Monday, January 5, 2026

Poster abstract submission

Approval Status Not Started

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Country Sweden

Type of organization Industry / company

Poster title

EbsArgent™, a synergistic ebselen–silver combination targeting bacterial thioredoxin reductase with bactericidal activity against a wide range of multidrug-resistant bacteria

Poster abstract

Background:
The global rise of antimicrobial resistance has created an urgent need for antibacterial agents with novel mechanisms of action and low propensity for cross-resistance with current antibiotics. EbsArgent™ is a combination of ebselen and silver with bactericidal activity through inhibition of bacterial thioredoxin reductase (TrxR), a target not addressed by current clinical antibiotics. TrxR is essential for bacterial redox homeostasis yet structurally and functionally distinct from the mammalian enzyme, supporting selective antibacterial activity.

Methods:Antibacterial activity was assessed by broth microdilution (EUCAST) to determine MIC and MIC90 values against panels of multidrug-resistant (MDR) clinical isolates. Early time-kill assays were performed against an MDR Escherichia coli clinical isolate (ESBL/NDM-positive) at 0.5–2×MIC. Resistance development was assessed by serial passage and high-inoculum selection. In vivo efficacy and tolerability were explored in murine peritonitis and thigh infection models.

Results:EbsArgent™ exhibited potent activity against MDR pathogens (typical MIC 0.125–1 µg/mL for E. coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Acinetobacter baumannii, Staphylococcus aureus and Salmonella spp.). MIC90 values were 1 µg/mL for E. coli (n=111) and 2 µg/mL for K. pneumoniae (n=100), with similarly narrow distributions for P. aeruginosa and A. baumannii. Activity was retained against E. coli strains with high-level silver resistance where $AgNO_3$ monotherapy was inactive, and no detectable resistance emerged under standardized selection conditions. In early time-kill assays, EbsArgent™ produced rapid, concentration-dependent killing, reaching near-complete loss of viable counts within 10–20 min at 1–2×MIC, whereas ebselen, $AgNO_3$ or gentamicin alone induced partial early reductions followed by regrowth (Figure). In vivo, EbsArgent™ produced $\log_{10}$ reductions in bacterial burden relative to vehicle controls in intraperitoneal and localized thigh infection models within a single

day of treatment.
Conclusions:EbsArgent™ shows potent in vitro activity against MDR Gram-negative pathogens with exceptionally rapid bactericidal kinetics, consistent with acute disruption of bacterial viability. Together with low mammalian cell toxicity and good tolerability in mice, these data support EbsArgent™ as a differentiated redox-targeting antibacterial modality that circumvents current MDR profiles and warrants further development.

Research topic

Small molecule therapeutics

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