716. *In vitro* and *In vivo* Nonclinical Efficacy of AR-501 (Gallium Citrate)

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Background. Gallium nitrate citrate exhibits strong antibacterial activity and was recently shown to be safe and efficacious when intravenously administered to cystic fibrosis patients in a Phase 2 clinical study conducted by the University of Washington. We are developing an inhaled formulation of gallium citrate (AR-501), which is being tested in a Phase 1/2a clinical study. The *in vitro* antimicrobial activities, drug resistance profile, activities in combination with selected antibiotics, and *in vivo* animal efficacy if the inhaled vs. IV formulation is being presented.

Methods. MIC tests were performed on strains using the CLSI susceptibility test standards. Resistance testing exposed bacteria to 20 cycles at ranges above and below the MIC level of the drug used.SPF mice (C57BL/6J, 7–9 weeks) were inoculated intranasally with *P. aeruginosa* under ketamine/xylazine anesthesia. Inhalation of AR-501 used an Aeroneb Solo nebulizer. Gallium levels were determined by elemental analysis using atomic absorption spectroscopy. CFU levels were measured by enumeration of bacterial colonies following serial dilution of tissue homogenates.

Results. *In vitro* efficacy: MIC testing demonstrates the efficacy of AR-501 against gram (−), gram (+) and several species of mycobacteria of clinical isolates and the comparative antibacterial response with antibiotics. Resistance testing showed that AR-501 exhibited lower propensity to develop resistance than the antibiotics tested. *In vivo* efficacy: AR-501 Inhalation also increased the median survival time compared with IV dosing in the murine model. Bacterial clearance was increased when Tobramycin and AR-501 are co-administered. Comparative analysis of AR-501 after IH route demonstrate increased gallium levels in BAL and reduced levels in the kidney in contrast to IV route.

Conclusion. *In vitro* studies demonstrate the susceptibility of gram (−), gram (+) and mycobacteria pathogens and the dose range of AR-501 compared with SOC antibiotics. *In vivo* studies confirm the therapeutic efficacy of AR-501 in bacterial pneumonia by IH delivery and demonstrate that bacterial clearance is enhanced when SOC antibiotics are used in combination with AR-501.

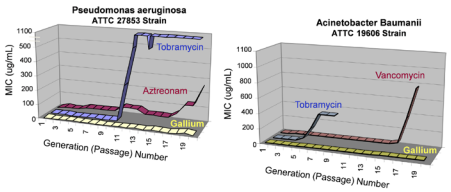


Figure 2. Differential distribution of gallium in tissues and BAL following inhalation or intravenous delivery.

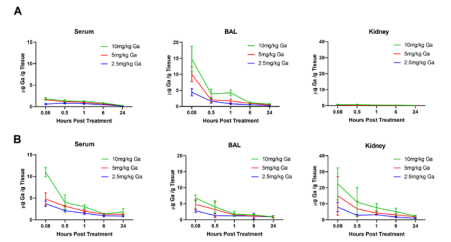
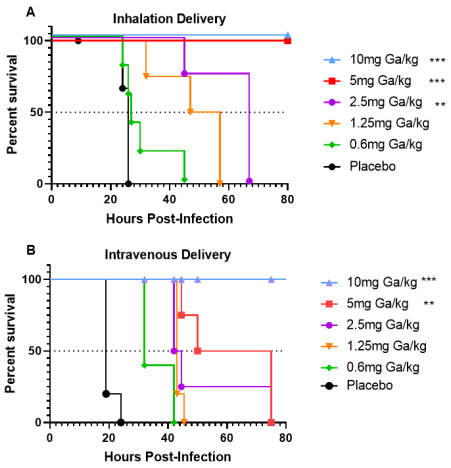
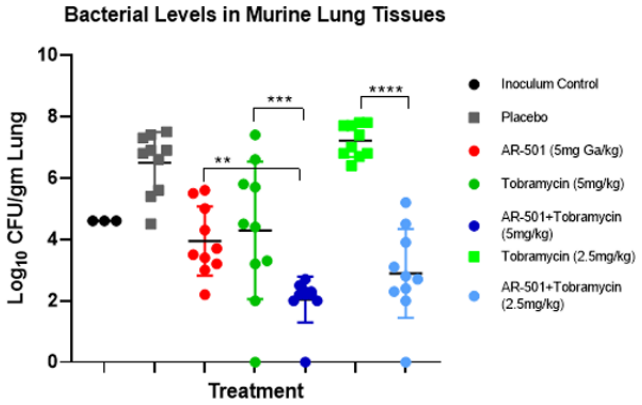


Fig 2. Gallium levels were measured in serum, kidney and bronchial lavage samples over 24 hours after delivery by inhalation (A) or intravenous (B) routes. C57BL/6J mice (n=6 per group) were dosed with AR-501 and samples collected after 0.08, 0.5, 1, 6, and 24 hours post-treatment for gallium measurement.





Disclosures. **All authors:** No reported disclosures.

717. Lefamulin (LEF) vs. Moxifloxacin (MOX) in Patients With Community-Acquired Bacterial Pneumonia (CABP) at Risk for Poor Efficacy or Safety Outcomes: Pooled Subgroup Analyses From the Lefamulin Evaluation Against Pneumonia (LEAP) 1 and LEAP 2 Phase 3 Noninferiority Clinical Trials

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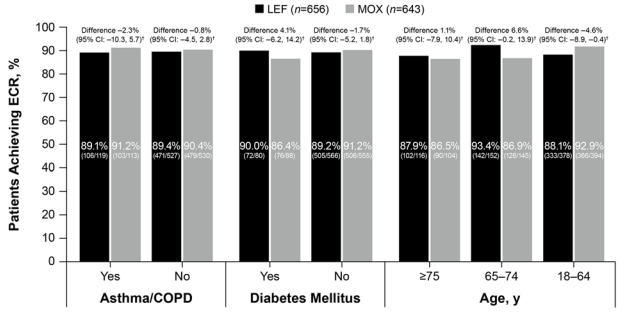
Background. In the United States, CABP is the second most common cause of hospitalization and a leading cause of infectious death. Patients with chronic obstructive pulmonary disease (COPD)/asthma or diabetes are at risk for CABP and associated mortality. Similarly, patients with underlying cardiac or liver disease are at risk for potential cardiac or liver toxicities, respectively, associated with CABP antimicrobials, and patients aged ≥65 years are at risk for both efficacy/safety concerns. We report pooled efficacy/safety outcomes in at-risk subgroups from the LEAP 1 and 2 phase 3 trials.

Methods. In LEAP 1, patients with CABP (PORT III–V) received IV LEF 150 mg q12h for 5–7 days or MOX 400mg q24h for 7 days, with optional IV-to-oral switch (600 mg LEF q12h or 400 mg MOX q24h). In LEAP 2, patients with CABP (PORT II–IV) received oral LEF 600 mg q12h for 5 days or MOX 400 mg q24h for 7 days. Both studies assessed early clinical response (ECR; 96 ± 24 hours after first dose) in the intent-to-treat (ITT; all randomized patients) population (FDA primary endpoint) and investigator assessment of clinical response (IACR) at test-of-cure (TOC; 5–10 days after last dose) in the modified ITT (≥1 study drug dose) and clinically evaluable (met predefined evaluability criteria) populations (EMA coprimary endpoints). Pooled analyses used a 10% noninferiority margin. Safety was assessed in all randomized and treated patients.

Results. 1289 ITT patients were randomized to LEF (n = 646) or MOX (n = 643); of whom, 297 (23.0%) were aged 65–74 years and 220 (17.1%) were ≥75 years; 232 patients (18.0%) had COPD/asthma and 168 (13.0%) had diabetes mellitus (DM). At baseline, 501 patients (38.9%) had history of hypertension, 73 (5.7%) had history of arrhythmia, and 263 (20.4%) had transaminitis. The figure shows efficacy by age and in COPD/asthma and DM patients. Treatment-emergent adverse events, electrocardiogram assessments, and laboratory results in patients at risk for cardiac and hepatic safety concerns are shown in Tables 1 and 2.

Conclusion. In pooled analyses of LEAP 1 and 2, LEF efficacy was high and similar to MOX in patients at risk of efficacy concerns and LEF showed a safety profile similar to that of MOX in patients at risk of safety concerns. LEF is a promising new option for IV/oral monotherapy of CABP in patients at risk of poor outcomes due to CABP or to antimicrobial therapy for CABP.

Figure. ECR* Rates by Subgroup (ITT Population)



*Patients achieved ECR if they were alive and showed improvement in ≥2 CABP signs/symptoms, had no worsening in any CABP sign/symptom, and had not received a concomitant nonstudy antibiotic for CABP.
†Weighted treatment difference and confidence interval (CI) were computed using the method of Miettinen and Nurminen and adjusted for study, with the inverse variance of effect size as stratum weights.