HY-133, a chimeric endolysin in the clinical development for nasal decolonization of *Staphylococcus aureus*

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Available methods for decolonization of methicillin-resistant *Staphylococcus aureus* (MRSA) strains, such as mupirocin, face challenges such as resistance development, microbiome disruption, and lengthy treatment protocols, underscoring the need for better solutions. HY-133 is a recombinant agent targeting *S. aureus*, which employs a chimeric design combining the CHAP domain from phage K with lysostaphin's cell wall-binding domain.

Its in-vitro activity has been confirmed by the extensive testing against more than 1,000 methicillin-susceptible *S. aureus* (MSSA) and MRSA strains including a large diversity of *spa* types and phenotypic variants. The rapidity of bactericidal action was demonstrated through time-kill studies, which showed significant bacterial reduction within two hours. Animal studies have confirmed HY-133's safety and efficacy.

The use of designed bacteriophage endolysins instead of classical antibiotics offers several advantages: (i) rapid activity for effective eradication at hospital admission, (ii) activity independent of resistance to classic antibiotics (e.g., methicillin- and mupirocin-resistant strains) and low potential for endolysin resistance development, and (iii) microbiome preservation due to high specificity for *S. aureus*.

HY-133 has recently entered a phase 1 clinical trial, designed as a randomized, double-blind, placebo-controlled study, which evaluates its safety, tolerability, and efficacy, including effects on the nasal microbiome. HY-133 is applied as a nasal formulation manufactured in GMP quality. The study protocol includes single-dose, multiple-dose and dose-escalation groups.

The ongoing clinical trial represents a pivotal development in using selective lytic phage proteins for *S. aureus* eradication, potentially changing strategies for preventing nosocomial infections. The study results will be crucial for assessing the efficacy of HY-133.