RECCE®327: A Novel Synthetic Anti-Infective for the Treatment of Antimicrobial-Resistant Bacterial Sepsis Infections

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Introduction

Antibacterial resistance is a major public and global health concern, with an urgent unmet need for novel antibiotics to fight infections caused by antimicrobial resistant bacteria. Existing antibiotics are derived from natural biological products, and bacterial pathogens have developed mutations to become resistant to their effects. Over the last few decades, attempts to generate "new" antibiotics have largely focussed on modifying existing antibiotics or using novel combinations, to reverse resistance and prolong their shelf-life. Such approaches might prove useful in the short-term, but it is likely bacteria will once again mutate to become resistant to such modified natural antibiotics.

In contrast, Recce Pharmaceuticals is developing RECCE®327, an entirely synthetic antibiotic. Being synthetic, bacteria have not been previously exposed to any compound like RECCE®327 in the environment; environmental exposure is believed to have contributed to the development of bacterial resistance to many natural antibiotics. RECCE®327 also has a novel mechanism of action, meaning the existing resistance of a bacterial pathogen to another antibiotic has no effect on the efficacy of RECCE®327.

Thus far, Recce Pharmaceuticals has primarily been developing RECCE®327 for the treatment of significant or life-threatening infections with the goal of using it to treat sepsis, as well as primary sites of infections occurring in internal organs. Sepsis is associated with a mortality rate of 25-30%, and mortality due to septic shock is 50-85% with an estimated global burden of 30 million episodes and 6 million deaths. While a range of bacterial species can cause sepsis (including *S. aureus, E. coli, Streptococci, Klebsiella, Pseudomonas* and others) influenced by source of infection (for example community-acquired, versus hospital-acquired), a critical feature threatening effective treatment is the increasing prevalence of antimicrobial resistant infections.

In this regard, RECCE®327 is being specifically developed for the treatment of serious and/or life-threatening bacterial infections and sepsis, including their multidrug-resistant forms. The United States FDA has awarded RECCE®327 Qualified Infectious Disease Product (QIPD) designation under the Generating Antibiotic Initiatives Now (GAIN) Act.

Results

IN VITRO STUDIES: Pre-clinical testing of RECCE®327 using *in vitro* culture assays demonstrated broad-spectrum antibacterial activity against a wide range of Gram-positive and Gram-negative bacterial pathogens, including multi-drug resistant strains. This includes life-threatening ESKAPE pathogens, notably *Enterococcus faecalis, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter spp.*

ANIMAL STUDIES: The proof-of-concept that RECCE®327 can effectively treat systemic bacterial infection has been demonstrated in a range of rodent models. Intravenous delivery of RECCE®327 produced significant reductions in urinary tract infection with *E. coli* (in rats), and vaginal infections with *Neisseria gonorrhoeae* and kidney infection with *Mycobacterium fortuitum* (in mice). In other studies, respiratory delivery had significant efficacy against nasal *Streptococcus pneumoniae* infection and lung infection with *Mycobacterium abscessus* in mice, indicating broader utility.

CLINICAL TRIAL: The RECCE327-001 Phase I clinical safety trial was successfully completed, with volunteers intravenously infused with doses up to 6,000 mg. While the study currently remains blinded, there were no serious adverse events and IV delivery of RECCE®327 appeared to have a good safety profile to allow continued clinical development.

Materials and Methods

RECCE®327 is composed of a mixture of copolymer polyethylene-polyacrolein copolymers in the presence of polyethylene glycol and water, and was aseptically prepared under GLP or GMP conditions as required.

IN VITRO STUDIES: The efficacy of RECCE®327 at bacterial killing was determined by measuring the Minimum Inhibitory Concentration (MIC) using the broth microdilution method.

ANIMAL STUDIES: The efficacy of RECCE®327 at killing bacteria in vivo was evaluated in a range of rodent infection models. Typically, mice or rats were infected with a bacterial pathogen, then treated with a range of doses of RECCE®327. For the sepsis program, RECCE®327 was delivered by intravenous infusion.

Materials and Methods

CLINICAL TRIAL: A first in human clinical trial of RECCE®327 was recently completed (RECCE327-001). The trial was a double blinded, randomized, placebo-controlled, single-ascending dose

Conclusions

RECCE®327 is being developed as a novel, next-generation anti-infective ultimately for the treatment of drug-resistant sepsis infections. It has demonstrated broad-spectrum activity, including against multidrug-resistant strains of pathogenic bacteria. It has proven effective in a range of animal infection models. Moreover, RECCE®327 has recently indicated an excellent safety profile in a Phase I clinical trial. The RECCE®327 anti-infective therefore provides an opportunity to address the urgent issue of life-threatening infections that are untreatable due to resistance to current antibiotic therapeutics.

Work is continuing in our sepsis program to: 1) further dissect the mechanism of action of RECCE®327; 2) commence an evaluation of the ability of RECCE®327 to prevent death from bacterial-induced sepsis in mouse models; 3) perform a Phase II clinical trial examining the efficacy of RECCE®327 against urinary tract infections, a common precursor of sepsis.

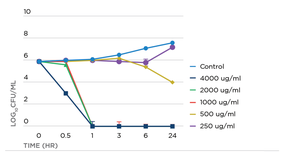
Beyond sepsis, RECCE®327 has numerous potential applications. It is under evaluation for its potential to treat burn wound infections and will shortly commence a Phase II clinical trial examining the efficacy of RECCE®327 against infections in diabetic foot ulcers. These latter programs involve the development of the anti-infective as a gel formulation which would also have potential use for the treatment of wound infections.

Learning Objectives:

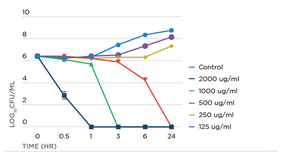
At the end of the session, attendees will be able to
1) Appreciate the challenges of antimicrobial resistance in bacterial sepsis.
2) Understand a new antibiotic technology developed to combat antimicrobial-resistant bacteria.
3) Describe the approach taken by biotechnology companies to develop new treatments for infectious diseases.

In Vitro Studies - Extremely Rapid Onset Effect

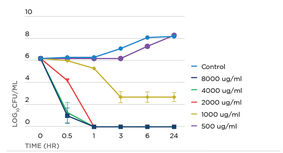
E. faecium ATCC 434



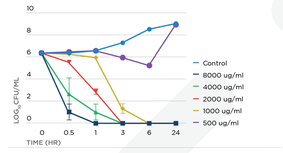
S. aureus ATCC 29213



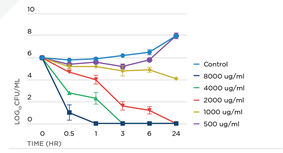
K. pneumoniae ATCC 43816



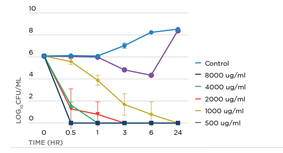
A. baumannii ATCC 17978



P. aeruginosa ATCC 27853

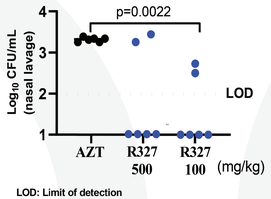


E. cloacae ATCC 13047



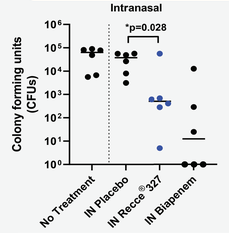
Animal Studies

S. pneumoniae Colonisation



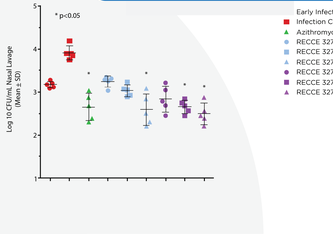
Mice infected with *S. pneumoniae* (clinical isolate – ATCC 49619) were treated nasally, twice daily for 5 days, with R327.
- Significantly reduced nasal infection by *S. pneumoniae*
- Eradicated infection in 8/12 treated mice

Pulmonary *M. abscessus*



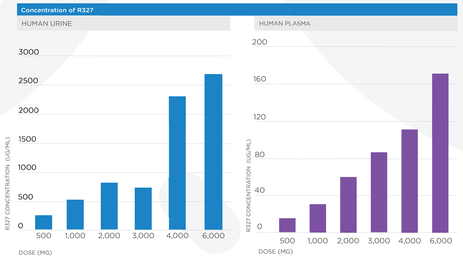
- In a pilot study (unoptimized conditions), mice infected in their lungs with *M. abscessus* were treated with R327, nasally (intranasal), twice daily for five days.
- Nasal R327 treatment significantly reduced *M. abscessus* levels

Efficacy Accute Bacterial Sinusitis



- Nasal cavities of mice infected with *S. pneumoniae* (clinical isolate - ATCC 49619)
- Treatment of anaesthetised mice with R327 by both intranasal and intravenous routes significantly reduced nasal infection by *S. pneumoniae*

Clinical Trial



Concentration of R327 in Urine Compared to Plasma	Ratio Urine/Plasma
In over 60 healthy subjects	16x
	17x
	14x
	9x
	21x
	16x

- **R327 primary route of elimination** appears to be through the kidney to the ureters and bladder.
- **High concentrations of R327** noted in the urine of Phase I healthy subjects.
- **Insight consistent** with pre-clinical *in-vivo* kidney and UTI bacterial infection studies.
- **Opportunities for therapeutic in array of UTIs (uncomplicated UTI - single dose, complicated UTI, recurrent UTI, treatment resistant etc.)**
- Suggests **broader anti-infective treatment model** in pre-sepsis.