Population	Intervention and comparison	Outcomes reported
19 sites in North America	***M. avium* complex or *M. abscessus*.** **Double blind phase (n=89):** LAI + SOC (n = 44) Placebo + SOC (n = 45) *Open-label phase (n=78)* LAI + SOC (n = 35) Placebo + SOC (n = 43) **Mean age 58.5 (SD ±15.8) yrs** 19% had CF 64% had predominantly *M. avium complex* infection, and 36% had predominantly *M. abscessus* infection.	**Comparison** *Double-blind phase:* Empty liposome via a customized investigational eFlow Technology nebulizer added to ongoing, stable multidrug regimen (placebo) *Open-label phase: none*	• 6-minute walk test • Safety
Winthrop et al 2021 Open label cohort study 127 sites in North America, Europe, Australasia, and Asia	**Inclusion criteria** N=163 adults with treatment refractory MAC lung disease who were enrolled in the CONVERT study and did not meet the primary endpoint of culture conversion by Month 6 or had recurrent MAC infection (positive MAC culture after conversion) by Month 6 (confirmed at Month 8 when sputum data were unblinded). LAI naïve cohort (n = 90) Prior-LAI cohort (n = 73) **LAI naïve**: Mean age (SD): 64.8 (10.3) yrs. Female: 60.0% Median NTM lung disease duration: 3.7 (range 0.8 to 19.6) yrs **Prior-LAI**: Mean age (SD): 64.9 (9.12) yrs Female: 69.9% Median NTM lung disease duration: 5.4 (range 0.8 to 33.2) yrs	**Intervention** Once daily LAI + GBT **Comparison** Nil	**Critical outcomes** • Culture conversion **Important Outcomes** • Safety
Abbreviations ATS-American Thoracic Society; CF-Cystic fibrosis; GBT-Guideline-Based Treatment; LAI-Liposomal Amikacin Inhaled; MAC-Mycobacterium Avium Complex; mg-milligram; n-number; PNTM-Pulmonary Non-Tuberculosis Mycobacterium; RCT-Randomised Controlled Trial; SD-Standard Deviation; SOC-standard of care; yrs-years			

5. Results

In patients of all ages with non-tuberculous mycobacterial pulmonary disease (NTM PD) caused by mycobacterium avium complex (MAC) with limited treatment options[4] who do not have cystic fibrosis what is the clinical effectiveness and safety of nebulised liposomal amikacin with guideline-based therapy (GBT) compared with no treatment with nebulised liposomal amikacin?

Results from the included studies involved adult patients/participants only.

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Culture conversion **Certainty of evidence:** Very low to high	Culture conversion means that the patient no longer tests positive for the MAC organisms in their sputum. This is a critical marker of treatment success to patients and clinicians as it indicates whether treatment should continue and when treatment can end. Culture conversion should be attained by 6 months of treatment with nebulised liposomal amikacin plus GBT. Two randomised trials: one phase 2 double blind RCT (Olivier et al 2017, n = 89) and one open-label phase 3 controlled study (CONVERT study; Griffith et al 2018, n = 336) provided evidence relating to the effectiveness of LAI in converting culture positive NTM PD caused by MAC, after 3 and 6 months of treatment respectively. Evidence for the culture conversion beyond six months and for sustainability and durability of conversion was provided by two open label follow-up studies of the patients recruited to the CONVERT study. Griffith et al 2021 (n = 75) evaluated the sustainability and durability among those participants who converted (converters) in the first 6 months and remained negative at 8 months evaluation following the CONVERT study. The study by Winthrop et al 2021 (n = 163) evaluated the efficacy and safety of open label LAI treatment in both LAI-naïve or prior-LAI patients who failed to convert (non-converters) or relapsed during the 6-month trial phase of the CONVERT study. **At 84 days** • Olivier et al 2017 (n = 89) reported the change in semi-quantitative mycobacterial culture results from baseline to day 84 for LAI vs placebo: 2.0 SD vs 1.5 SD, p= 0.072. NS **(MODERATE)** • Olivier et al 2017 reported culture conversion rates of LAI 32% [14/44] in patients treated with LAI vs 9% [4/45] in patients treated with placebo, p = 0.006. (**MODERATE)** • Olivier et al 2017 reported a shorter time to first negative sputum culture with LAI vs placebo: HR 5.68, 95% CI 1.25 to 25.79, p = 0.0129. **(MODERATE)** **At 168 days** • After an open-label follow-up phase, Olivier et al 2017 reported conversion rates of LAI 31.4% [11/35] vs placebo 9.3% [4/43]. At 28-days after end of study follow-up, conversion rates were LAI 31.4% [11/35] vs placebo 7.0% [3/43]. **(LOW)** **At 6 months** • Griffith et al 2018 reported culture conversion rates of 29% [65/224] in patients treated with LAI + GBT vs GBT alone 8.9% [10/112]; adjusted odds

[4] Limited treatment options include patients that have refractory disease, macrolide-resistant disease or patients with contraindications or intolerance to guideline-based therapy.

Outcome	Evidence statement
	ratio 4.22, 95% CI 2.08 to 8.57, p<0.001. HR 3.90, 95% CI 2.00 to 7.60. **(HIGH)** • Winthrop et al 2021 (n=163) in an open-label parallel group study evaluated the conversion rates amongst patients who did not convert at the end of the 6-month open label randomised phase of the CONVERT study. At 6 months, the authors reported a cumulative sputum culture conversion of 26.7% [24/90] in LAI-naïve patients, increasing to 30/90 (33.3%) by Month 12. The study also reported cumulative culture conversion of 7/73 (9.6%) in prior-LAI patients at 6 months increasing to 10/73 (13.7%) at 12 months. **(VERY LOW)** **At 12 months** • Griffith et al 2021 reported sustained conversion rates at 12 months: LAI + GBT 41/224 (18.3%) vs GBT alone 3/112 (2.7%), p<0.0001 (ITT analysis), and LAI + GBT 41/65 (63.1%) vs GBT alone 3/10 (30.0%), p=0.0644 (converter analysis). **(MODERATE)** **At end of treatment (up to 16 months)** • Griffith et al 2021 reported sustained conversion at the end of treatment of LAI + GBT 52/224 (23.2%) vs GBT alone 3/112 (2.7%), p< 0.0001; LAI + GBT 52/65 (80.0%) vs GBT alone 3/10 (30.0%), p= 0.0014 (converter analysis). **(MODERATE)** **At 3 months from the end of treatment** • Griffith et al 2021 reported durable conversion rates at 3-month follow-up from end of treatment of LAI + GBT 36/224 (16.1%) vs GBT alone 0/112, p<0.0001 (ITT analysis); LAI + GBT 36/65 (55.4%) vs GBT alone 0/10, p=0.0017 (converter analysis). **(LOW)** **At 12 months after treatment** • Griffith et al 2021 reported negative culture results 12 months after treatment rates of LAI + GBT 30 (13.4%) vs GBT alone 0, p<0.0001 (ITT analysis); LAI + GBT 30/65 (46.2%) vs GBT alone 0/10, p<0.0001 (converter analysis). **(LOW)** • Conversion rates regardless of treatment duration were LAI + GBT 41/224 (18.3%) vs GBT alone 0/112, p<0.0001 (ITT analysis); LAI + GBT 41/65 (63.1%) vs GBT alone 0/10, p=0.0002 (converter analysis). **(LOW)** **These studies provide very low to high certainty evidence that LAI + GBT produces significantly higher culture conversion rates compared to placebo or GBT alone at 84 days to 6 months follow-up. They also provide low to moderate certainty evidence that the culture conversion is sustained at 12 months of treatment and persists at 3 months follow-up following discontinuation of treatment.**
Health-related Quality of Life (HrQOL) **Certainty of evidence:** Low to moderate	Health-related quality of life can be measured by respiratory-specific subjective scales such as the St George's Respiratory Questionnaire (SGRQ). Quality of life is a critical outcome for patients and their carers as it provides a holistic evaluation and indication of the patient's general health and their and their carer's perceived wellbeing. A difference of 4 or more points is considered an MCID for the St George's Respiratory Questionnaire. Two RCTs (Olivier et al 2017, Griffith et al 2018) evaluated the effect of LAI on HrQOL at 84 days to 6 months. • At 84 days, one double blind placebo-controlled RCT (Olivier et al 2017) reported a change from baseline in SGRQ, QOL, QOL bronchiectasis, and NTM module scores between non-CF patients treated with LAI (n = 36) -

Outcome	Evidence statement
	7.935 (SD 14.1998) vs placebo (n = 36) -2.829 (13.6733), p= 0.2039. **(MODERATE)** • At 6 months, one open-label RCT (Griffith et al 2018) reported least squares mean (SE) changes from baseline in SGRQ score: LAI + GBT vs GBT alone: 4.2 (2.0) vs 0.4 (2.2), MD [SE] 3.8 [1.6], 95% CI 0.67 to 6.94. **(LOW)** **These studies provide low to moderate certainty evidence that LAI + GBT produced numerical improvements in SGRQ score changes from baseline at 84 days and at 6 months. These were not statistically significant.**
Mortality **Certainty of evidence:** **n/a**	This outcome is critical to patients because it reflects how long people live after treatment, although it does not provide information about patients' health and wellbeing during that time. Mortality reported within any timeframe is relevant. **No evidence was identified for mortality.**
Important outcomes	
6-minute walk test **Certainty of evidence:** Very low to moderate	The 6-minute walk test is an important outcome for patients as it is an objective marker of their exercise capacity. Changes in the 6-minute walk test would be expected to be seen at 4 to 6 months and may be monitored up to the end of treatment (no longer than 18 months from initiation). There are no recorded MCIDs. Two RCTs (Olivier et al 2017 and Griffith et al 2018) evaluated the effect of LAI on the 6MWT at 84 days to 6 months • One double-blind RCT (Olivier et al 2017) reported a mean (SD) distance walked at 84 days, LAI +20.6 (SD, 62.4) meters vs placebo -25.0 (100.2) meters, p= 0.017. **(MODERATE)** • At 168 days (end of open-label phase), Olivier et al 2017 reported a change in mean (SD) 6MWTs of prior-LAI (n = 35), +142.4 (105.9) meters vs prior-placebo (n = 43), -228.4 (88.1) meters, MD 70.8 metres, p= 0.012. **(VERY LOW)** • At 6 months, one open label RCT (Griffith et al 2018) reported a mean 6-minute walk test Change in 6MWT distance from baseline to Month 6 of LAI + GBT (n = 223) -1.5 (-23.6 to 20.6) vs GBT alone (n = 112) 1.5 (-22.2 to 25.3). Least squares MD [SE] -3.0 [9.0], 95% CI -20.64 to 14.65, p= 0.74. **(LOW)** • An open label follow-up to the CONVERT study, Griffith et al 2021 reported mean changes in 6MWT from baseline in 75 patients who converted during the double-blind phase of the CONVERT study. At 3 months follow-up after 12 months of treatment in total, the mean change in 6MWT from baseline was: LAI + GBT 83.4 (SD 20.9 ± 83.4) m, p= 0.096; GBT only group was not calculable **(LOW)** **These studies provide very low to moderate certainty evidence on the effectiveness of adding LAI to GBT in terms of 6MWT improvements. However, the data are conflicting. While the double-blind study (Olivier et al 2017) reports a significant improvement in 6MWT at 84 days which is also observed at 168 days follow-up, in the study by Griffith et al 2018. In the follow-up study by Griffith et al 2021, there was no significant difference between treatment arms in the change from baseline in the 6MWT distance at 6 months and no significant improvement in 6MWT at 3 months follow-up after 12 months of LAI treatment.**
Lung function **Certainty of evidence:** **Moderate**	Lung function is usually measured by spirometry and gives an objective measure of how well the lungs are working. Measures would include, but not be limited to forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC). This is an important outcome for patients as it is an objective marker of the change in their lung function. Changes would be expected after 4 to 6 months of treatment. There are no recorded MCIDs.

Outcome	Evidence statement
	One RCT (Olivier et al 2017) reported the increases in FEV1 per cent predicted in both arms of the study: • At 84 days, increases in FEV1 were: LAI 0.32 ± 0.5% vs placebo 0.16 ± 6.0%. (It was not reported whether these were mean or median differences; no p-value was reported. **(MODERATE)** **This study provides moderate certainty evidence for a small, clinically insignificant increase in FEV1 with both LAI and placebo at 84 days of treatment.**
Adherence to treatment **Certainty of evidence:** Low	Adherence to treatment is important to patients because it is vital to the function of the medication that it is taken regularly as prescribed in order to gain the maximum effect, improve outcomes, and prevent complications. It is not known what the lowest level of adherence is needed for treatment success. • One open-label follow-up study (Griffith et al 2021) reported low certainty evidence for high adherence rate (81.5%) in adults treated with LAI + GBT. Comparative adherence rates with GBT alone were not reported. No measures of statistical significance were reported. **(LOW)** **This study provided low certainty evidence for high adherence rates in adults treated with LAI + GBT. Comparative adherence rates with GBT alone were not reported.**
Radiographic changes **Certainty of evidence:** **n/a**	Changes to the appearance of x-rays and computerised tomography scans are important to patients as they are used to help determine treatment success and requirement for further treatment. Changes would be expected after 4 to 6 months of treatment. **No evidence was identified for radiographic changes.**
Safety	
Safety **Certainty of evidence:** Very low to high	The benefits of LAI treatment may be countered by the presence of serious treatment-emergent adverse events (grade 3, 4 or 5) including (but not limited to) pneumonia, exacerbation of underlying airways conditions, renal toxicity, haemoptysis, and ototoxicity. Treatment-emergent adverse events could also lead to treatment discontinuation, thereby limiting patients' ability to derive benefit from treatment. Ototoxic and nephrotoxic effects are common treatment-limiting adverse effects to aminoglycoside antibiotics like amikacin. The liposomal amikacin formulation LAI was designed to facilitate targeted and localized drug delivery to the lungs while minimizing systemic exposure. Significant ototoxicity or nephrotoxicity with LAI treatment will therefore negate the theoretical benefits of administering amikacin as a nebulised liposome enclosed product. The safety of LAI treatment was evaluated in two randomised studies (Olivier et al 2017 and Griffith et al 2018 (CONVERT study)). Longer-term safety was evaluated in two open follow-up studies to the CONVERT study; one in patients who converted after the 6-month trial period (Griffith et al 2021) and another in patients who did not convert after the trial period (Winthrop et al 2021). **At 84 days** **Serious adverse effects** • **In the double-blind placebo-controlled RCT (Olivier et al 2017), the overall incidence of serious adverse events was higher in the LAI group than in the placebo group (18.2% vs 8.9%). (MODERATE)** *Treatment-emergent adverse events (TEAE) included:* • Grade 3: LAI 4/44 (9.1%) vs placebo 5/45 (11.1%) **(LOW)** • Grade 4: LAI 0 (0%) vs placebo 0 (0%) **(VERY LOW)** • Grade 5: LAI 1/44 (2.3%) vs placebo 0/45 (0%) **(LOW)** **TEAE leading to discontinuation**

Outcome	Evidence statement
	• In the double-blind phase of the RCT by Olivier et al 2017 17/44 (15.9%) patients in the LAI group and none in the placebo group discontinued the study drug because of TEAE. **(LOW)** **At 168 days** **Serious adverse effects** • **During the open-label phase of the study by Olivier et al 2017, the incidence rates of serious adverse events were prior-LAI 14.3% vs prior-placebo 11.6%. (VERY LOW)** *TEAE leading to discontinuation* • occurred in fewer patients initially treated with LAI compared to those who received placebo during the double-blind phase of the RCT by Olivier et al 2017: LAI 6 (17.1%) vs placebo 12 (27.9%) **(VERY LOW)** **Renal adverse effects** • **Events related to nephrotoxicity were infrequent in both arms. (LOW)** **At 6 months** *Serious adverse effects* • In the open-label RCT (Griffith et al 2018), serious TEAEs were reported in both groups: LAI+GBT 45**/**223 (20.2%) vs GBT alone 20/112 (17.9%) **(HIGH***)* **TEAEs leading to death** • **In the open-label RCT (Griffith et al 2018), TEAEs leading to death were reported in both groups: LAI+GBT 6/223 (2.7%) patients vs GBT alone 5/112 (4.5%). (HIGH)** *Audiologic* TEAEs • Audiologic TEAEs were reported in both arms of the open-label RCT study by Griffiths et al 2018 including tinnitus: LAI+GBT 17/223 (7.6%) vs GBT alone 1/112 GBT (0.9%) **(HIGH)** **At up to 16 months** Griffiths et al 2021 reported adverse outcomes for patients who were culture-negative at 8 months who were followed up for up to 16 months (end of treatment – EOT). • Any serious TEAE: LAI + GBT 6/65 (9.2%) vs GBT alone 6/10 (60.0%) **(LOW)** • COPD exacerbation: LAI + GBT 1/65 (1.5%) vs GBT alone 2 (20.0%) **(LOW)** • Drug hypersensitivity: LAI + GBT 1/65 (1.5) vs GBT alone 0 **(VERY LOW)** • Infective exacerbation of bronchiectasis: LAI + GBT 1 (1.5%) vs GBT alone 1 (10.0%) **(LOW)** • Infective exacerbation of COPD: LAI + GBT 1 (1.5%) vs GBT alone 0 **(VERY LOW)** • Lung adenocarcinoma: LAI + GBT 1 (1.5%) vs GBT alone 0 **(VERY LOW)** • Lung infection pseudomonal: LAI + GBT 1 (1.5%) vs GBT alone 0 **(VERY LOW)** • Pneumatosis intestinalis: LAI + GBT 1 (1.5) vs GBT alone 0 (**VERY LOW)** • Pneumonia: LAI + GBT 1 (1.5%) vs GBT alone 0 **(VERY LOW)** • Pneumothorax: LAI + GBT 1 (1.5%) vs GBT alone 0 **(VERY LOW)** **These studies provide very low to high certainly evidence on the safety of LAI+GBT compared with GBT alone. TEAEs including serious effects including those leading to discontinuation were more common in the LAI group and were mostly respiratory effects. Renal effects are minimal. The**

Outcome	Evidence statement
	most common audiovestibular effects associated with LAI were tinnitus and dizziness.

Abbreviations
6MWT-6 minute walk test; ATS-American Thoracic Society; CF-Cystic fibrosis; CI-Confidence Interval; COPD-Chronic Obstructive Pulmonary Disease; CT-Computer Tomography; EOT-End of Treatment; FEV1-Force Expiratory Volume in 1 second; FVC-Forced Vital Capacity; GBT-Guideline-Based Treatment; HR-Hazard Ratio; IQR-Inter Quartile Range; ITT-Intention to Treat; LAI-Liposomal Amikacin Inhaled; MAC-Mycobacterium Avium Complex; MCID-minimal clinically important differences; MD-Mean Difference; MIC-Minimum Inhibitory Concentration; NS-Not Significant; NTM-Non-Tuberculosis Mycobacterium; OR-Odds Ratio; PD-Pulmonary Disease; PNTM-Pulmonary Non-Tuberculosis Mycobacterium; QOL-Quality of Life; RCT-Randomised Controlled Trial; SD-Standard Deviation; SGRQ-Saint George's Respiratory Questionnaire; TEAE treatment-emergent adverse event

In patients of all ages with NTM PD caused by MAC with limited treatment options1 who do not have cystic fibrosis what is the cost-effectiveness of nebulised liposomal amikacin with GBT compared with no treatment with nebulised liposomal amikacin?

Outcome	Evidence statement
Cost effectiveness	**No evidence was identified for cost effectiveness.**

From the evidence selected, are there any data to suggest that there are particular subgroups of patients that would benefit from treatment with nebulised liposomal amikacin more than others?

Outcome	Evidence statement
Subgroups	**No evidence was identified regarding any subgroups of patients that would benefit more from treatment with nebulised liposomal amikacin with GBT compared with treatment with GBT alone.**

6. Discussion

This evidence review considered the clinical effectiveness and safety of adding inhaled liposomal amikacin to guideline-based therapy in patients with non-tuberculous mycobacterial pulmonary disease (NTM PD) caused by mycobacterium avium complex (MAC) with limited treatment options who do not have cystic fibrosis. The critical outcomes of interest were mortality, culture conversion and quality of life. Other important outcomes included the 6-minute walking distance measurements (6MWT), lung function, adherence, radiographic changes, and safety. Evidence on cost-effectiveness was also sought.

Evidence was available from two RCTs (one phase two double-blind RCT (Olivier et al 2017) and one open-label RCT (Griffith et al 2018; CONVERT study) as well as two open-label studies (Griffith et al 2021 and Winthrop et al 2021) that followed up patients that responded and did not respond (converters and non-converters respectively) in the CONVERT study. The two RCTs compared LAI + GBT with GBT alone. Olivier et al 2017 employed a placebo in form of plain liposome to evaluate any respiratory side effects of the novel method of inhalation employed whilst the study by Griffith et al 2018 was an open label study that did not involve the use of placebo. However, investigators and patients were blinded to the results during the first 6 to 8 months of the trial, so it is less likely to have biased the results because investigators could not have escalated other GBT measures in response to late conversion. The two open follow-up studies aimed to establish the sustainability and durability of conversion in converted patients, to establish whether a non-converter could continue to convert beyond the first phase 6-month phase of the CONVERT study and to evaluate the longer-term safety of LAI.

In total, the studies involved 425 patients: 89 in the study by Olivier et al 2017 and 336 in the CONVERT study (Griffith et al 2018). The two RCTs both reported statistically significant improved culture conversion rates with LAI +GBT compared with placebo or GBT alone at 84 days and six months. The longer follow-up studies demonstrated the sustainability and durability of the conversion when patients were followed up to receive at least 12 months of treatment and when followed up off treatment for up to 12 months.

No significant improvement in Quality of Life, as measured by SGRQ QOL was observed in either of the studies. The data on Functional QOL as measured by 6MWT were conflicting. The study by Oliver et al 2017 reported a clinically significant improvement in 6MWT in the LAI + GBT arm at 84 days, which remained significant at 168 days, the study by Griffith et al 2018 did not record any significant improvement and recorded a non-significant deterioration in 6MWT in the LAI + GBT arm. Although LAI as add-on therapy to GBT was associated with a strong microbiological response, a clinical benefit of LAI treatment is yet to be conclusively demonstrated, as highlighted by the lack of a consistent results on the effects of LAI on 6MWT results at 6 months in CONVERT and Olivier et al 2017. While Olivier et al 2017 reported a statistically significant improvement in 6MWT with LAI, Griffith et al 2018 did not record any significant improvement rather it reported a non-significant deterioration.

No studies on the effect of LAI therapy on mortality (a critical outcome to this review) were identified.

Both RCTs and the two follow-up studies showed that adverse effects are more common in patients receiving LAI. Severe adverse effects, including those linked with death and those resulting in treatment discontinuation, were mostly respiratory effects. Renal adverse effects were not frequent and were evenly distributed between treatment and control groups. Audiovestibular side effects were more common in the LAI group and were mostly tinnitus and dizziness.

There were limitations to the studies that reduced the certainty of the results. Most of the results were of very low, low or moderate certainty. The level of imprecision was not calculable for many outcomes due to poor reporting of results and no measures of statistical significance. The double-blind RCT (Olivier et al 2017) included patients who did not meet the PICO criteria (19% had CF, 64% had predominantly MAC infection, and 36% had predominantly *Mycobacterium abscessus* (Mabs) infection. This heterogeneity could have confounded the results. The open-label RCT (Griffith et al 2018) lacked a masked comparison with an inhaled comparator. This could have biased the results but is unlikely to have exaggerated the benefit in the LAI arm as the investigator might have been more likely to intensify GBT measures in unwell patients in the control group. Results were unblinded in the open follow-up studies (Griffith et al 2021 and Winthrop et al 2021) and randomisation was not preserved in the patients in the converter analysis. Despite this, the results on culture conversion in Griffith et al 2021 remained consistent when analysed both on an ITT or converter basis.

No studies on the cost effectiveness LAI therapy were identified.

No studies on subgroups of patients who are more likely to benefit from LAI therapy were identified.

7. Conclusion

We found very low to high certainty evidence on the clinical effectiveness of adding LAI to GBT compared to placebo or GBT alone. Very low to high certainty evidence from two RCTs reported a significant improvement in culture conversion in LAI treatment patients at 84 day and 6 months compared with placebo or GBT alone. Data from two open label follow-up studies provided low to moderate certainty evidence that the culture conversion induced by LAI treatment is sustained at the end of the treatment and persists at 28 days to 3 months follow-up at the end of treatment. Low to moderate quality evidence on the effects of LAI on QOL measured by SGRQ and very low to moderate certainty evidence for functional QOL measured by 6MWT did not consistently support a benefit of LAI treatment. There was moderate certainty evidence for a small and non-clinically significant increase in lung function (measured by increase in FEV_1) in both patients treated with LAI and those treated with placebo. One open-label follow-up study reported low certainty evidence for a high treatment adherence rate (81.5%) in adults treated with LAI + GBT. Comparative adherence rates with GBT alone were not reported. We found no studies evaluating the effect of LAI on mortality or radiographic changes.

We found very low to high certainty evidence on the safety of adding LAI to GBT compared with GBT alone. Both RCTs and the two follow-up studies showed the adverse effects are more common in patients receiving LAI. Severe adverse effects, including those linked with death and those resulting in treatment discontinuation were mostly respiratory effects. Renal adverse effects were not frequent and were evenly distributed between treatment and control groups. Audiovestibular side effects more common in the LAI group were mostly tinnitus and dizziness.

We found no studies evaluating the cost effectiveness of LAI + GBT compared with no treatment with LAI.

We found no results which identified whether there are any particular subgroups of patients who might benefit from treatment with LAI more than others.

Appendix A PICO document

The review questions for this evidence review are:

1. In patients of all ages with non-tuberculous mycobacterial pulmonary disease (NTM PD) caused by mycobacterium avium complex (MAC) with limited treatment options[5] who do not have cystic fibrosis what is the clinical effectiveness of nebulised liposomal amikacin with guideline-based therapy (GBT) compared with no treatment with nebulised liposomal amikacin?
2. In patients of all ages with NTM PD caused by MAC with limited treatment options who do not have cystic fibrosis what is the safety of nebulised liposomal amikacin with GBT compared with no treatment with nebulised liposomal amikacin?
3. In patients of all ages with NTM PD caused by MAC with limited treatment options who do not have cystic fibrosis what is the cost-effectiveness of nebulised liposomal amikacin with GBT compared with no treatment with nebulised liposomal amikacin?
4. From the evidence selected, are there any data to suggest that there are particular subgroups of patients that would benefit from treatment with nebulised liposomal amikacin more than others?

P –Population and Indication	Patients of all ages with a diagnosis of non-tuberculous mycobacterial pulmonary disease (NTM PD) caused by mycobacterium avium complex (MAC) with limited treatment options who do not have cystic fibrosis. [NTM PD caused by MAC may also be referred to as MAC PD] [Pulmonary disease may also be referred to as lung disease]
I – Intervention	Nebulised liposomal amikacin delivered once daily with guideline-based therapy. Guideline-based therapy is derived from the 2017 British Thoracic Society guidelines (Haworth et al 2017) and is usually based on a regimen of: 1. Rifampicin; and 2. Ethambutol; and 3. A macrolide Antibiotic treatment should continue for a minimum of 12 months after culture conversion.
C – Comparator(s)	Guideline-based therapy (as described in Intervention) with no nebulised liposomal amikacin.
O – Outcomes	**Clinical Effectiveness** *Critical to decision-making:* • Culture conversion Culture conversion means that the patient no longer tests positive for the MAC organisms in their sputum. This is a critical marker of treatment success to patients and clinicians as it indicates whether treatment should continue and when treatment can end. Culture conversion should be attained by 6 months of treatment with nebulised liposomal amikacin plus

[5] Limited treatment options include patients that have refractory disease, macrolide-resistant disease or patients with contraindications or intolerance to guideline-based therapy.

	GBT. There are no recorded minimal clinically important differences (MCIDs). • Health-related quality of life Health-related quality of life can be measured by respiratory-specific subjective scales such as the St George's Respiratory Questionnaire. Quality of life is a critical outcome for patients and their carers as it provides a holistic evaluation and indication of the patient's general health and their and their carer's perceived wellbeing. A difference of 4 or more points is considered an MCID for the St George's Respiratory Questionnaire. • Mortality This outcome is critical to patients because it reflects how long people live after treatment, although it does not provide information about patients' health and wellbeing during that time. Mortality reported within any timeframe is relevant. *Important to decision-making:* • 6-minute walk test The 6-minute walk test is a non-specific exercise test that is used to assess a person's aerobic capacity and endurance. It is an important outcome for patients as it is an objective marker of their exercise capacity. Changes in the 6-minute walk test would be expected to be seen at 4 to 6 months and may be monitored up to the end of treatment (no longer than 18 months from initiation). There are no recorded MCIDs. • Lung function Lung function is usually measured by spirometry and gives an objective measure of how well the lungs are working. Measures would include, but not be limited to forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC). This is an important outcome for patients as it is an objective marker of the change in their lung function. Changes would be expected after 4 to 6 months of treatment. There are no recorded MCIDs. • Adherence to treatment Adherence to treatment is important to patients because it is vital to the function of the medication that it is taken regularly as prescribed in order to gain the maximum effect, improve outcomes, and prevent complications. It is not known what the lowest level of adherence is needed for treatment success. • Radiographic changes Changes to the appearance of x-rays and computerised tomography scans are important to patients as they are used to help determine treatment success and requirement for further treatment. Changes would be expected after 4 to 6 months of treatment. **Safety** • Presence of serious treatment-emergent adverse events (grade 3, 4 or 5) including (but not limited to) pneumonia, exacerbation of underlying airways conditions, renal toxicity, haemoptysis, and ototoxicity.

	• Treatment-emergent adverse events leading to treatment discontinuation. **<u>Cost effectiveness</u>**
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher-level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	All ages
Date limits	2011-2021
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, and guidelines
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase and the Cochrane Library were searched limiting the search to papers published in English language in the last 10 years. Conference abstracts, commentaries, letters, editorials, and case reports were excluded.

Search dates: 01 January 2011 and 30 July 2021

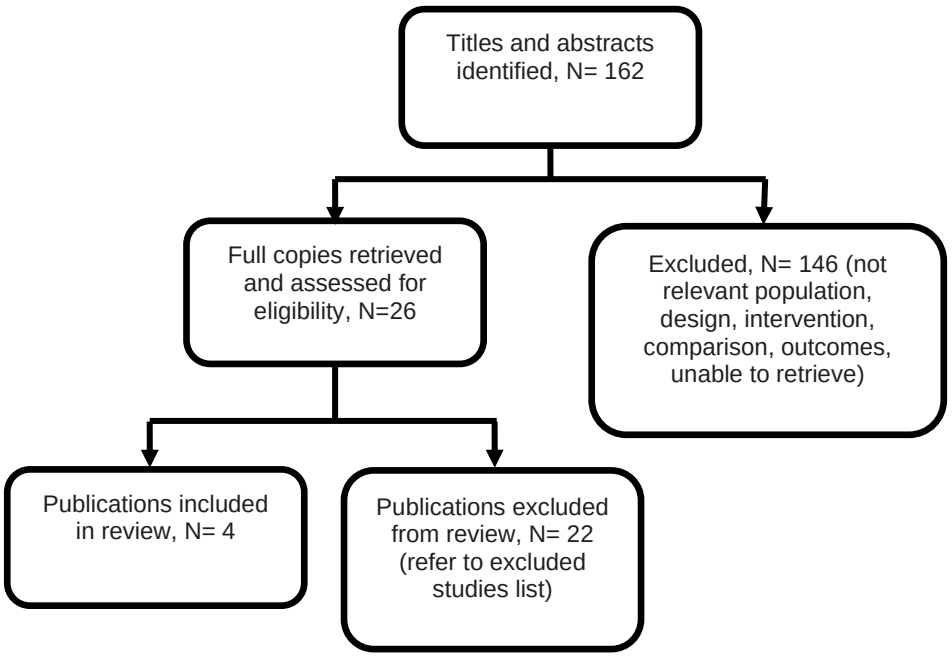
Medline search strategy:

1	Mycobacterium avium Complex/
2	mycobacterium infections/ or mycobacterium infections, nontuberculous/ or mycobacterium avium-intracellular infection/
3	Lung Diseases/ and mycobacter*.mp.
4	(((lung or pulmonary) adj3 (infection? Or disease? Or disorder?)) and mycobacter*).ti,ab,kw.
5	(((lung or pulmonary) adj3 (infection? Or disease? Or disorder?)) and (nontubercul* or non-tubercul*)).ti,ab,kw.
6	1 or 2 or 3 or 4 or 5
7	Amikacin/
8	(amikacin or arikayce?).ti,ab,kw.
9	7 or 8
10	Administration, Inhalation/
11	Nebulizers and Vaporizers/
12	(inhal* or nebuli* or vapor* or vapour* or liposom*).ti,ab,kw.
13	10 or 11 or 12
14	6 and 9 and 13
15	(amikacin or arikayce?).ti. or Amikacin/tu
16	6 and 15
17	14 or 16
18	(comment or editorial or letter or review).pt. or case report.ti,ab.
19	17 not 18
20	exp animals/ not humans/
21	19 not 20
22	6 and 9
23	limit 22 to (meta analysis or “systematic review” or “reviews (maximizes specificity)”)
24	21 or 23
25	limit 24 to (22 English language and yr=”2011 -Current”)

Appendix C Evidence selection

The combined literature searches identified 162 references. These were screened using their titles and abstracts and 26 references were obtained in full text and assessed for relevance. Of these, four references are included in the evidence summary. The remaining 22 references were excluded and are listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection – decision and rationale if excluded
Griffith DE, Eagle G, Thomson R, Aksamit TR, Hasegawa N, Morimoto K, et al. CONVERT Study Group. Amikacin liposome inhalation suspension for treatment-refractory lung disease caused by Mycobacterium avium complex (CONVERT). A prospective, open-label, randomized study. American Journal of Respiratory Critical Care Medicine. 2018. 198(12): 1559-1569.	Included
Griffith DE, Thomson R, Flume P, Aksamit TR, Field SK, Addrizzo-Harris DJ, et al. CONVERT Study Group. Amikacin liposome inhalation suspension for refractory Mycobacterium avium complex lung disease: sustainability and durability of culture conversion and safety of long-term exposure. Chest. 2021. S0012-3692(21)00703-0.	Included
Winthrop KL, Flume PA, Thomson R, Mange KC, Yuen DW, Ciesielska M, et al. INS-312 Study Group. Amikacin liposome inhalation suspension for MAC lung disease: a 12-month open-label extension study. Annals of American Thoracic Society. 2020.	Included

Appendix D Excluded studies table

Study reference	Reason for exclusion
Aznar ML, Marras TK, Elshal AS, Mehrabi M, Brode SK. Safety and effectiveness of low-dose amikacin in nontuberculous mycobacterial pulmonary disease treated in Toronto, Canada. BMC Pharmacology & Toxicology. 2019;20(1):37.	Does not meet the PICO criteria; intervention is low dose IV amikacin
Chang CL, Chen LC, Yu CJ, Hsueh PR, Chien JY. Different clinical features of patients with pulmonary disease caused by various Mycobacterium avium-intracellulare complex subspecies and antimicrobial susceptibility. International Journal of Infectious Diseases. 2020;98:33-40.	Patient and disease characteristics study not an evaluation of treatment.
Daley CL, Iaccarino JM, Lange C, Cambau E, Wallace RJ, Jr, Andrejak C, et al. Treatment of Nontuberculous Mycobacterial Pulmonary Disease: An Official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline. Clinical Infectious Diseases. 2020;71(4): e1-e36.	Guidelines are excluded from the review scope. No outcomes reported
Davis KK, Kao PN, Jacobs SS, Ruoss SJ. Aerosolized amikacin for treatment of pulmonary Mycobacterium avium infections: an observational case series. BMC Pulm Med. 2007; 7:2.	Does not meet the PICO criteria, not liposomal amikacin
Deresinski S. Treatment of pulmonary mycobacterium avium complex infection with inhaled liposomal. Clinical Infectious Diseases. 2019;68(4): III-IV.	Commentaries are excluded from the review scope
European Medicines Agency. Arikayce liposomal 2020 [Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/arikayce-liposomal.	Background only
Golia A, Mahmood BR, Fundora Y, Thornby KA, Chahine EB. Amikacin Liposome Inhalation Suspension for Mycobacterium avium Complex Lung Disease. Sr Care Pharm. 2020;35(4):162-70.	A summary of the available literature rather than systematic review or report of any primary studies based on the information from the abstract.
Jhun BW, Yang B, Moon SM, Lee H, Park HY, Jeon K, et al. Amikacin Inhalation as Salvage Therapy for Refractory Nontuberculous Mycobacterial Lung Disease. Antimicrobial Agents & Chemotherapy. 2018;62(7):07.	Does not meet the PICO criteria, not liposomal amikacin
Jin X, Oh J, Cho JY, Lee S, Rhee SJ. Population Pharmacokinetic Analysis of Amikacin for Optimal Pharmacotherapy in Korean Patients with Nontuberculous Mycobacterial Pulmonary Disease. Antibiotics. 2020;9(11):06.	This paper evaluated treatment naïve patients not treatment resistant therefore outside of PICO
Kang N, Jeon K, Kim H, Kwon OJ, Huh HJ, Lee NY, et al. Outcomes of Inhaled Amikacin-Containing Multidrug Regimens for Mycobacterium abscessus Pulmonary Disease. Chest. 2021;20:20.	This paper evaluated treatment naïve patients not treatment resistant therefore outside of PICO
Kim BG, Kim H, Kwon OJ, Huh HJ, Lee NY, Baek SY, et al. Outcomes of Inhaled Amikacin and Clofazimine-Containing Regimens for Treatment of Refractory Mycobacterium avium Complex Pulmonary Disease. Journal of Clinical Medicine. 2020;9(9):14.	Does not meet the PICO criteria, not liposomal amikacin
Lee H, Sohn YM, Ko JY, Lee SY, Jhun BW, Park HY, et al. Once-daily dosing of amikacin for treatment of Mycobacterium abscessus lung disease. International Journal of Tuberculosis & Lung Disease. 2017;21(7):818-24.	Does not meet the PICO criteria, not liposomal amikacin

Olivier KN, Shaw PA, Glaser TS, Bhattacharyya D, Fleshner M, Brewer CC, et al. Inhaled amikacin for treatment of refractory pulmonary nontuberculous mycobacterial disease. Annals of the American Thoracic Society. 2014;11(1):30-5.	Does not meet the PICO criteria, not liposomal amikacin
Raaijmakers J, Schildkraut J, Hoefsloot W, van Ingen J. The role of amikacin in the treatment of nontuberculous mycobacterial disease. Expert Opinion on Pharmacotherapy. 2021:1-14.	Expert opinion – Non-systematic review of the literature
Rubino CM, Onufrak NJ, van Ingen J, Griffith DE, Bhavnani SM, Yuen DW, et al. Population Pharmacokinetic Evaluation of Amikacin Liposome Inhalation Suspension in Patients with Treatment-Refractory Nontuberculous Mycobacterial Lung Disease. European Journal of Drug Metabolism & Pharmacokinetics. 2021;46(2):277-87.	This paper evaluated pharmacokinetics rather than clinical efficacy therefore outside of PICO. Not a clinical outcomes study
Rubino CM, Onufrak NJ, van Ingen J, Griffith DE, Bhavnani SM, Yuen DW, et al. Correction to: Population Pharmacokinetic Evaluation of Amikacin Liposome Inhalation Suspension in Patients with Treatment-Refractory Nontuberculous Mycobacterial Lung Disease. European Journal of Drug Metabolism & Pharmacokinetics. 2021;46(4):573-4.	Correction to paper above
Safdar A. Aerosolized amikacin in patients with difficult-to-treat pulmonary nontuberculous mycobacteriosis. European Journal of Clinical Microbiology & Infectious Diseases. 2012;31(8):1883-7.	Does not meet the PICO criteria, not liposomal amikacin
Siebinga H, Robb F, Thomson AH. Population pharmacokinetic evaluation and optimization of amikacin dosage regimens for the management of mycobacterial infections. Journal of Antimicrobial Chemotherapy. 2020;75(10):2933-40.	Does not meet the PICO criteria; intervention is low dose IV amikacin
Swenson C, Del Parigi A. Amikacin Liposome Inhalation Suspension as a Treatment Option for Refractory Nontuberculous Mycobacterial Lung Disease Caused by Mycobacterium avium Complex. Mayo Clin Proc. 2020;95(1):201-2.	Letters are excluded from the review scope.
Swenson C, Lapinel NC, Ali J. Clinical Management of Respiratory Adverse Events Associated With Amikacin Liposome Inhalation Suspension: Results From a Patient Survey. Open Forum Infectious Diseases. 2020;7(4):ofaa079.	Brief report of survey, therefore excluded from the review scope
Yagi K, Ishii M, Namkoong H, Asami T, Iketani O, Asakura T, et al. The efficacy, safety, and feasibility of inhaled amikacin for the treatment of difficult-to-treat non-tuberculous mycobacterial lung diseases. BMC Infectious Diseases. 2017;17(1):558.	Does not meet the PICO criteria, not liposomal amikacin
Zhang Y, Hill AT. Amikacin liposome inhalation suspension as a treatment for patients with refractory mycobacterium avium complex lung infection. Expert Review of Respiratory Medicine. 2021;15(6):737-44.	This is not a systematic review; it is an expert review of available literature.

Appendix E Evidence table

For abbreviations see list after table

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Griffith DE, Eagle G, Thomson R, Aksamit TR, Hasegawa N, Morimoto K, Addrizzo-Harris DJ, O'Donnell AE, Marras TK, Flume PA, Loebinger MR, Morgan L, Codecasa LR, Hill AT, Ruoss SJ, Yim J-J, Ringshausen FC, Field SK, Philley JV, Wallace Jr, RJ, van Ingen J, Coulter C, Nezamis J, Winthrop KL, CONVERT Study Group. Amikacin liposome inhalation suspension for treatment-refractory lung disease caused by Mycobacterium avium complex (CONVERT). A prospective, open-label, randomized study. American Journal of Respiratory Critical Care Medicine. 2018. 198(12): 1559-1569 **[CONVERT STUDY]** **Study location** 18 countries in North America, Asia-Pacific region, and Europe; United States (141 patients) and Japan (48 patients) were the largest contributors.	**Adults (18 years or older) with MAC-positive sputum or bronchoscopy cultures within 6 months before screening and at screening** **Inclusion criteria** Off aminoglycoside for at least 1 month at screening' MAC positive while on stable GBT for at least 6 months and either on GBT or had stopped GBT less than 12 months before screening; fulfilling ATS/IDSA criteria for MAC lung disease; evidence of lung pathology on a chest radiograph or chest CT **Exclusion Criteria** CF; active pulmonary tuberculosis; immunodeficiency syndromes, MAC isolates with amikacin resistance on culture screening (MIC 0.64	**Interventions** LAI 590 mg once daily, by inhalation aerosolized via eFlow nebulizer over approximately 14 minutes, in addition to GBT (already prescribed anti-mycobacterial regimen based on the 2007 ATS/IDSA Guidelines) **Comparators** GBT	**Critical outcomes** **Culture conversion** Sputum culture conversion at month 6 • At month 6 LAI + GBT 29% [65 of 224] patients [29.0%] vs GBT alone 8.9% [10 of 112 patients]; adjusted odds ratio, 4.22, 95% CI 2.08 to 8.57; p< 0.001; HR 3.90, 95% CI 2.00 to 7.60 **Health-related QOL** Change in SGRQ score from baseline at 6 months • At month 6 Least squares mean (SE) changes from baseline: LAI + GBT 4.2 (2.0) vs GBT alone 0.4 (2.2); MD [SE], 3.8 [1.6]; 95% CI, 0.67–6.94. **Important outcomes** **6-minute walk test** Change in 6MWT distance from baseline to Month 6. • LAI + GBT (n = 223) -1.5 (-23.6 to 20.6) vs GBT alone (n = 112) 1.5 (-22.2 to 25.3). Least squares MD [SE], -3.0	This study was appraised using the JBI checklist for RCTs 1. Yes 2. No 3. Yes 4. No 5. No 6. Yes 7. Yes 8. Yes 9. Yes 10. Yes 11. Yes 12. Yes 13. Yes **Other comments:** Randomisation used an interactive web response system provided by the sponsor and was stratified by current smoking status and prior GBT. Neither the participants not the investigators were blinded to the treatment being received by the patients. An open-label non-placebo-controlled design was selected to provide a more complete assessment of the LAI safety profile, because the nebulisation of placebo (empty liposomes) may have made it difficult to distinguish adverse effects associated with liposome inhalation from LAI. Patients and investigators

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Study type A randomized, open-label, parallel group, multicentre study **Study aim** A study to evaluate the effectiveness of LAI 590 mg administered once daily when added to GBT in participants with NTM lung infection caused by MAC that were refractory to treatment. **Study dates** May 2015 to July 2018	mg/ml); active malignancies **Total sample size** 336 participants **No. of participants in each treatment group** LAI + GBT (n = 224) GBT alone (n = 112) **Baseline characteristics** The overall mean age of enrolled patients was 64.7 years (SD, 9.8) most were female (69.3%) and white (69.9%). Treatment arms were generally well balanced; however, the LAI + GBT arm had a higher proportion of females (73.7%) than the GBT alone arm (60.7%). Patients in the LAI + GBT arm had a slightly longer median duration of MAC lung disease (4.5 ± 5.5 yrs.) compared with those in the GBT alone arm (3.3 ± 3.9 yrs). Antibiotic combinations in the GBT regimens were similar across treatment arms.		[9.0]; 95% CI, -20.64 to 14.65; P= 0.74 **Safety n (%)** *Any serious TEAE:* • Any serious TEAE: LAI + GBT 45 (20.2) vs GBT 20 (17.9) • Pneumothorax: LAI + GBT 3 (1.3) vs GBT 1 (0.9) • Haemoptysis: LAI + GBT 6 (2.7) vs GBT 5 (4.5) • Pneumonia: LAI + GBT 8 (3.6) vs GBT 2 (1.8) • COPD exacerbation: LAI + GBT 7 (3.1) vs GBT 1 (0.9) • Infective exacerbation of bronchiectasis: LAI + GBT 5 (2.2) vs GBT 3 (2.7) • Dyspnoea: LAI + GBT 3 (1.3) vs GBT 0 • Worsening of MAC infection: LAI + GBT 1 (0.4) vs GBT 2 (1.8) • Pulmonary cavitation: LAI + GBT 0 vs GBT 2 (1.8) • Acute myocardial infarction: LAI + GBT 0 vs GBT 2 (1.8) *TEAE leading to death*: • TEAE leading to death: LAI + GBT, 6 (2.7) vs GBT 5 (4.5) • Respiratory failure: LAI + GBT, 2 (0.9) vs GBT 1 (0.9) • COPD exacerbation: LAI + GBT, 1 (0.4) vs GBT 0 • Pulmonary embolism: LAI + GBT, 1 (0.4) vs GBT 0 • Interstitial lung disease: LAI + GBT, 0 vs GBT 1 (0.9)	were blinded to sputum culture results until the Month 8 visit. In general, demographics and baseline characteristics were well balanced across the LAI + GBT and GBT alone groups, although there was a slight imbalance between groups in the proportion of female patients (73.7 vs 60.7%, respectively) and in the median duration of MAC lung disease (4.5 vs 3.3 years) **Source of funding:** Editorial assistance was provided by Richard Boehme of ediTech Media Ltd and funded by Insmed Incorporated. Financial support for this study was provided by Insmed Incorporated.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			• Lung infection: LAI + GBT, 1 (0.4) vs GBT 0 • Worsening of MAC infection: LAI + GBT, 0 vs GBT 1 (0.9) • Pneumonia: LAI + GBT, 0 vs GBT 1 (0.9) • Cardiogenic shock: LAI + GBT, 0 vs GBT 1 (0.9) • Cachexia: LAI + GBT, 1 (0.4) vs GBT 0 *TEAE leading to discontinuation of LAI:* LAI + GBT 39 (17.5) vs GBT 0 *TEAE leading to discontinuation of GBT:* LAI + GBT 9 (4.0) vs GBT 3 (2.7) *TEAE leading to discontinuation of LAI: LAI and GBT:* LAI + GBT 4 (1.8) vs GBT 0 *Serious TEAE leading to discontinuation of LAI:* LAI + GBT 12 (5.4) vs GBT 0 *TEAE: pulmonary exacerbation:* LAI + GBT, 57 (25.6) vs GBT 18 (16.1) *Serious TEAE: pulmonary exacerbation:* LAI + GBT 20 (9.0) vs GBT 8 (7.1) *TEAE: ototoxicity-related:* • Tinnitus: LAI + GBT 17 (7.6) vs GBT 1 (0.9) • Dizziness: LAI + GBT 14 (6.3) vs GBT 3 (2.7) • Hearing loss*: LAI + GBT 10 (4.5) vs GBT 7 (6.3) • Balance disorder: LAI + GBT 3 (1.3) vs GBT 0	

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			• Vertigo: LAI + GBT 2 (0.9) vs GBT 0 • Presyncope: LAI + 1 (0.4) vs GBT 0 *TEAE in >10% of patients in either arm:* • Dysphonia: LAI + GBT 102 (45.7) vs GBT 1 (0.9) • Cough 83: LAI + GBT -37.2 vs GBT 17 (15.2) • Dyspnoea: LAI + GBT 48 (21.5) vs GBT 10 (8.9) • Haemoptysis: LAI + GBT 39 (17.5) vs GBT 15 (13.4) • Fatigue: LAI + GBT 36 (16.1) vs GBT 8 (7.1) • Diarrhoea: LAI + GBT 28 (12.6) vs GBT 5 (4.5) • Nausea: LAI + GBT 25 (11.2) vs GBT 4 (3.6) • Oropharyngeal pain: LAI + GBT 24 (10.8) vs GBT 2 (1.8)	
Griffith DE, Thomson R, Flume PA, Aksamit TR, Field SK, Addrizzo-Harris DJ, et al. Amikacin Liposome Inhalation Suspension for Refractory Mycobacterium avium Complex Lung Disease: Sustainability and Durability of Culture Conversion and Safety of Long-term Exposure. Chest. 2021;19:19. **Study location**	**Inclusion criteria** Patients who met protocol-defined culture conversion by month 6 (i.e., three consecutive monthly negative sputum culture results for MAC) in the original CONVERT primary analysis. **Exclusion Criteria** None reported **Total sample size** 75 patients	**Interventions** LAI 590 mg once daily, by inhalation aerosolized via eFlow nebulizer over approximately 14 minutes, in addition to their already prescribed anti-mycobacterial regimen (based on the 2007 ATS/IDSA Guidelines) **Comparators** Continued on already prescribed anti-mycobacterial regimen (based on the 2007 ATS/IDSA Guidelines)	Patients who were culture negative at 8 months review were followed up for up to 16 months EOT. They were followed up again after 3 months off treatment and then again after 12 months off treatment. **Critical outcomes** **Culture conversion** Sustained conversion at 12 months of treatment • **ITT Analysis**: LAI + GBT 41/224 (18.3%) vs GBT alone 3/112 (2.7%), p< .0.0001	This study was appraised using the JBI checklist for RCTs 1. Yes 2. No 3. Yes 4. No 5. No 6. Yes 7. Yes 8. Yes 9. Yes 10. Yes 11. Yes 12. Yes

Study details	Population	Interventions	Study outcomes	Appraisal and funding
127 sites in North America, Europe, Australasia, and Asia **Study type** **Follow-up to randomized, open-label, parallel, multicentre study** **Study aim** The study aim was to evaluate whether, in patients who achieved culture conversion by month 6 in the CONVERT study, conversion was sustained and durable and whether there are any additional safety issues associated with a full treatment course of 12 months after conversion. **Study dates** May 2015 to April 2019	**No. of participants in each treatment group** LAI + GBT (n = 65) GBT alone (n = 10) **Baseline characteristics** Patients who achieved conversion were predominantly White and female without a history of smoking. At baseline, the median duration of NTM lung disease in the converter group was 4.0 yrs (IQR 2.0 to 7.0) for patients treated with LAI + GBT and 3.0 years (IQR 1.8 to 6.0) for patients treated with GBT alone; 89.2% (n = 58/65) and 90.0% (n = 9/10) were receiving a multidrug regimen at baseline.		• **Converter Analysis**: LAI + GBT 41/65 (63.1%) vs GBT alone 3/10 (30.0%), p=0.0644 Sustained conversion at end of treatment • **ITT Analysis**: LAI + GBT 52/224 (23.2%) vs GBT alone 3/112 (2.7%), p< 0.0001 • **Converter Analysis**: LAI + GBT 52/65 (80.0%) vs GBT alone 3/10 (30.0%), p= 0.0014 Durable conversion at 3-months follow-up *Full 12 months of post-conversion treatment group:* • **ITT Analysis**: LAI + GBT 36/224 (16.1%) vs GBT alone 0/112, p< 0.0001 • **Converter Analysis**: LAI + GBT 36/65 (55.4%) vs GBT alone 0/10, p=0.0017 *Conversion regardless of treatment duration* • **ITT Analysis**: LAI + GBT 41/224 (18.3%) vs GBT alone 0/112, p< 0.0001 • **Converter Analysis**: LAI + GBT 41/65 (63.1%) vs GBT alone 0/10, p= 0.0002 Negative culture results 12 months after treatment *Full 12 months of post-conversion treatment group*	13. Yes **Other comments:** Randomization in the initial CONVERT study used an interactive web response system provided by the sponsor and was stratified by current smoking status and prior GBT. Randomisation was not preserved in the exploratory converter analysis, and covariate imbalances may have been present that were not accounted for between the cohorts. An open-label non-placebo-controlled design was selected to provide a more complete assessment of the LAI safety profile, because the nebulization of placebo (empty liposomes) may have made it difficult to distinguish adverse effects associated with liposome inhalation from LAI. Patients and investigators were blinded to sputum culture results until the Month 8 visit 89% of patients in the LAI + GBT arm completed the study, but only 50% of patients in the GBT alone arm completed the study. The lower incidence of TEAE onset after 8 months may be related to early study withdrawals. **Source of funding:** Editorial assistance was provided by Richard Boehme of ediTech Media Ltd and funded by Insmed Incorporated. Financial support for

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			• **ITT Analysis:** LAI + GBT 30 (13.4%) vs GBT alone 0, p< 0.0001 • **Converter Analysis**: LAI + GBT 30/65 (46.2%) vs GBT alone 0/10, p< 0.0001 *Conversion regardless of treatment duration* • **ITT Analysis:** LAI + GBT 35/224 (15.6%) vs GBT alone 0/112, p< 0.0001 • **Converter Analysis**: LAI + GBT 35/65 (53.8%) vs GBT alone 0/10, p< 0.0001 **Important outcomes** **6-minute walk test** • Mean change from baseline to 3 months (after 12-month treatment phase) LAI + GBT 83.4 (SD 20.9 ± 83.4 m; p= 0.096); GBT only group not calculable **Adherence** Adherence among the LAI + GBT arm who achieved conversion (n = 65), 81.5% of patients showed ≥ 80% treatment adherence. **Safety** Any serious TEAE: • at EOT, LAI + GBT 6 (9.2) vs GBT alone 6 (60.0) • On or Before Month 8, LAI + GBT 4 (6.2) vs GBT alone 1 (10.0) • After Month 8, LAI + GBT 4 (6.2) vs GBT alone 5 (50.0)	this study was provided by Insmed Incorporated.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			COPD exacerbation: • at EOT, LAI + GBT 1 (1.5) vs GBT alone 2 (20.0) • On or Before Month 8, LAI + GBT 1 (1.5) vs GBT alone 0 • After Month 8, LAI + GBT 0 vs GBT alone 2 (20.0) Drug hypersensitivity: • at EOT, LAI + GBT 1 (1.5) vs GBT alone 0 • On or Before Month 8, LAI + GBT 1 (1.5) vs GBT alone 0 • After Month 8, LAI + GBT 0 vs GBT alone 0 Infective exacerbation of bronchiectasis: • at EOT, LAI + GBT 1 (1.5) vs GBT alone 1 (10.0) • On or Before Month 8, LAI + GBT — vs GBT alone 1 (10.0) • After Month 8, LAI + GBT 1 (1.5) vs GBT alone 0 Infective exacerbation of COPD: • at EOT, LAI + GBT 1 (1.5) vs GBT alone 0 • On or Before Month 8, LAI + GBT 1 (1.5) vs GBT alone 0 • After Month 8, LAI + GBT 0 vs GBT alone 0 Lung adenocarcinoma: • at EOT, LAI + GBT 1 (1.5) vs GBT alone 0 • On or Before Month 8, LAI + GBT 0 vs GBT alone 0 • After Month 8, LAI + GBT 1 (1.5) vs GBT alone 0	

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			Lung infection pseudomonal: • at EOT, LAI + GBT 1 (1.5) vs GBT alone 0 • On or Before Month 8, LAI + GBT 0 vs GBT alone 0 • After Month 8, LAI + GBT 1 (1.5) vs GBT alone 0 Pneumatosis intestinalis: • at EOT, LAI + GBT 1 (1.5) vs GBT alone 0 • On or Before Month 8, LAI + GBT 0 vs GBT alone 0 • After Month 8, LAI + GBT 1 (1.5) vs GBT alone 0 Pneumonia: • at EOT, LAI + GBT 1 (1.5) vs GBT alone 0 • On or Before Month 8, LAI + GBT 1 (1.5) vs GBT alone 0 • After Month 8, LAI + GBT 0 vs GBT alone 0 Pneumothorax: • at EOT, LAI + GBT 1 (1.5) vs GBT alone 0 • On or Before Month 8, LAI + GBT 1 (1.5) vs GBT alone 0 • After Month 8, LAI + GBT 0 vs GBT alone 0	
Olivier KN, Griffith DE, Eagle G, McGinnis JP, 2nd, Micioni L, Liu K, et al. Randomized Trial of Liposomal Amikacin for Inhalation in Nontuberculous Mycobacterial Lung Disease. American Journal	Adults with PNTM disease as defined by the American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) **Inclusion criteria**	**Interventions** *Double-blind phase:* LAI at a dose of 590 mg via a customized investigational eFlow Technology nebulizer (PARI Pharma GmbH, Starnberg, Germany) added	Patients were followed up for 84 days during the double-blind phase, for another 84 days for the open-label phase and then, after a 28 day follow-up from end of study, patients were followed up for a further 12 months on standard of care. **Critical outcomes**	This study was appraised using the JBI checklist for RCTs 1. Unclear 2. Unclear 3. Yes 4. Yes 5. Yes 6. Unclear

Study details	Population	Interventions	Study outcomes	Appraisal and funding
of Respiratory & Critical Care Medicine. 2017;195(6):814-23. **Study location** 19 sites in North America **Study type** Phase 2 placebo-controlled double-blind RCT, followed by open-label extension study **Study aim** The study aim was to evaluate the efficacy and tolerability of a LAI in patients with treatment-refractory PNTM disease **Study dates** April 2012 to June 2015	Ongoing ATS/IDSA guidelines–based multidrug treatment for at least 6 months prior to screening, and persistently positive cultures for *M. avium* complex or *M. abscessus*. **Exclusion Criteria** Current smoking; FEV_1 less than 30% of predicted; clinically significant cardiac, pulmonary, hepatic, or renal disease; systemic immune deficiency; and malignancy. Patients were not excluded because of amikacin resistance **Total sample size** *Double-blind phase:* 89 patients *Open-label phase:* 78 patients **No. of participants in each treatment group** **Double blind phase:** LAI + SOC (n = 44) Placebo + SOC (n = 45) *Open-label phase* LAI + SOC (n = 35) Placebo + SOC (n = 43)	to ongoing, stable multidrug regimen. *Open-label phase:* LAI at a dose of 590 mg via a customized investigational eFlow Technology nebulizer (PARI Pharma GmbH, Starnberg, Germany) added to ongoing, stable multidrug regimen. **Comparators** *Double-blind phase:* Empty liposome via a customized investigational eFlow Technology nebulizer (PARI Pharma GmbH, Starnberg, Germany) added to ongoing, stable multidrug regimen. *Open-label phase:* Nil	**Culture conversion** Change in semi-quantitative mycobacterial culture results from baseline to day 84 • LAI SD 2.0 vs Placebo SD 1.5, p= 0.072. NS Number of subjects with negative NTM culture • At day 84: LAI 32% [14/44] vs 9% [4/45]; p= 0.006 • At day 168 (after open-label phase: LAI 11/35 vs placebo 4/43 • At 28-day end of study follow-up: LAI 11/35 vs placebo 3/43 Time to negative NTM culture • During the 84-day double-blind treatment phase: HR 5.68, 95% CI (1.25 to 25.79), p= 0.0129. **Health-related quality of life** • Change from baseline to Day 84 in SGRQ, QOL, QOL bronchiectasis, and NTM module scores: LAI (n = 36) -7.935 (SD 14.1998) vs placebo (n = 36) -2.829 (13.6733). **Important outcomes** **6-minute walk test**	7. Yes 8. Yes 9. Yes 10. Yes 11. Yes 12. Yes 13. Yes **Other comments:** The first phase of this study was reported to be a double-blind placebo controlled RCT but the method of randomisation and allocation concealment was not reported. Apart from QOL (which was self-reported), it is not clear whether assessments were carried out by the same treating physician, whether assessment was done independently and how outcome assessors were blinded to treatment assignment. The study included both CF (19%) and non-CF patients. It also included a mixture of patients with MAC (64%) and Mabs. Patients in both arms of the double-blind phase were well balanced. Apart from QOL, the outcomes for non-CF and MAC infected patients were not reported separately; therefore, care should be taken in applying these results to a more specific population of non-CF MAC PNTM disease patients. 9 patients in that LAI arm discontinued study drug in the double-blind phase including 1 death (albeit investigators reported the death as unrelated to the trial). Another 9 patients discontinued LAI treatment during the open-label phase. Efficacy and safety

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	Baseline characteristics **Mean age 58.5 (SD, ±15.8) years** 19% had CF, 64% had predominantly *M. avium complex* infection, and 36% had predominantly *M. abscessus* infection. 72 (approximately 81%) of 89 patients had been treated with a standard multidrug regimen for NTM for at least 12 months, and 42 [47%] of 89 had been treated for more than 24 months prior to randomization. At baseline, no notable between-group differences in lung function or percentage of patients with negative sputum cultures were observed. Because baseline SQS scores were not stratified, imbalances were noted, with higher SQS mycobacterial growth (>21) at baseline in a greater proportion of patients in the placebo group (25 [55.6%] of 45) than in the LAI group (19 [43.2%] of 44). However, the imbalance was not statistically		Improvement in Mean (SD) distance walked in the 6-minute-walk test • At 84 days, LAI +20.6 (SD 62.4) m versus -25.0 (100.2) m, p= 0.017 • At 168 days end of open-label phase: prior-LAI (n = 35), +42.4 (105.9) m vs prior-placebo (n = 43), -28.4 (88.1) m, MD 70.8 m, p= 0.012. **Lung function** **Increase in FEV_1 per cent predicted at 84 days,** • LAI 0.3 ± 5.5% vs placebo 0.16 ± 6.0% (p = NR) **Safety** Serious adverse events *Double-blind phase:* • LAI 8/44 (18.2%) vs Placebo 4/45 (8.9%). *Open label phase:* • LAI 5/35 (14.3%) vs Placebo 5/42 (11.6%). Presence of serious TEAE (grade 3, 4 or 5) *Double blind phase:* • Grade 3: severe: LAI 4(9.1%) vs placebo 5 (11.1%) • Grade 4 life-threatening: 0 vs 0 • Grade 5 death: LAI 1(2.3%) vs placebo 0	analyses were performed using the modified intent-to-treat population (mITT) defined as all randomized patients who received at least one 1 dose of study drug. **Source of funding:** This study was supported by Insmed Incorporated, and in part by the intramural research programs of the National Institute of Allergy and Infectious Diseases (NIAID) (Cooperative Research and Development Agreement 2011-0473) and the NHLBI and the National Institutes of Health (NIH).

Study details	Population	Interventions	Study outcomes	Appraisal and funding
	significant. Antibiotic combinations in the GBT regimens were similar across treatment arms.		• TEAEs leading to treatment discontinuation: LAI 7 (15.9) vs placebo 0 • Audiovestibular TEAEs: 5 (11.4%) vs 5 (11.1%) • Renal TEAEs 1 (2.3%) vs 0 *Open label phase:* • Grade 3: severe: LAI 4(9.1%) vs placebo 5 (11.1%) • Grade 4 life-threatening: 0 vs 0 • Grade 5 death: 1(2.3%) vs 0 • TEAEs leading to treatment discontinuation: 7 (15.9%) vs 0 • Audiovestibular TEAEs: 2 (5.7%) vs 2 (2.7%) • Renal TEAEs 1 (2.9%) vs 0	
Winthrop KL, Flume PA, Thomson R, Mange KC, Yuen DW, Ciesielska M, et al. Amikacin Liposome Inhalation Suspension for Mycobacterium avium Complex Lung Disease: A 12-Month Open-Label Extension Clinical Trial. Annals of the American Thoracic Society. 2021;18(7):1147-57. **Study location** 127 sites in North America, Europe, Australasia, and Asia **Study type** Open label cohort study	**Inclusion criteria** Treatment refractory MAC lung disease who were enrolled in the CONVERT study and did not meet the primary endpoint of culture conversion by Month 6 or had recurrent MAC infection (positive MAC culture after conversion) by Month 6 (confirmed at Month 8 when sputum data were unblinded). **Exclusion Criteria** **Nil**	**Interventions** Once daily LAI + GBT **Comparators** Nil	**Critical outcomes** **Culture conversion** **LAI-Naïve cohort:** cumulative sputum culture conversion in 26.7% of patients (n = 24) by Month 6, increasing to 33.3% (n = 30) by Month 12 **Prior-LAI cohort**: cumulative sputum culture conversion in 9.6% of patients (n=7) by Month 6 (up to 14 months of total LAI exposure), increasing to 13.7% (n = 10) by month 12 (up to 20 months of total LAI exposure) **Important outcomes** **Safety** • Any TEAE: LAI-naïve 90 (100%) vs prior-LAI 68 (93.2%)	This study was appraised using the JBI Critical Appraisal Checklist for Cohort Studies. 1. Yes 2. Yes 3. Yes 4. Yes 5. No 6. Yes 7. Yes 8. Yes 9. Yes 10. Yes 11. Yes **Other comments:** No attempt was reported to deal with confounding factors. For example, at the investigator's discretion, brief interruptions of LAI were allowed to

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Study aim To evaluate the 12-month safety, tolerability, and efficacy of once-daily LAI + GBT. **Study dates** February 2016, to October 2018	**Total sample size** 163 **No. of participants in each treatment group** LAI naïve cohort (n = 90) Prior-LAI cohort (n = 73) **Baseline characteristics** **LAI naïve**: The mean (standard deviation [SD]) age of patients in the LAI-naïve cohort was 64.8 (10.3) years; most were female (60.0%) and white (66.7%), with a median NTM lung disease duration of 3.7 (range 0.8 to 19.6) years. **Prior-LAI**: The mean (SD) age of patients in the prior-LAI cohort was 64.9 (9.12) years; most were female (69.9%) and white (56.2%), with a median NTM lung disease duration of 5.4 (range 0.8 to 33.2) years		• Grade 3: severe: LAI-naïve 29 (32.2%) vs prior-LAI 13 (17.8%) • Grade 4: life threatening LAI-naive 3 (3.3%) vs prior-LAI 1 (1.4%) • Grade 5: death: LAI-naive 4 (4.4%) vs prior-LAI 2 (2.7%) • TEAE: pulmonary exacerbation: LAI-naive 29 (32.2%) vs prior-LAI 22 (30.1%) • TEAE leading to discontinuation of LAI: LAI-naive 22 (24.4%) vs prior-LAI 6 (8.2%) • TEAE leading to discontinuation of GBT: LAI-naive 8 (8.9%) vs prior-LAI 4 (5.5%) • TEAE leading to discontinuation of LAI and GBT: LAI-naive 5 (5.6%) vs prior-LAI (1.4%) • TEAE leading to death: LAI-naive 4 (4.4%) prior-LAI 2 (2.7%) • COPD exacerbation: LAI-naive 1 (1.1%) vs prior-LAI 1 (1.4%) • COPD exacerbation: LAI-naive 4 (4.4%) vs prior-LAI 1 (1.4%) Serious TEAE occurring in >3% patients: LAI-naive vs prior-LAI • Pneumonia: LAI-naive 4 (4.4%) vs prior-LAI 3 (4.1%) • Serious TEAE: pulmonary exacerbation: LAI-naive 17 (18.9%) vs prior-LAI (9.6%)	manage adverse respiratory events. However, there was no report of how many patients this affected nor any analysis of how this could have affected the results. All patients received at least one dose of LAI. The median duration of treatment was 11.6 (range 0 to 13) months; 62.2% (n = 56) completed the protocol-defined 12-month treatment phase and 64.4% (n = 58) completed the end-of-study visit. Reasons for study discontinuation included AEs (22.2% [n = 20]) and withdrawal by patient (8.9% [n = 8]). Consistent with the design of the study and potential for enrolment bias, patients who tolerated LAI in CONVERT may have been more likely to enrol in INS-312. With up to 20 months of LAI exposure. Limitations include the non-randomized, open-label extension design with no comparator arm. Patients had different durations of post-conversion treatment, limiting assessments of response sustainability. The relatively small size of the cohorts limited potential sub-analyses and extrapolation to different subgroups of patients with refractory MAC lung disease. The inherent high variability in 6MWT distance among patients with refractory MAC lung disease found in CONVERT (31) and INS-312 makes it difficult to draw conclusions regarding potential functional improvement with treatment.

Study details	Population	Interventions	Study outcomes	Appraisal and funding
			• Serious TEAE leading to discontinuation of LAI: LAI-naive 9 (10.0%) vs prior-LAI (4.1%) • Bronchospasm: LAI-naive 2 (2.2%) vs prior-LAI 10 (13.7%) • Dyspnoea: LAI-naive 16 (17.8%) vs prior-LAI (12.3%) • Wheezing: LAI-naive 5 (5.6%) vs prior-LAI 1 (1.4%) • Haemoptysis: LAI-naive 11 (12.2%) vs prior-LAI 11 (5.1%)	**Source of funding:** Editorial assistance was provided by Richard Boehme of ediTech Media Ltd and funded by Insmed Incorporated. Financial support for this study was provided by Insmed Incorporated.

Abbreviations
6MWT-6 minute walk test; ATS-American Thoracic Society; CF-Cystic fibrosis; CI-Confidence Interval; COPD-Chronic Obstructive Pulmonary Disease; CT-Computer Tomography; EOT-End of Treatment; FEV1-Force Expiratory Volume in 1 second; GBT-Guideline-Based Treatment; HR-Hazard Ratio; IQR-Inter Quartile Range; ITT-Intention to Treat; LAI-Liposomal Amikacin Inhaled; m-metres; MAC-Mycobacterium Avium Complex; MD-Mean Difference; mg-milligram; MIC-Minimum Inhibitory Concentration; n-number; NHLBI-National Heart, Lung, and Blood Institute; NIAID-National Institute of Allergy and Infectious Diseases; NIH-National Institute for Health; NS-Not Significant; NTM-Non-Tuberculosis Mycobacterium; OR-Odds Ratio; PD-Pulmonary Disease; PNTM-Pulmonary Non-Tuberculosis Mycobacterium; QOL-Quality of Life; RC'-Randomised Controlled Trial; SD-Standard Deviation; SGRQ-Saint George's Respiratory Questionnaire; SOC-Standard of care; SQS-semiquantitative scale; TEAE-treatment-emergent adverse event, yr-year

Appendix F Quality appraisal checklists

JBI Critical Appraisal Checklist for RCTs

1. Was true randomisation used for assignment of participants to treatment groups?
2. Was allocation to treatment groups concealed?
3. Were treatment groups similar at the baseline?
4. Were participants blind to treatment assignment?
5. Were those delivering treatment blind to treatment assignment?
6. Were outcomes assessors blind to treatment assignment?
7. Were treatment groups treated identically other than the intervention of interest?
8. Was follow-up complete and if not, were differences between groups in terms of their follow-up adequately described and analysed?
9. Were participants analysed in the groups to which they were randomised?
10. Were outcomes measured in the same way for treatment groups?
11. Were outcomes measured in a reliable way?
12. Was appropriate statistical analysis used?
13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomisation, parallel groups) accounted for in the conduct and analysis of the trial?

JBI Critical Appraisal Checklist for Cohort Studies

1. Were the two groups similar and recruited from the same population?
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?
3. Was the exposure measured in a valid and reliable way?
4. Were confounding factors identified?
5. Were strategies to deal with confounding factors stated?
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?
7. Were the outcomes measured in a valid and reliable way?
8. Was the follow-up time reported and sufficient to be long enough for outcomes to occur?
9. Was follow-up complete, and if not, were the reasons to loss to follow-up described and explored?
10. Were strategies to address incomplete follow-up utilised?
11. Was appropriate statistical analysis used?

Appendix G GRADE profiles

Table 2a. In patients of all ages with non-tuberculous mycobacterial pulmonary disease (NTM PD) caused by mycobacterium avium complex (MAC) with limited treatment options who do not have cystic fibrosis, what is the clinical effectiveness and safety of nebulised liposomal amikacin with guideline-based therapy (GBT) compared with no treatment with nebulised liposomal amikacin?

Outcome measure, units and timepoint in study (for continuous outcomes indicate if benefit is indicated by higher or lower result)									
QUALITY					**Summary of findings**			**IMPORTANCE**	**CERTAINTY**
					No of patients		**Effect**		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**LAI + GBT**	**Placebo + GBT**	**Result**		
Culture Conversion (2 randomised studies, one open-label follow-up study)									
Change in semi-quantitative mycobacterial culture results from baseline to day 84									
1 double-blinded RCT Olivier et al 2017	No serious limitations	Serious indirectness[1]	No serious inconsistency	Not calculable	44	45	LAI SD 2.0 vs placebo SD 1.5, p= 0.072. NS	Critical	Moderate
Number of subjects with negative NTM culture at 84 days, n (%) (higher value indicates benefit)									
1 double-blinded RCT Olivier et al 2017	No serious limitations	Serious indirectness[1]	No serious inconsistency	Not calculable	44	45	LAI 14/44 (32%) vs placebo 4/45 (9%), p= 0.006	Critical	Moderate
Number of subjects with negative NTM culture at 168 days (after open-label phase), n (%) (higher value indicates benefit)									
Open label phase following 1 double-blinded RCT Olivier et al 2017	No serious limitations	Very serious indirectness[2]	No serious inconsistency	Not calculable	35	43	Prior LAI‡ 11/35 (31%) vs prior placebo‡ 4/43 (9%)	Critical	Low

Number of subjects with negative NTM culture at 196 days (28-day end of study follow-up), n (%) (higher value indicates benefit)									
Open label phase following 1 double-blinded RCT Olivier et al 2017	No serious limitations	Very serious indirectness[2]	No serious inconsistency	Not calculable	35	43	Prior LAI‡ 11/35 (31%) vs prior placebo‡ 3/43 (7%)	Critical	Low
Time to negative NTM culture at 84 days, HR (95% CI) (lower value indicates benefit)									
1 double-blinded RCT Olivier et al 2017	No serious limitations	Serious indirectness[1]	No serious inconsistency	No serious imprecision	44	45	HR 5.68, 95% CI 1.25 to 25.79, p= 0.0129	Critical	Moderate
Sputum culture conversion at 6 months, n (%), OR, HR (higher value indicates benefit)									
1 open-label RCT Griffith et al 2018	No serious limitations	No serious indirectness	No serious inconsistency	No serious imprecision	224	112	LAI + GBT 65/224 (29%) vs GBT alone 10/112 (8.9%); adjusted OR 4.22, 95% CI (2.08 to 8.57), p< 0.001 HR 3.90, 95% CI 2.00 to 7.60	Critical	High
Sustained conversion at end of treatment (12 to 16 months) (ITT analysis), n (%) (higher value indicates benefit)									
1 open label follow-up study Griffith et al 2021	No serious limitations	Serious indirectness[3]	No serious inconsistency	Not calculable	224	112	LAI + GBT 52/224 (23.2%) vs GBT alone 3/112 (2.7%), p< 0.0001	Critical	Moderate
Sustained conversion at end of treatment (12 to 16 months) (converter analysis), n (%) (higher value indicates benefit)									
1 open label follow-up study Griffith et al 2021	No serious limitations	Serious indirectness[3]	No serious inconsistency	Not calculable	65	10	LAI + GBT 52/65 (80.0%) vs GBT alone 3/10 (30.0%), p=0.0014	Critical	Moderate

Sustained conversion at 12 months of treatment (ITT analysis), n (%) (higher value indicates benefit)									
1 open label follow-up study Griffith et al 2021	No serious limitations	Serious indirectness[3]	No serious inconsistency	Not calculable	224	112	LAI + GBT 41/224 (18.3%) vs GBT alone 3/112 (2.7%), p< 0.0001	Critical	Moderate
Sustained conversion at 12 months of treatment (converter analysis), n (%) (higher value indicates benefit)									
1 open label follow-up study Griffith et al 2021	No serious limitations	Serious indirectness[3]	No serious inconsistency	Not calculable	65	10	LAI + GBT 41/65 (63.1%) vs GBT alone 3/10 (30.0%), p=0.0644	Critical	Moderate
Durable conversion at 3 months follow-up: full 12 months post conversion treatment (ITT analysis), n (%) (higher value indicates benefit)									
1 open label follow-up study Griffith et al 2021	No serious limitations	Serious indirectness[3]	No serious inconsistency	Serious imprecision[4]	224	112	LAI + GBT 36/224 (16.1%) vs GBT alone 0/112, p< 0.0001	Critical	Low
Negative culture results 12 months after treatment: full 12 months post conversion treatment (converter analysis), n (%) (higher value indicates benefit)									
1 open label follow-up study Griffith et al 2021	No serious limitations	Serious indirectness[3]	No serious inconsistency	Serious imprecision[4]	65	10	LAI + GBT 30/65 (13.4%) vs GBT alone 0/10, p< 0.0001	Critical	Low
Negative culture results 12 months after treatment: conversion regardless of treatment duration (ITT analysis), n (%) (higher value indicates benefit)									
1 open label follow-up study Griffith et al 2021	No serious limitations	Serious indirectness[3]	No serious inconsistency	Serious imprecision[4]	224	112	LAI + GBT 30/65 (46.2%) vs GBT alone 0/10, p< 0.0001	Critical	Low

Negative culture results 12 months after treatment: conversion regardless of treatment duration (converter analysis), n (%) (higher value indicates benefit)									
1 open label follow-up study Griffith et al 2021	No serious limitations	Serious indirectness[3]	No serious inconsistency	Serious imprecision[4]	65	10	LAI + GBT 35/65 (53.8%) vs GBT alone 0/10, p< 0.0001	Critical	Low
Negative culture results 12 months after treatment: full 12 months post-conversion treatment (ITT analysis), n (%) (higher value indicates benefit)									
1 open label follow-up study Griffith et al 2021	No serious limitations	Serious indirectness[3]	No serious inconsistency	Serious imprecision[4]	224	112	LAI + GBT 36/224 (16.1%) vs GBT alone 0/112, p<0.0001	Critical	Low
Durable conversion at 3-month follow-up: full 12 months post-conversion treatment (converter analysis), n (%) (higher value indicates benefit)									
1 open label follow-up study Griffith et al 2021	No serious limitations	Serious indirectness[3]	No serious inconsistency	Serious imprecision[4]	65	10	LAI + GBT 36/65 (55.4%) vs GBT alone 0/10, p=0.0017	Critical	Low
Durable conversion at 3-month follow-up: conversion regardless of treatment duration (ITT analysis), n (%) (higher value indicates benefit)									
1 open label follow-up study Griffith et al 2021	No serious limitations	Serious indirectness[3]	No serious inconsistency	Serious imprecision[4]	224	112	LAI + GBT 41/224 (18.3%) vs GBT alone 0/112, p<0.0001	Critical	Low
Durable conversion at 3-month follow-up: conversion regardless of treatment duration (converter analysis), n (%) (higher value indicates benefit)									
1 open label follow-up study Griffith et al 2021	No serious limitations	Serious indirectness[3]	No serious inconsistency	Serious imprecision[4]	65	10	LAI + GBT 41/65 (63.1%) vs GBT alone 0/10, p= 0.0002	Critical	Low

Health-related quality of life (Two RCTS)									
Change from baseline in mean (SD) St George's Respiratory Questionnaire QOL, QOL bronchiectasis, and NTM module scores at 84 days (higher value indicates benefit)									
1 double-blinded RCT Olivier et al 2017	No serious limitations	Serious indirectness[1]	No serious inconsistency	Not calculable	36	36	LAI -7.935 (SD 14.1998) vs placebo -2.829 (SD 13.6733)	Critical	Moderate
Least Square Mean change from baseline in St George's Respiratory Questionnaire score at 6 months, LSMD (SE) (higher positive values are favourable)									
1 open-label RCT Griffith et al 2018	Serious limitations[5]	No serious indirectness	No serious inconsistency	Serious imprecision [6]	224	112	LSM change from baseline LAI + GBT 4.2 (2.0) vs GBT alone 0.4 (2.2) LSMD [SE] 3.8 [1.6], 95% CI 0.67 to 6.94	Critical	Low
6-minute walk test (two RCTs and one open-label follow-up study)									
Change from baseline in mean distance walked in the 6-minute-walk test at 84 days, m (SD) (higher values are favourable)									
1 double-blinded RCT Olivier et al 2017	No serious limitations	Serious indirectness[1]	No serious inconsistency	Not calculable	44	45	LAI +20.6 (SD 62.4) m vs placebo -25.0 (100.2) m, p=0.017	Important	Moderate
Change from baseline in mean distance walked in the 6-minute-walk test at 168 days, m (SD) (higher values are favourable)									
Open-label follow up phase of 1 double-blinded RCT Olivier et al 2017	Serious limitations[5]	Very serious indirectness[2]	No serious inconsistency	Not calculable	35	43	Prior-LAI‡ +42.4 (SD 105.9) m vs prior placebo$^{\Psi}$ -28.4 (SD 88.1)m MD 70.8m, p= 0.012	Important	Very low
Change from baseline in mean 6-minute-walk test distance at month 6, m (higher values are favourable)									
1 open-label RCT Griffith et al 2018	No serious limitations	No serious indirectness	No serious inconsistency	Serious imprecision[7]	223	112	LAI + GBT -1.5, 95% CI (-23.6 to 20.6) vs GBT alone 1.5, 95% CI (-22.2 to 25.3). Least squares MD [SE] -3.0 [9.0], 95% CI -20.64 to 14.65, p=0.74	Important	Low

Change from baseline in mean distance walked in the 6-minute-walk test at 3 months from EOT, mean (SD) (higher values are favourable)									
1 open-label follow-up study Griffith et al 2021	Serious limitations[5]	Serious indirectness[3]	No serious inconsistency	Not calculable	47	1	LAI + GBT 20.9 (83.4) m, p = 0.096 GBT only group not calculable	Important	Low
Adherence to treatment (one open-label follow-up study)									
Adherence to treatment: converter analysis, % ≥ 80% treatment adherence (higher values are favourable)									
1 open-label follow-up study Griffith et al 2021	Serious limitations[5]	Serious indirectness[3]	No serious inconsistency	Not calculable	65	10	LAI + GBT 81.5% vs GBT only not reported	Important	Low
Lung Function (one RCT)									
Increase in FEV_1 percent predicted at 84 days, % (higher values are favourable)									
1 double-blinded RCT Olivier et al 2017	No serious limitations	Serious indirectness[1]	No serious inconsistency	Not calculable	44	45	LAI 0.32 ± 5.5%[γ] vs placebo 0.16 ± 6.0% (p-value not reported)	Important	Moderate
Safety (two RCTs and one open-label follow-up study)									
Serious adverse events at 84 days, n (%) (lower values are favourable)									
1 double-blinded RCT Olivier et al 2017	No serious limitations	Serious indirectness[1]	No serious inconsistency	Not calculable	44	45	LAI 8/44 (18.2%) vs placebo 4/45 (8.9%)	Important	Moderate
Serious adverse events at 168 days, n (%) (lower values are favourable)									
Open phase following 1 double-	Serious limitations[5]	Very serious indirectness[2]	No serious inconsistency	Not calculable	35	42	Prior LAI[‡] 5/35 (14.3%) vs prior placebo 5/42 (11.6%)	Important	Very low

blinded RCT Olivier et al 2017									
Presence TEAE - grade 3 at 84 days, n (%) (lower values are favourable)									
1 double-blinded RCT Olivier et al 2017	No serious limitations	Serious indirectness[1]	No serious inconsistency	Not calculable	44	45	LAI 4/44 (9.1%) vs placebo 5/45 (11.1%)	Important	Moderate
Presence TEAE - grade 3 at 168 days, n (%) (lower values are favourable)									
Open phase following 1 double-blinded RCT Olivier et al 2017	Serious limitations[5]	Very serious indirectness[2]	No serious inconsistency	Not calculable	35	42	Prior LAI‡ 4/35 (11.4%) vs prior-placebo 8/42 (18.6%)	Important	Low
Presence of TEAE - grade 4 at 84 days, n (%) (lower values are favourable)									
1 double-blinded RCT Olivier et al 2017	No serious limitations	Serious indirectness[1]	No serious inconsistency	Serious imprecision [4]	44	45	LAI 0 (0%) vs placebo 0 (0%)	Important	Low
Presence of TEAE - grade 4 at 168 days, n (%) (lower values are favourable)									
Open phase following 1 double-blinded RCT Olivier et al 2017	No serious limitations	Very serious indirectness[2]	No serious inconsistency	Serious imprecision [4]	35	42	Prior LAI‡ 0 (0%) vs prior placebo 0 (0%)	Important	Very low

Presence of TEAE - grade 5 at 84 days, n (%) (lower values are favourable)									
1 double-blinded RCT Olivier et al 2017	No serious limitations	Serious indirectness[1]	No serious inconsistency	Serious imprecision [4]	44	45	LAI 1/44 (2.3%) vs placebo 0/45 (0%)	Important	Low
Presence of TEAE - grade 5 at 168 days, n (%) (lower values are favourable)									
Open phase following 1 double-blinded RCT Olivier et al 2017	No serious limitations[3]	Very serious indirectness[2]	No serious inconsistency	Serious imprecision [4]	35	42	Prior LAI‡ 1/35 (2.9%) vs prior placebo 0/42 (0%)	Important	Very low
TEAEs leading to treatment discontinuation at 84 days, n (%) (lower values are favourable)									
1 double-blinded RCT Olivier et al 2017	No serious limitations	Serious indirectness[1]	No serious inconsistency	Serious imprecision [4]	44	45	LAI 17/44 (15.9%) vs placebo 0/45 (0%)	Important	Low
TEAEs leading to treatment discontinuation at 168 days, n (%) (lower values are favourable)									
Open phase following 1 double-blinded RCT Olivier et al 2017	Serious limitations[5]	Very serious indirectness[2]	No serious inconsistency	Not calculable	35	42	Prior LAI‡ 6/35 (17.1%) vs prior placebo 12/42 (27.9 %)	Important	Very low
Audiovestibular TEAEs at 84 days, n (%) (lower values are favourable)									
1 double-blinded RCT	No serious limitations	Serious indirectness[1]	No serious inconsistency	Not calculable	44	45	LAI 5/44 (11.4%) vs placebo 5/45 (11.1%)	Important	Moderate

Olivier et al 2017									
Audiovestibular TEAEs at 168 days, n (%) (lower values are favourable)									
Open phase following 1 double-blinded RCT Olivier et al 2017	Serious limitations[5]	Very serious indirectness[2]	No serious inconsistency	Not calculable	35	42	Prior LAI‡ 2/35 (5.7%) vs prior placebo 2/42 (4.7%)	Important	Very low
Renal TEAEs at 84 days, n (%) (lower values are favourable)									
1 double-blinded RCT Olivier et al 2017	No serious limitations	Serious indirectness[1]	No serious inconsistency	Serious imprecision [4]	44	45	LAI 1/44 (2.3%) vs placebo 0 (0%)	Important	Low
Renal TEAEs at 168 days, n (%) (lower values are favourable)									
Open phase following 1 double-blinded RCT Olivier et al 2017	No serious limitations	Very serious indirectness[2]	No serious inconsistency	Serious imprecision [4]	35	42	Prior LAI‡ 1/35 (2.9%) vs prior placebo 0 (0%)	Important	Very low
Any serious TEAE at 6 months									
Any serious TEAE at 6 months, n (%) (lower values are favourable)									
1 open-label RCT Griffith et al 2018	No serious limitations	No serious indirectness	No serious inconsistency	Not calculable	223	112	LAI + GBT 45 (20.2%) vs GBT 20 (17.9%)	Important	High
Pneumothorax at 6 months, n (%) (lower values are favourable)									
1 open-label RCT	No serious limitations	No serious indirectness	No serious inconsistency	Not calculable	223	112	LAI + GBT 3 (1.3%) vs GBT 1 (0.9%)	Important	High

Griffith et al 2018									
Haemoptysis at 6 months, n (%) (lower values are favourable)									
1 open-label RCT Griffith et al 2018	No serious limitations	No serious indirectness	No serious inconsistency	Not calculable	223	112	LAI + GBT 6 (2.7%) vs GBT 5 (4.5%)	Important	High
Pneumonia at 6 months, n (%) (lower values are favourable)									
1 open-label RCT Griffith et al 2018	No serious limitations	No serious indirectness	No serious inconsistency	Not calculable	223	112	LAI + GBT 8 (3.6%) vs GBT 2 (1.8%)	Important	High
Serious COPD exacerbation at 6 months, n (%) (lower values are favourable)									
1 open-label RCT Griffith et al 2018	No serious limitations	No serious indirectness	No serious inconsistency	Not calculable	223	112	LAI + GBT 7 (3.1%) vs GBT 1 (0.9%)	Important	High
Infective exacerbation of bronchiectasis at 6 months, n (%) (lower values are favourable)									
1 open-label RCT Griffith et al 2018	No serious limitations	No serious indirectness	No serious inconsistency	Not calculable	223	112	LAI + GBT 5 (2.2%) vs GBT 3 (2.7%)	Important	High
Dyspnoea at 6 months, n (%) (lower values are favourable)									
1 open-label RCT Griffith et al 2018	No serious limitations	No serious indirectness	No serious inconsistency	Serious imprecision [4]	223	112	LAI + GBT 3 (1.3%) vs GBT 0 (0%)	Important	Moderate
Worsening of MAC infection at 6 months, n (%) (lower values are favourable)									
1 open-label RCT Griffith et al 2018	No serious limitations	No serious indirectness	No serious inconsistency	Not calculable	223	112	LAI + GBT 1 (0.4%) vs GBT 2 (1.8%)	Important	High

Pulmonary cavitation at 6 months, n (%) (lower values are favourable)									
1 open-label RCT Griffith et al 2018	No serious limitations	No serious indirectness	No serious inconsistency	Serious imprecision [4]	223	112	LAI + GBT 0 (0%) vs GBT 2 (1.8%)	Important	Moderate
Acute myocardial infarction at 6 months, n (%) (lower values are favourable)									
1 open-label RCT Griffith et al 2018	No serious limitations	No serious indirectness	No serious inconsistency	Serious imprecision [4]	223	112	LAI + GBT 0 (0%) vs GBT 2 (1.8)	Important	Moderate
TEAE leading to death at 6 months, n (%) (lower values are favourable)									
1 open-label RCT Griffith et al 2018	No serious limitations	No serious indirectness	No serious inconsistency	Not calculable	223	112	LAI + GBT 6 (2.7%) vs GBT 5 (4.5%)	Important	High
Respiratory failure at 6 months, n (%) (lower values are favourable)									
1 open-label RCT Griffith et al 2018	No serious limitations	No serious indirectness	No serious inconsistency	Not calculable	223	112	LAI + GBT 2 (0.9%) vs GBT 1 (0.9%)	Important	High
COPD exacerbation at 6 months leading to death, n (%) (lower values are favourable)									
1 open-label RCT Griffith et al 2018	No serious limitations	No serious indirectness	No serious inconsistency	Serious imprecision [4]	223	112	LAI + GBT 1 (0.4%) vs GBT 0 (0%)	Important	Moderate
Pulmonary embolism at 6 months, *n (%)* (lower values are favourable)									
1 open-label RCT Griffith et al 2018	No serious limitations	No serious indirectness	No serious inconsistency	Serious imprecision [4]	223	112	LAI + GBT 1 (0.4%) vs GBT 0 (0%)	Important	Moderate
Interstitial lung disease at 6 months, n (%) (lower values are favourable)									
1 open-label RCT	No serious limitations	No serious indirectness	No serious inconsistency	Serious imprecision [4]	223	112	LAI + GBT 0 (0%) vs GBT 1 (0.9%)	Important	Moderate

Griffith et al 2018									
Lung infection at 6 months, n (%) (lower values are favourable)									
1 open-label RCT Griffith et al 2018	No serious limitations	No serious indirectness	No serious inconsistency	Serious imprecision [4]	223	112	LAI + GBT 1 (0.4%) vs GBT 0 (0%)	Important	Moderate
Worsening of MAC infection at 6 months, n (%) (lower values are favourable)									
1 open-label RCT Griffith et al 2018	No serious limitations	No serious indirectness	No serious inconsistency	Serious imprecision [4]	223	112	LAI + GBT 0 (0%) vs GBT 1 (0.9%)	Important	Moderate
Pneumonia at 6 months, n (%) (lower values are favourable)									
1 open-label RCT Griffith et al 2018	No serious limitations	No serious indirectness	No serious inconsistency	Serious imprecision [4]	223	112	LAI + GBT 0 (0%) vs GBT 1 (0.9%)	Important	Moderate
Cardiogenic shock at 6 months, n (%) (lower values are favourable)									
1 open-label RCT Griffith et al 2018	No serious limitations	No serious indirectness	No serious inconsistency	Serious imprecision [4]	223	112	LAI + GBT 0 (0%) vs GBT 1 (0.9%)	Important	Moderate
Cachexia at 6 months, n (%) (lower values are favourable)									
1 open-label RCT Griffith et al 2018	No serious limitations	No serious indirectness	No serious inconsistency	Serious imprecision [4]	223	112	LAI + GBT 1 (0.4%) vs GBT 0 (0%)	Important	Moderate
TEAE leading to discontinuation at 6 months									
***TEAE leading to discontinuation of* LAI *at 6 months, n (%)* (lower values are favourable)**									
1 open-label RCT Griffith et al 2018	No serious limitations	No serious indirectness	No serious inconsistency	Serious imprecision [4]	223	112	LAI + GBT 39 (17.5%) vs GBT 0 (0%)	Important	Moderate

***TEAE leading to discontinuation of GBT at 6 months*, n (%) (lower values are favourable)**									
1 open-label RCT Griffith et al 2018	No serious limitations	No serious indirectness	No serious inconsistency	Not calculable	223	112	LAI + GBT 9 (4.0%) vs GBT 3 (2.7%)	Important	High
***TEAE leading to discontinuation o*f LAI *and GBT at 6 months,* n (%) (lower values are favourable)**									
1 open-label RCT Griffith et al 2018	No serious limitations	No serious indirectness	No serious inconsistency	Serious imprecision [4]	223	112	LAI + GBT 4 (1.8%) vs GBT 0 (0%)	Important	Moderate
***Serious TEAE leading to discontinuation of* LAI *at 6 months, n (%)* (lower values are favourable)**									
1 open-label RCT Griffith et al 2018	No serious limitations	No serious indirectness	No serious inconsistency	Serious imprecision [4]	223	112	LAI + GBT 12 (5.4%) vs GBT 0 (0%)	Important	Moderate
TEAE: pulmonary exacerbation at 6 months, n (%) (lower values are favourable)									
1 open-label RCT Griffith et al 2018	No serious limitations	No serious indirectness	No serious inconsistency	Not calculable	223	112	LAI + GBT 57 (25.6%) vs GBT 18 (16.1%)	Important	High
Serious TEAE: pulmonary exacerbation at 6 months, n (%) (lower values are favourable)									
1 open-label RCT Griffith et al 2018	No serious limitations	No serious indirectness	No serious inconsistency	Not calculable	223	112	LAI + GBT 20 (9.0%) vs GBT 8 (7.1%)	Important	High
TEAE: ototoxicity-related at 6 months									
***Tinnitus at 6 months*, n (%) (lower values are favourable)**									
%1 open-label RCT Griffith et al 2018	No serious limitations	No serious indirectness	No serious inconsistency	Not calculable	223	112	LAI + GBT 17 (7.6%) vs GBT 1 (0.9%)	Important	High

***Dizziness at 6 months*, n (%) (lower values are favourable)**									
1 open-label RCT Griffith et al 2018	No serious limitations	No serious indirectness	No serious inconsistency	Not calculable	223	112	LAI + GBT 14 (6.3%) vs GBT 3 (2.7%)	Important	High
***Hearing loss at 6 months*, n (%) (lower values are favourable)**									
1 open-label RCT Griffith et al 2018	No serious limitations	No serious indirectness	No serious inconsistency	Not calculable	223	112	LAI + GBT 10 (4.5%) vs GBT 7 (6.3%)	Important	High
***Balance disorder at 6 months*, n (%) (lower values are favourable)**									
1 open-label RCT Griffith et al 2018	No serious limitations	No serious indirectness	No serious inconsistency	Serious imprecision [4]	223	112	LAI + GBT 3 (1.3%) vs GBT 0 (0%)	Important	Moderate
***Vertigo at 6 months*, n (%) (lower values are favourable)**									
1 open-label RCT Griffith et al 2018	No serious limitations	No serious indirectness	No serious inconsistency	Serious imprecision [4]	223	112	LAI + GBT 2 (0.9%) vs GBT 0 (0%)	Important	Moderate
***Presyncope at 6 months*, n (%) (lower values are favourable)**									
1 open-label RCT Griffith et al 2018	No serious limitations	No serious indirectness	No serious inconsistency	Not calculable	223	112	LAI + GBT 1 (0.4%) vs GBT 0 (0%)	Important	High
TEAE in >10% of patients in either arm at 6 months									
***Dysphonia at 6 months,* n (%) (lower values are favourable)**									
1 open-label RCT Griffith et al 2018	No serious limitations	No serious indirectness	No serious inconsistency	Not calculable	223	112	LAI + GBT 102 (45.7%) vs GBT 1 (0.9%)	Important	High
***Cough at 6 months,* n (%) (lower values are favourable)**									
1 open-label RCT	No serious limitations	No serious indirectness	No serious inconsistency	Not calculable	223	112	LAI + GBT 83 (37.2%) vs GBT 17 (15.2%)	Important	High

Griffith et al 2018									
***Dyspnoea at 6 months,* n (%) (lower values are favourable)**									
1 open-label RCT Griffith et al 2018	No serious limitations	No serious indirectness	No serious inconsistency	Not calculable	223	112	LAI + GBT 48 (21.5%) vs GBT 10 (8.9%)	Important	High
***Haemoptysis at 6 months*, n (%) (lower values are favourable)**									
1 open-label RCT Griffith et al 2018	No serious limitations	No serious indirectness	No serious inconsistency	Not calculable	223	112	LAI + GBT 39 (17.5%) vs GBT 15 (13.4%)	Important	High
Fatigue at 6 months, n (%) (lower values are favourable)									
1 open-label RCT Griffith et al 2018	No serious limitations	No serious indirectness	No serious inconsistency	Not calculable	223	112	LAI + GBT 36 (16.1%) vs GBT 8 (7.1%)	Important	High
Diarrhoea at 6 months, n (%) (lower values are favourable)									
1 open-label RCT Griffith et al 2018	No serious limitations	No serious indirectness	No serious inconsistency	Not calculable	223	112	LAI + GBT 28 (12.6%) vs GBT 5 (4.5%)	Important	High
Nausea at 6 months, n (%) (lower values are favourable)									
1 open-label RCT Griffith et al 2018	No serious limitations	No serious indirectness	No serious inconsistency	Not calculable	223	112	LAI + GBT 25 (11.2%) vs GBT 4 (3.6%)	Important	High
Oropharyngeal pain at 6 months, n (%) (lower values are favourable)									
1 open-label RCT Griffith et al 2018	No serious limitations	No serious indirectness	No serious inconsistency	Not calculable	223	112	LAI + GBT 24 (10.8%) vs GBT 2 (1.8%)	Important	High

Any serious TEAE at 12 to 16 months maximum (lower values are favourable)									
1 open label follow-up study Griffith et al 2021	Serious limitations[5]	Serious indirectness[3]	No serious inconsistency	Not calculable	65	10	LAI + GBT 6 (9.2%) vs GBT alone 6 (60.0%)	Important	Low
Any serious TEAE at 8 months maximum (lower values are favourable)									
1 open label follow-up study Griffith et al 2021	Serious limitations[5]	Serious indirectness[3]	No serious inconsistency	Not calculable	65	10	LAI + GBT 4 (6.2%) vs GBT alone 1 (10.0%)	Important	Low
COPD exacerbation: at 16 months maximum, n (%) (lower values are favourable)									
1 open label follow-up study Griffith et al 2021	Serious limitations[5]	Serious indirectness[3]	No serious inconsistency	Not calculable	65	10	LAI + GBT 1 (1.5%) vs GBT alone 2 (20.0%)	Important	Low
COPD exacerbation: at 8 months maximum, n (%) (lower values are favourable)									
1 open label follow-up study Griffith et al 2021	Serious limitations[5]	Serious indirectness[3]	No serious inconsistency	Serious imprecision [4]	65	10	LAI + GBT 1 (1.5%) vs GBT alone 0 (0%)	Important	Very low
COPD exacerbation: at 8 to 24 months, n (%) (lower values are favourable)									
1 open label follow-up study Griffith et al 2021	Serious limitations[5]	Serious indirectness[3]	No serious inconsistency	Serious imprecision [4]	65	10	LAI + GBT 0 (0%) vs GBT alone 2 (20.0%)	Important	Very low

Drug hypersensitivity: at 16 months maximum, n (%) (lower values are favourable)									
1 open label follow-up study Griffith et al 2021	Serious limitations[5]	Serious indirectness[3]	No serious inconsistency	Serious imprecision [4]	65	10	LAI + GBT 1 (1.5%) vs GBT alone 0 (0%)	Important	Very low
Drug hypersensitivity: at 8 months maximum, n (%) (lower values are favourable)									
1 open label follow-up study Griffith et al 2021	Serious limitations[5]	Serious indirectness[3]	No serious inconsistency	Serious imprecision	65	10	LAI + GBT 1 (1.5%) vs GBT alone 0 (0%)	Important	Very low
Drug hypersensitivity: at 8 to 24 months, n (%) (lower values are favourable)									
1 open label follow-up study Griffith et al 2021	Serious limitations[5]	Serious indirectness[3]	No serious inconsistency	Serious imprecision [4]	65	10	LAI + GBT 0 (0%) vs GBT alone 0 (0%)	Important	Very low
Infective exacerbation of bronchiectasis: at 16 months maximum, n (%) (lower values are favourable)									
1 open label follow-up study Griffith et al 2021	Serious limitations[5]	Serious indirectness[3]	No serious inconsistency	Not calculable	65	10	LAI + GBT 1 (1.5) vs GBT alone 1 (10.0%)	Important	Low
Infective exacerbation of bronchiectasis: at 8 months maximum, n (%) (lower values are favourable)									
1 open label follow-up study Griffith et al 2021	Serious limitations[5]	Serious indirectness[3]	No serious inconsistency	Serious imprecision [4]	65	10	LAI + GBT 0 (0%) vs GBT alone 1 (10.0%)	Important	Very low

Infective exacerbation of bronchiectasis: at 8 to 24 months, n (%) (lower values are favourable)									
1 open label follow-up study Griffith et al 2021	Serious limitations[5]	Serious indirectness[3]	No serious inconsistency	Serious imprecision [4]	65	10	LAI + GBT 1 (1.5%) vs GBT alone 0 (0%)	Important	Very low
Infective exacerbation of COPD: at 16 months maximum, n (%) (lower values are favourable)									
1 open label follow-up study Griffith et al 2021	Serious limitations[5]	Serious indirectness[3]	No serious inconsistency	Serious imprecision [4]	65	10	LAI + GBT 1 (1.5%) vs GBT alone 0 (0%)	Important	Very low
Infective exacerbation of COPD: at 8 months maximum, n (%) (lower values are favourable)									
1 open label follow-up study Griffith et al 2021	Serious limitations[5]	Serious indirectness[3]	No serious inconsistency	Serious imprecision [4]	65	10	LAI + GBT 1 (1.5%) vs GBT alone 0 (0%)	Important	Very low
Infective exacerbation of COPD: at 8 to 24 months, n (%) (lower values are favourable)									
1 open label follow-up study Griffith et al 2021	Serious limitations[5]	Serious indirectness[3]	No serious inconsistency	Serious imprecision [4]	65	10	LAI + GBT 0 (0%) vs GBT alone 0 (0%)	Important	Very low

Lung adenocarcinoma: at 16 months maximum, n (%) (lower values are favourable)									
1 open label follow-up study	Serious limitations[5]	Serious indirectness[3]	No serious inconsistency	Serious imprecision [4]	65	10	LAI + GBT 1 (1.5%) vs GBT alone 0 (0%)	Important	Very low

Griffith et al 2021									
Lung adenocarcinoma: at 8 months maximum, n (%) (lower values are favourable)									
1 open label follow-up study Griffith et al 2021	Serious limitations[5]	Serious indirectness[3]	No serious inconsistency	Serious imprecision [4]	65	10	LAI + GBT 0 (0%) vs GBT alone 0 (0%)	Important	Very low
Lung adenocarcinoma: at 8 to 24 months, n (%) (lower values are favourable)									
1 open label follow-up study Griffith et al 2021	Serious limitations[5]	Serious indirectness[3]	No serious inconsistency	Serious imprecision [4]	65	10	LAI + GBT 1 (1.5%) vs GBT alone 0 (0%)	Important	Very low
Lung infection pseudomonal: at 16 months maximum, n (%) (lower values are favourable)									
1 open label follow-up study Griffith et al 2021	Serious limitations[5]	Serious indirectness[3]	No serious inconsistency	Serious imprecision [4]	65	10	LAI + GBT 1 (1.5%) vs GBT alone 0	Important	Very low
Lung infection pseudomonal: at 8 months maximum, n (%) (lower values are favourable)									
1 open label follow-up study Griffith et al 2021	Serious limitations[5]	Serious indirectness[3]	No serious inconsistency	Serious imprecision [4]	65	10	LAI + GBT 0 (0%) vs GBT alone 0 (0%)	Important	Very low
Lung infection pseudomonal: at 8 to 24 months, n (%) (lower values are favourable)									
1 open label follow-up study	Serious limitations[5]	Serious indirectness[3]	No serious inconsistency	Serious imprecision [4]	65	10	LAI + GBT 1 (1.5%) vs GBT alone 0 (0%)	Important	Very low

Griffith et al 2021									
Pneumatosis intestinalis: at 16 months maximum, n (%) (lower values are favourable)									
1 open label follow-up study Griffith et al 2021	Serious limitations[5]	Serious indirectness[3]	No serious inconsistency	Serious imprecision [4]	65	10	LAI + GBT 1 (1.5%) vs GBT alone 0 (0%)	Important	Very low
Pneumatosis intestinalis: at 8 months maximum, n (%) (lower values are favourable)									
1 open label follow-up study Griffith et al 2021	Serious limitations[5]	Serious indirectness[3]	No serious inconsistency	Serious imprecision [4]	65	10	LAI + GBT 0 (0%) vs GBT alone 0 (0%)	Important	Very low
Pneumatosis intestinalis: at 8 to 24 months, n (%) (lower values are favourable)									
1 open label follow-up study Griffith et al 2021	Serious limitations[5]	Serious indirectness[3]	No serious inconsistency	Serious imprecision [4]	65	10	LAI + GBT 1 (1.5%) vs GBT alone 0 (0%)	Important	Very low
Pneumonia: at 16 months maximum, n (%) (lower values are favourable)									
1 open label follow-up study Griffith et al 2021	Serious limitations[5]	Serious indirectness[3]	No serious inconsistency	Serious imprecision [4]	65	10	LAI + GBT 1 (1.5%) vs GBT alone 0(0%)	Important	Very low
Pneumonia: at 8 months maximum, n (%) (lower values are favourable)									
1 open label follow-up study	Serious limitations[5]	Serious indirectness[3]	No serious inconsistency	Serious imprecision [4]	65	10	LAI + GBT 1 (1.5%) vs GBT alone 0 (0%)	Important	Very low

Griffith et al 2021									
Pneumonia: at 8 to 24 months, n (%) (lower values are favourable)									
1 open label follow-up study Griffith et al 2021	Serious limitations[5]	Serious indirectness[3]	No serious inconsistency	Serious imprecision [4]	65	10	LAI + GBT 0 (0%) vs GBT alone 0(0%)	Important	Very low
Pneumothorax: at 16 months maximum, n (%) (lower values are favourable)									
1 open label follow-up study Griffith et al 2021	Serious limitations[3]	Serious indirectness[3]	No serious inconsistency	Serious imprecision [4]	65	10	LAI + GBT 1 (1.5%) vs GBT alone 0 (0%)	Important	Very low
Pneumothorax: at 8 months maximum, n (%) (lower values are favourable)									
1 open label follow-up study Griffith et al 2021	Serious limitations[5]	Serious indirectness[3]	No serious inconsistency	Serious imprecision [4]	65	10	LAI + GBT 1 (1.5%) vs GBT alone 0 (0%)	Important	Very low
COPD exacerbation: at 16 months maximum, n (%) (lower values are favourable)									
1 open label follow-up study Griffith et al 2021	Serious limitations[5]	Serious indirectness[3]	No serious inconsistency	Not calculable	65	10	LAI + GBT 1 (1.5%) vs GBT alone 2 (20.0%)	Important	Low
COPD exacerbation: at 8 months maximum, n (%) (lower values are favourable)									
1 open label follow-up study	Serious limitations[5]	Serious indirectness[3]	No serious inconsistency	Serious imprecision [4]	65	10	LAI + GBT 1 (1.5%) vs GBT alone 0 (0%)	Important	Very low

Griffith et al 2021									

Abbreviations
6MWT-6 minute walk test; ATS-American Thoracic Society; CF-Cystic fibrosis; CI-Confidence Interval; COPD-Chronic Obstructive Pulmonary Disease; CT-Computer Tomography; EOT-End of Treatment; FEV1-Force Expiratory Volume in 1 second; FVC-Forced Vital Capacity; GBT-Guideline-Based Treatment; HR-Hazard Ratio; IQR-Inter Quartile Range; ITT-Intention to Treat; LAI-Liposomal Amikacin Inhaled; LSMD-Least Square Mean Difference; MAC-Mycobacterium Avium Complex; MCID-minimal clinically important differences; MD-Mean Difference; MIC-Minimum Inhibitory Concentration; NHLBI-National Heart, Lung, and Blood Institute; NIAID-National Institute of Allergy and Infectious Diseases; NIH-National Institute for Health; NS-Not Significant; NTM-Non-Tuberculosis Mycobacterium; OR-Odds Ratio; PD-Pulmonary Disease; PNTM-Pulmonary Non-Tuberculosis Mycobacterium; QOL-Quality of Life; RCT-Randomised Controlled Trial; SD-Standard Deviation; SE-Standard Error; SGRQ-Saint George's Respiratory Questionnaire; SOC-Standard of care; SQS-semiquantitative scale; TEAE-treatment-emergent adverse event

Footnotes

1. Serious indirectness due to inclusion of patients with conditions other than that specified in the PICO for this review.
2. Very serious indirectness due to inclusion of patients with conditions other than that specified in the PICO for this review. Both groups of patients were being treated with LAI+GBT so there is no comparator which meets the criteria specified in the PICO. The difference between the two groups was that one had had previous treatment with LAI+GBT, whilst the other had been treated with GBT only.
3. Serious indirectness as only patients who had responded to previous LAI+GBT were included in this follow-up study
4. Serious imprecision zero results in at least one arm
5. Serious limitations due to lack of blinding, allocation concealment and blinding of assessors.
6. Serious imprecision: results cannot exclude an appreciable benefit with GBT alone
7. Serious imprecision due to wide confidence interval

‡ All patients in the open-label phase received LAI. "LAI" and "placebo" here refer to treatment assignment in the double-blind phase.

ϒ Study does not report whether measurements were It was not reported whether these were mean or median differences, now whether reported as SE or SD

Table 2b. Patients of all ages with non-tuberculous mycobacterial pulmonary disease (NTM PD) caused by mycobacterium avium complex (MAC) who were enrolled in the CONVERT study and did not meet the primary endpoint of culture conversion by Month 6 or had recurrent MAC infection (positive MAC culture after conversion) by Month 6 (confirmed at Month 8 when sputum data were unblinded) and were treated with LAI + GBT in the follow-up study.

Outcome measure, units and timepoint in study (for continuous outcomes indicate if benefit is indicated by higher or lower result)									
QUALITY					**Summary of findings**			**IMPORTANCE**	**CERTAINTY**
					No of patients receiving treatment with LAI + GBT		**Effect**		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**LAI-naive**	**Prior-LAI**	**Result**		
Culture Conversion (one follow-up cohort study)									
Cumulative sputum culture conversion at 6 months, n (%) (higher value indicates benefit)									
1 follow-up cohort study Winthrop et al 2021	No serious limitations	Serious indirectness[1]	Not applicable	Not calculable	90	73	LAI-naïve: 24 (26.7%) vs prior-LAI 7 (9.6%)	Critical	Very low
Cumulative sputum culture conversion at up to 20 months, n (%) (higher value indicates benefit)									
1 follow-up cohort study Winthrop et al 2021	No serious limitations	Serious indirectness[1]	Not applicable	Not calculable	90	73	LAI-naïve: 30 (33%) vs prior-LAI 10 (13.7%)	Critical	Very low
Safety									
Any TEAE, n (%) (lower value indicates benefit)									
1 follow-up cohort study Winthrop et al 2021	Serious limitations[2]	Serious indirectness[1]	Not applicable	Not calculable	90	73	LAI-naive 90 (100%) vs prior-LAI 68 (93.2%)	Important	Very low
Grade 3: severe, n (%) (lower value indicates benefit)									
1 follow-up cohort study	Serious[2] limitations	Serious indirectness[1]	Not applicable	Not calculable	90	73	LAI-naive 29 (32.2%) vs prior-LAI 13 (17.8%)	Important	Very low

Winthrop et al 2021									
Grade 4: Life threatening, n (%) (lower value indicates benefit)									
1 follow-up cohort study Winthrop et al 2021	No serious limitations	Serious indirectness[1]	Not applicable	Not calculable	90	73	LAI-naive 3 (3.3%) vs prior-LAI 1 (1.4%)	Important	Very low
Grade 5: death, n (%) (lower value indicates benefit)									
1 follow-up cohort study Winthrop et al 2021	No serious limitations	Serious indirectness[1]	Not applicable	Not calculable	90	73	LAI-naive 4 (4.4%) vs prior-LAI 2 (2.7%)	Important	Very low
Pulmonary exacerbation, n (%) (lower value indicates benefit)									
1 follow-up cohort study Winthrop et al 2021	Serious[2] limitations	Serious indirectness[1]	Not applicable	Not calculable	90	73	LAI-naive 29 (32.2%) vs prior-LAI 22 (30.1%)	Important	Very low
TEAE leading to discontinuation of LAI, n (%) (lower value indicates benefit)									
1 follow-up cohort study Winthrop et al 2021	Serious[2] limitations	Serious indirectness[1]	Not applicable	Not calculable	90	73	LAI-naive 22 (24.4%) vs prior-LAI 6 (8.2%)	Important	Very low
TEAE leading to discontinuation of GBT, n (%) (lower value indicates benefit)									
1 follow-up cohort study Winthrop et al 2021	Serious[2] limitations	Serious indirectness[1]	Not applicable	Not calculable	90	73	LAI-naive 8 (8.9%) vs prior-LAI 4 (5.5%)	Important	Very low
TEAE leading to discontinuation of LAI and GBT, n (%) (lower value indicates benefit)									
1 follow-up cohort study Winthrop et al 2021	Serious[2] limitations	Serious indirectness[1]	Not applicable	Not calculable	90	73	LAI-naive 5 (5.6%) vs prior-LAI 1 (1.4%)	Important	Very low
TEAE leading to death, n (%) (lower value indicates benefit)									
1 follow-up cohort study	No serious limitations	Serious indirectness[1]	Not applicable	Not calculable	90	73	LAI-naive 4 (4.4%) vs prior-LAI 2 (2.7%)	Important	Very low

Winthrop et al 2021									
COPD exacerbation, n (%) (lower value indicates benefit)									
1 follow-up cohort study Winthrop et al 2021	Serious[2] limitations	Serious indirectness[1]	Not applicable	Not calculable	90	73	LAI-naive 4 (4.4%) vs prior-LAI 1 (1.4%)	Important	Very low
Lower respiratory tract infection, n (%) (lower value indicates benefit)									
1 follow-up cohort study. Winthrop et al 2021	Serious[2] limitations	Serious indirectness[1]	Not applicable	Serious[3] imprecision	90	73	LAI-naive 0 (0%) vs prior-LAI 1 (1.4%)	Important	Very low
***Serious TEAE occurring in >3% of patients*, n (%) (lower value indicates benefit)**									
MAC infection worsening or progression									
1 follow-up cohort study Winthrop et al 2021	Serious[2] limitations	Serious indirectness[1]	Not applicable	Serious imprecision	90	73	LAI-**n**aïve 5 (5.6%) vs prior-LAI 0 (0%)	Important	Very low
***Pneumonia*, n (%) (lower value indicates benefit)**									
1 follow-up cohort study Winthrop et al 2021	Serious[2] limitations	Serious indirectness[1]	Not applicable	Not calculable	90	73	LAI-naive 4 (4.4%) vs prior-LAI 3 (4.1%)	Important	Very low
Serious TEAE									
***Pulmonary exacerbation*, n (%) (lower value indicates benefit)**									
1 follow-up cohort study Winthrop et al 2021	Serious[2] limitations	Serious indirectness[1]	Not applicable	Not calculable	90	73	LAI-naive 17 (18.9%) vs prior-LAI 7 (9.6%)	Important	Very low
***Serious TEAE leading to discontinuation of LAI*, n (%) (lower value indicates benefit)**									
1 follow-up cohort study Winthrop et al 2021	Serious[2] limitations	Serious indirectness[1]	Not applicable	Not calculable	90	73	LAI-naive 9 (10.0%) vs prior-LAI 3 (4.1%)	Important	Very low

***Bronchospasm*, n (%) (lower value indicates benefit)**									
1 follow-up cohort study Winthrop et al 2021	Serious[2] limitations	Serious indirectness[1]	Not applicable	Not calculable	90	73	LAI-naive 2 (2.2%) vs prior-LAI 10 (13.7%)	Important	Very low
***Dyspnoea*, n (%) (lower value indicates benefit)**									
1 follow-up cohort study Winthrop et al 2021	Serious[2] limitations	Serious indirectness[1]	Not applicable	Not calculable	90	73	LAI-naive 16 (17.8%) vs prior-LAI 9 (12.3%)	Important	Very low
***Wheezing*, n (%) (lower value indicates benefit)**									
1 follow-up cohort study Winthrop et al 2021	Serious[2] limitations	Serious indirectness[1]	Not applicable	Not calculable	90	73	LAI-naive 5 (5.6%) vs prior-LAI 1 (1.4%)	Important	Very low
***Haemoptysis*, n (%) (lower value indicates benefit)**									
1 follow-up cohort study Winthrop et al 2021	Serious[2] limitations	Serious indirectness[1]	Not applicable	Not calculable	90	73	LAI-naive 11 (12.2%) vs prior-LAI 11 (5.1%)	Important	Very low
Abbreviations COPD-Chronic Obstructive Pulmonary Disease; GBT-Guideline-Based Treatment; LAI-Liposomal Amikacin Inhaled; n-number; %-percentage; TEAE-treatment-emergent adverse event									

Footnotes

1. Serious indirectness due to lack of comparator group. Both groups of patients were being treated with LAI+GBT. The difference between the two groups was that one had had previous treatment with LAI+GBT, whilst the other had been treated with GBT only
2. Serious limitations due to lack of blinding, allocation concealment and blinding of assessors
3. Serious imprecision zero results in at least one arm

Glossary

Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results, which is caused by the way the study is designed or conducted.
Clinical importance	A benefit from treatment that relates to an important outcome such as length of life and is large enough to be important to patients and health professionals.
Cohort study	Research study in which the health or other characteristic of patients is monitored (or 'followed up') for a period of time, with events recorded as they happen. This contrasts with retrospective studies.
Confidence interval (CI)	A way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. A wide confidence interval indicates a lack of certainty about the true effect of the test or treatment - often because a small group of patients has been studied. A narrow confidence interval indicates a more precise estimate (for example, if a large number of patients have been studied).
Conversion regardless of treatment duration	Additional analyses that assessed culture status at the end of treatment regardless of the duration of post-conversion treatment
Converter analysis	Proportion of patients who achieved conversion by month 6 and showed sustained and durable conversion.
Cost effectiveness study	An analysis that assesses the cost of achieving a benefit by different means. The benefits are expressed in non-monetary terms related to health, such as life years gained (that is, the number of years by which life is extended as a result of the intervention). Options are often compared on the cost incurred to achieve 1 outcome (for example, cost life year gained).
Double-blinding	The purpose of 'blinding' is to protect against bias. In a double-blind study, neither the patients nor the researchers/doctors know which study group the patients are in.
GRADE (Grading of recommendations assessment, development and evaluation)	A systematic and explicit approach to grading the quality of evidence and the strength of recommendations developed by the GRADE working group.
Hazard Ratio	The hazard or chance of an event occurring in the treatment arm of a study as a ratio of the chance of an event occurring in the control arm over time.
Intention to Treat	An assessment of the people taking part in a trial, based on the group they were initially (and randomly) allocated to. This is regardless of whether or not they dropped out, fully adhered to the treatment or switched to an alternative treatment. Intention-to-treat analysis (ITT) analyses are often used to assess clinical effectiveness because they mirror actual practice, when not everyone adheres to the treatment, and the treatment people have may be changed according to how their condition responds to it. Studies of drug treatments often use a

	modified ITT analysis, which includes only the people who have taken at least 1 dose of a study drug.
Interquartile range	In descriptive statistics, the interquartile range (IQR), also called the midspread, middle 50%, or H-spread, is a measure of statistical dispersion, being equal to the difference between 75th and 25th percentiles, or between upper and lower quartiles. In other words, the IQR is the first quartile subtracted from the third quartile; these quartiles can be clearly seen on a box plot on the data. It is a trimmed estimator, defined as the 25% trimmed range, and is a commonly used robust measure of scale. The IQR is a measure of variability, based on dividing a data set into quartiles. Quartiles divide a rank-ordered data set into four equal parts. The values that separate parts are called the first, second, and third quartiles; and they are denoted by Q1, Q2, and Q3, respectively.
Mean Difference	The mean difference (more correctly, 'difference in means') is a standard statistic that measures the absolute difference between the mean value in two groups in a clinical trial. It estimates the amount by which the experimental intervention changes the outcome on average compared with the control.
Minimal clinically important difference	The smallest change in a treatment outcome that people with the condition would identify as important (either beneficial or harmful), and that would lead a person or their clinician to consider a change in treatment.
Odds Ratio	Compares the odds (probability) of something happening in 1 group with the odds of it happening in another. An odds ratio of 1 shows that the odds of the event happening (for example, a person developing a disease or a treatment working) is the same for both groups. An odds ratio of greater than 1 means that the event is more likely in the first group than the second. An odds ratio of less than 1 means that the event is less likely in the first group than in the second group.
PICO (population, intervention, comparison and outcome) framework	A structured approach for developing review questions that divides each question into 4 components: the population (the population being studied); the interventions (what is being done); the comparators (other main treatment options); and the outcomes (measures of how effective the interventions have been).
P-value (p)	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that 1 seems to be more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance), it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 0.1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Semi-quantitative scale (SQS)	The endpoint used the 7-step semi-quantitative scale (SQS) for mycobacterial culture reporting in both solid and liquid growth media, with step 1 = culture negative in both solid and liquid media, step 2 = growth in liquid medium only, 3 = solid medium positive, 4 = 50 to 100

	colonies in solid medium & growth in liquid, 5 = >100 to 200 colonies in solid medium & growth in liquid, 6 = >200 to 500 colonies in solid medium & growth in liquid, 7 = >500 colonies in solid medium & growth in liquid. Full scale range is 1 (best score) to 7 (worst score). The change in step measures the growth at Day 84 compared to the growth at Baseline. The negative values represent reduction in colony growth.
St George's Respiratory Questionnaire (SGRQ)	The Saint George's Respiratory Questionnaire (SGRQ) is a self-reported disease specific, health-related quality of life (QOL) questionnaire. It was originally developed to measure the impact of Chronic Obstructive Pulmonary Disease (COPD) on a person's life but has also been studied and applied to non-COPD pulmonary populations.
Standard deviation (SD)	A measure of the spread, scatter or variability of a set of measurements. Usually used with the mean (average) to describe numerical data.
Standard error	The standard error describes how accurate the mean of any given sample from that population is likely to be compared to the true population mean. When the standard error increases i.e., the means are more spread out, it becomes more likely that any given mean is an inaccurate representation of the true population mean
Statistical significance	A statistically significant result is one that is assessed as being due to a true effect rather than random chance.

References

Included studies

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