Clinical Translation of an Inhaled Bismuth-Based Antibiotic Adjuvant for Drug-Resistant Pseudomonas aeruginosa

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Antimicrobial resistance (AMR) in Pseudomonas aeruginosa represents a major and growing challenge in the treatment of chronic and acute pulmonary infections, particularly in patients with cystic fibrosis and bronchiectasis. We previously demonstrated that bismuth compounds act as potent antibiotic adjuvants by disrupting bacterial iron homeostasis, leading to collapse of energy metabolism, inhibition of efflux pump activity, and restoration of antibiotic susceptibility across multiple drug classes.

Here, we describe the clinical translation strategy for an inhaled bismuth subcitrate–based adjuvant therapy, advancing this approach toward first-in-human evaluation. Central to this program is the availability of a patient-ready dry powder inhalation product that represents a step-change in the application of bismuth-based adjuvant therapy, enabling direct and localized delivery to infected lung tissue while limiting systemic exposure. This delivery-enabled approach transforms a well-characterised compound into a locally acting pulmonary therapy suitable for therapeutic use in AMR-driven lung infections.

The current development program focuses on execution of a regulatory-aligned preclinical package. Key elements include confirmation of antibiotic synergy across clinically relevant *P. aeruginosa* isolates, pulmonary safety and tolerability assessments following inhalation, and GLP toxicology studies informed by extensive prior human exposure data for oral bismuth compounds. The therapy is positioned as an add-on to standard-of-care antibiotics, aiming to enhance efficacy without altering existing treatment paradigms.

By targeting resistance mechanisms without direct bactericidal activity, inhaled bismuth therapy has the potential to extend the clinical utility of existing antibiotics while limiting selective pressure for resistance. This program exemplifies a pragmatic translational pathway for resistance-breaking adjuvants in pulmonary AMR, bridging robust mechanistic insight with near-term clinical readiness.