



## ARTICLE

Amikacin Liposome Inhalation Suspension for Refractory *Mycobacterium avium* Complex Lung Disease: Sustainability and Durability of Culture Conversion and Safety of Long-term Exposure

## CLINICAL QUESTION

In patients with treatment refractory *Mycobacterium avium* complex (MAC) lung disease who are initiated on amikacin liposomal inhalation solution (ALIS), is culture conversion at 6 months predictable of sustained and durable culture conversion?

## SUMMARY

The 2020 ATS/IDSA/ERS guidelines recommend a 3-4 drug regimen for the treatment of MAC lung disease. The total duration of treatment is guided by culture conversion. Once culture conversion is achieved it is recommended to continue antibiotic therapy for an additional 12 months. Treatment success, defined as achievement of culture negativity for 12 months, occurs in 50-85% of patients. In October 2018, the FDA approved amikacin liposomal inhalation suspension (ALIS) to be added to guideline-based therapy (GBT) for patients with treatment refractory MAC infection based on the results of a pivotal phase 3 study (CONVERT).

### Subjects:

In the phase 3 randomized open label trial, ALIS was studied to determine if culture conversion could be achieved in MAC patients who remained culture positive on GBT for at least 6 months. The key exclusion criterion was infection related to amikacin resistant MAC (MIC > 64 µg/ml). The patients in this analysis were those who met protocol-defined culture conversion by the 6<sup>th</sup> month of treatment (defined as three consecutive negative sputum culture for MAC obtained on a monthly basis) in the original CONVERT primary analysis.

### Study Design:

Patients were randomly assigned in a 2:1 ratio to ALIS 590 mg once daily plus GBT or GBT alone. Individuals who were still culture positive at the 6<sup>th</sup> month of treatment exited the study at month 8 after results of their month 6 culture were unblinded. Patients continued on their assigned treatment with a goal of 12 months of negative cultures. They were followed for an additional 12 months off treatment. The secondary endpoint reported in this study is the percentage of patients who had sustained conversion at the completion of 12 months of treatment post-conversion and durable culture conversion through 3 months after treatment in the ALIS plus GBT arm vs the GBT alone arm. Exploratory end points reported are the percentage of patients whose status remained culture negative 12 months after completion of all treatment and the number of patients with recurrence (relapse vs. reinfection) at the end of the study.

The percentage of randomized patients (intention-to-treat population) achieving culture conversion with sustainability while receiving treatment, durability 3 months after treatment, and the percentage whose



culture results remained negative at the end of study were analyzed using the Cochran-Mantel Haenszel test (stratified by smoking status and prior multidrug regimen). Patients with missing sputum culture data were considered to have positive culture results unless missing culture results were because of a patient's inability to produce sputum despite reasonable efforts. Patients who did not complete a full course of treatment (12 months after conversion) were considered to have positive culture results.

### Results:

336 patients were randomized to receive ALIS plus GBT (n = 224) or GBT alone (n = 112). A total of seventy-five patients achieved culture conversion at the end of six months (65 in the ALIS plus GBT arm, 10 in the GBT arm). Of the 65 subjects in the ALIS treatment arm who achieved culture conversion by month 6 (primary end point), 59 patients (90.8%) completed the study. Of the 10 patients in the GBT arm alone, 5 (50%) completed the study. 16.1% of patients (36/224) in the ALIS plus GBT arm and no patients (0/112) in the GBT alone arm achieved culture conversion that was both sustained at the completion of 12 months of treatment after conversion and durable 3 months after all MAC treatment (P < .0001).

63.1% [41/65] of patients in the ALIS plus GBT arm who achieved conversion showed a sustained response at the completion of 12 months of treatment post conversion compared with 30.0% (3/10) of converters in the GBT arm (P = .0644). 55.4% of patients (36/65) who achieved conversion in the ALIS plus GBT arm showed durable responses 3 months after treatment compared with none (0/10) in the GBT alone arm (P = .0017). At 12 months after the end of all MAC treatment, 46.2% of patients (30/65) who achieved conversion in the ALIS plus GBT arm continued to show negative culture results.

At the end of treatment (EOT), 7.7% (5/65) of patients in the ALIS + GBT arm showed sputum results positive for MAC that met the definition of relapse, 4.6% (3/65) had sputum results positive for MAC that met the definition of reinfection, and 7.7% (5/65) were missing culture data. In the GBT alone arm at EOT, 30.0% of patients (3/10) showed negative culture results, 30.0% of patient (3/10) showed sputum results positive for MAC that met the definition of relapse, 10% of patients (1/10) showed sputum results positive for MAC that met the definition of reinfection, and 30% of patients (3/10) had missing culture data. At EOT, most patients, regardless of treatment arm, had experienced treatment emergent adverse events that were respiratory in nature and occurred before month 8.

### GROUP OPINION

Compared with GBT alone, ALIS-treated patients were more likely to achieve successful microbiologic outcomes and continue to show negative culture results through completion of 12 months of treatment after culture conversion. Culture conversion at month 6 was predictive of both a sustained and durable culture conversion. ALIS is an effective treatment for patients with GBT-refractory pulmonary MAC. A low number of patients receiving ALIS plus GBT showed relapse of their initial strain of MAC. Finally, treatment with ALIS for up to 16 months did not result in new safety concerns or changes to the established safety profile of ALIS.