Recce Pharmaceuticals

Synthetic Anti-Infectives:
The New Approach the World Needs

ASX:RCE

Introduction

Antimicrobial resistance (AMR) is an urgent global health threat – multidrug resistant bacteria, or superbugs, are on the rise and have outpaced the development of effective antibiotics – threatening our ability to treat common infections and support modern medicine. Successful surgeries, chemotherapy treatment, and low maternal and neonatal mortality all depend on our ability to successfully treat infections.

With a historic lack of innovation in new antibiotic drug development the need for new antibiotics has never been greater as resistance has developed to most, if not all, currently approved antibiotics. The global antibiotic pipeline remains deficient with no new classes of antibiotics developed in over 30 years. Due to this, new types of resistant mechanisms and multidrug-resistant bacteria continue to emerge and spread globally.

By 2050, The World Health Organization (WHO) estimates antibiotic resistance associated deaths may increase to millions of deaths annually, overtaking deaths projected from cancer, diabetes or car accidents, if no action is taken.

The Infectious Diseases Society of America (IDSA) has named a group of nosocomial pathogens commonly associated with AMR as 'ESKAPE pathogens' based on an acronym encompassing their names. ESKAPE pathogens include both Gram-positive and Gram-negative species and are made up of *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species.*

A New Hope in Medicine – Recce Pharmaceuticals

Recce Pharmaceuticals Ltd (ASX: RCE) is an Australian listed company pioneering the development and commercialisation of New Classes of Synthetic Anti-Infectives designed to address the urgent global health problems of antibiotic resistant superbugs and emerging viral pathogens.

Recce's lead antibiotic candidate, RECCE® 327 represents the first of a new class of antibiotics in over 30 years. Recce has expanded its anti-infective pipeline with the addition of RECCE® 529, a new synthetic polymer formulation with an enhanced affinity for protein-based viruses and RECCE® 435, a broad-spectrum synthetic polymer antibiotic formulated for oral use.

Initially developed for the treatment of sepsis, a life-threatening blood infection for which no specific treatments exist, RECCE® 327 has demonstrated in preclinical studies it is a fast acting, broad-spectrum antibiotic effective against Gram-positive and Gram-negative bacteria, including antibiotic resistant superbugs.

In 2017, RECCE® 327 was awarded Qualified Infectious Disease Product (QIDP) designation under the Generating Antibiotic Initiatives Now (GAIN) Act – labelling RECCE® 327 for Fast Track designation, plus 10 years of market exclusivity post approval. Recce wholly owns its automated manufacturing facility and is currently producing in volumes to support planned human clinical trials. Parallel to the Phase I clinical trial, under the Therapeutic Goods Administration (TGA) Special Access Scheme (SAS), Category A, Recce is permitted to supply RECCE® 327 to Australian medical practitioners in defined circumstances.

Recce's synthetic polymer compounds have a unique mechanism of action against the hyper-mutation of bacteria and viruses that allow it to overcome antibiotic resistance as well as any changes in active virus sites.[1]

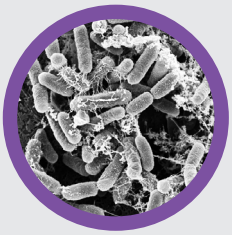
RECCE® Anti-Infectives' Universal Mechanism of Action

Recce is advancing new classes of synthetic polymer anti-infectives with rapid bactericidal and anti-viral activity.

Any bacteria present in the bloodstream is bad bacteria, which can often lead to sepsis. Doctors treating sepsis patients are in a race against time – each hour sepsis goes untreated the likelihood of patient mortality increases by 6%. RECCE® 327 is an efficacious broad-spectrum antibiotic delivered through intravenous (IV) infusion, to treat bacterial sepsis, including strains caused by multidrug resistant bacteria. Once RECCE® 327 enters the bloodstream, it is attracted to the plasma membranes of bacteria via hydrophobic interaction. It binds to the plasma membrane proteins, subsequently weakening the bacterial cell walls.

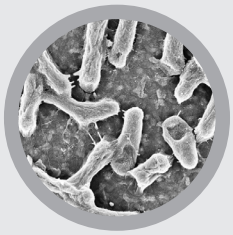
Due to the unique high metabolic pressure in bacteria, the cell walls collapse or burst (cell lysis), leading to bacterial cell death. Importantly, non-bacterial (eukaryotic) cells remain intact as they do not contain high internal pressures that result in cell lysis.

RECCE® 327 Mechanism of Action



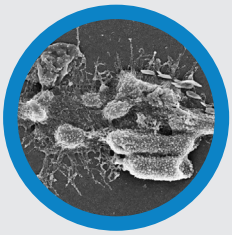
0 MINUTES

E. coli cells are healthy, smooth and intact



20 MINUTES

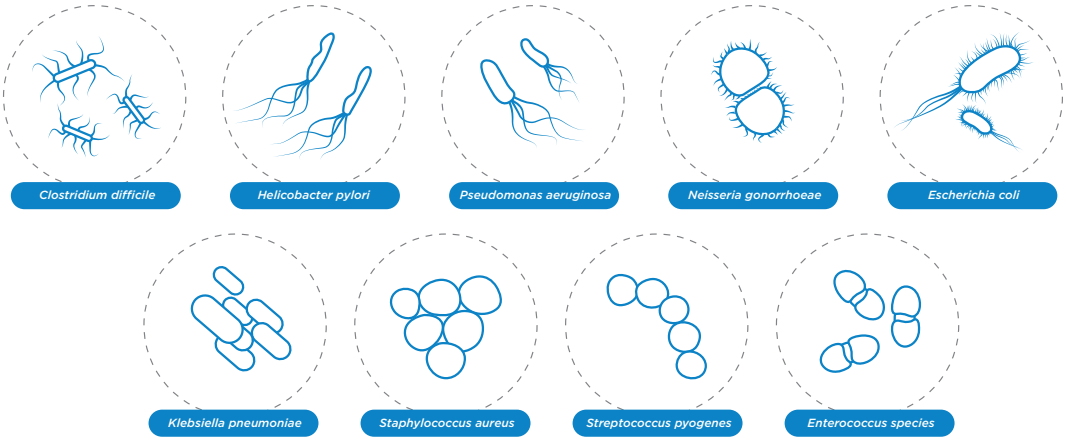
Significant cell-membrane weakening and disruption



3 HOURS

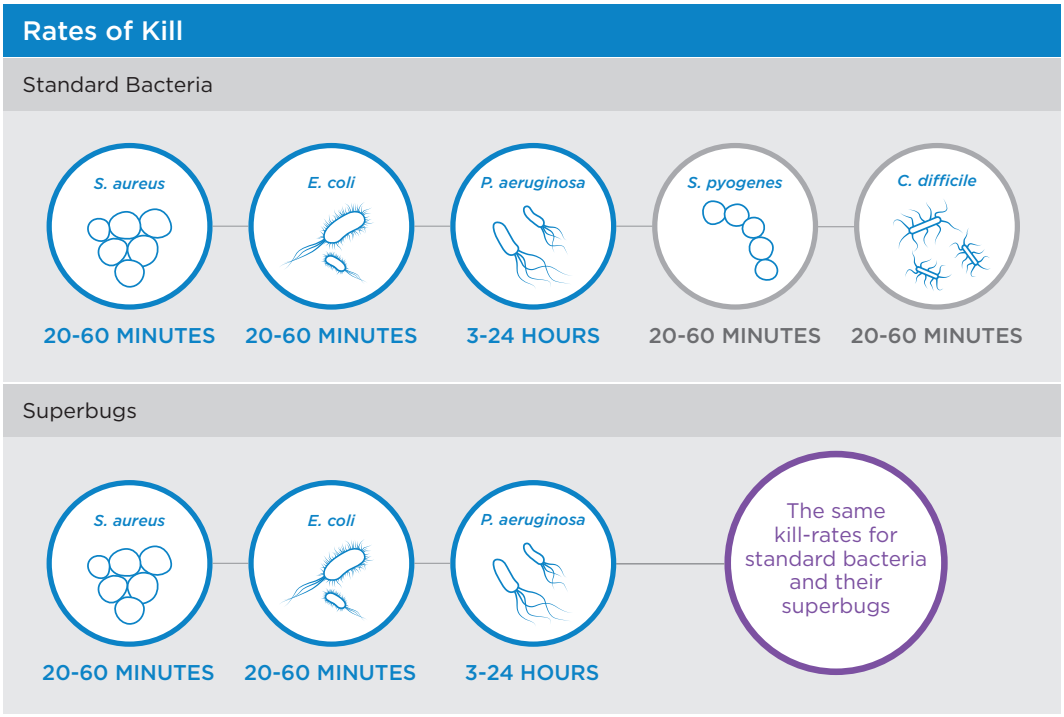
Cell lysis and bacteria are destroyed

Specifically, RECCE® 327 has demonstrated broad-spectrum capability against a range of Gram-positive and Gram-negative bacterial pathogens.



Despite advances in diagnostic tools, antibiotic resistance remains a challenge. Patients are often prescribed a cocktail of traditional antibiotics while waiting for cultures to determine the exact nature of the infection in order to prescribe the most suitable antibiotic.

The advantage of RECCE® 327 is that it displays the same kill-rates for standard bacteria and their superbugs forms. This is crucial for patients who may be rapidly deteriorating with no clear diagnostic determination of the infection or its cause.



Recce's synthetic anti-infectives have been designed to empower physicians with an efficacious treatment that can be used against a broad range of bacteria and viruses without contributing to resistance.

Applying a Synthetic Approach to Antibiotic Resistant Superbugs

Recce's lead candidate, RECCE® 327, is bactericidal, which means it kills the bacteria rather than inhibiting their growth. Even after repeated use, Recce's anti-infective compounds show no reduction in efficacy. Preclinical dose ranging studies demonstrated RECCE® 327's drug concentration in the blood has a large therapeutic window. It remains active long enough to effectively kill pathogenic bacteria, without persisting long enough to induce toxic effects.

Traditional antibiotics generally operate much like a 'lock and key' mechanism of action. When a traditional antibiotic is used against a bacterium, it often works until the bacteria mutates and the 'key' no longer functions. The new class of compounds synthesized by Recce are polymeric molecules designed to overcome these limitations. Rather than inhibiting a specific bacterial protein or process, RECCE® 327 can overcome potential bacterial mutations through its universal mechanism of action – operating like a 'master key'.

By introducing RECCE® 327 as a new treatment option to reduce the use of traditional antibiotics, there is potential to lower the selective pressure on bacteria and viruses that lead to the development of resistance.

RECCE® 327 A New Class of Antibiotic Tackling Multiple Pathogens and Indications

Unlike current antibiotics, which typically exhibit resistance, RECCE® 327 has demonstrated repeated capability against a range of Gram-positive and Gram-negative bacterial pathogens.

Assaying RECCE® 327 efficacy in bacterial pathogens

In addition to its lead indication of sepsis, Recce have evaluated RECCE® 327 as an IV treatment for kidney and urinary tract infections (UTIs) caused by *Escherichia coli (E. coli)*, which can often progress to sepsis.

In Recce's Methicillin-Resistant *Staphylococcus aureus* (MRSA superbug) study, rats with topical burns treated with RECCE® 327 demonstrated compelling *in-vivo* antibacterial activity. The results showed that RECCE® 327 was effective in reducing bacterial load within a wound and showed enhanced wound contraction compared to the best in class – Soframycin.

A further study was undertaken against MRSA, which showed significant *in-vivo* antibacterial activity in rats with topical burns treated with RECCE® 327.

RECCE® 327 continued to show efficacy at different dose levels with significant reduction in bacterial count in the infected wound when compared to the vehicle control ($p<0.05$). In this study Soframycin was applied twice daily at optimum therapeutic dose whereas a once daily application of RECCE® 327 demonstrated greater antibacterial efficacy reinforcing that RECCE® 327 may be a more effective antibiotic without additional toxicity considerations associated with similar doses of Soframycin.

GROUP 1

Burn wound with infection, **no treatment** – sterile topical saline, once daily.

GROUP 2

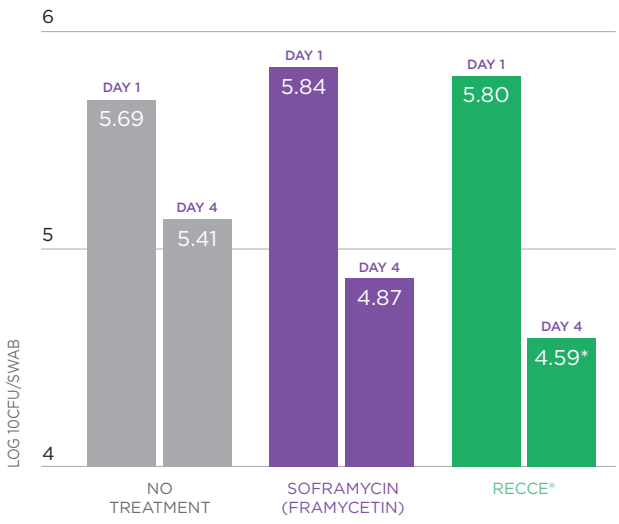
Burn wound with infection + Market drug – **Soframycin**, **twice daily**.

GROUP 3

Burn wound with infection + **RECCE® 327** – topical once daily.

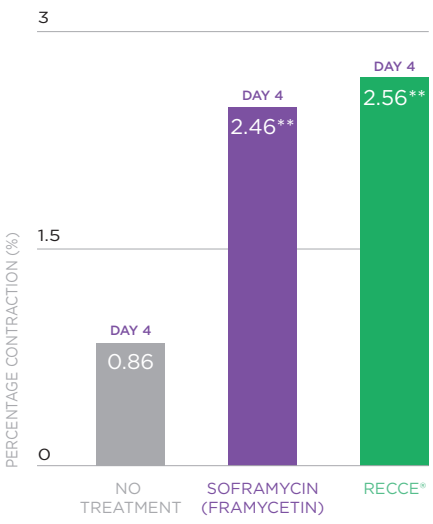
Bacterial Load on Wound

Methicillin-Resistant
Staphylococcus aureus (MRSA)



Wound Healing

Methicillin-Resistant
Staphylococcus aureus (MRSA)



RECCE® 327 mg/kg dosing is based upon 'total administered solution'. A significant proportion of RECCE® 327 administered solution quoted includes inactive components such as diluent/water and stabilizing medium. The Active Pharmaceutical Ingredient (API) as is sometimes the quoted mg/kg of the comparative product/s, likely to dramatically benefit by way of reduction to the otherwise stated RECCE® figure.

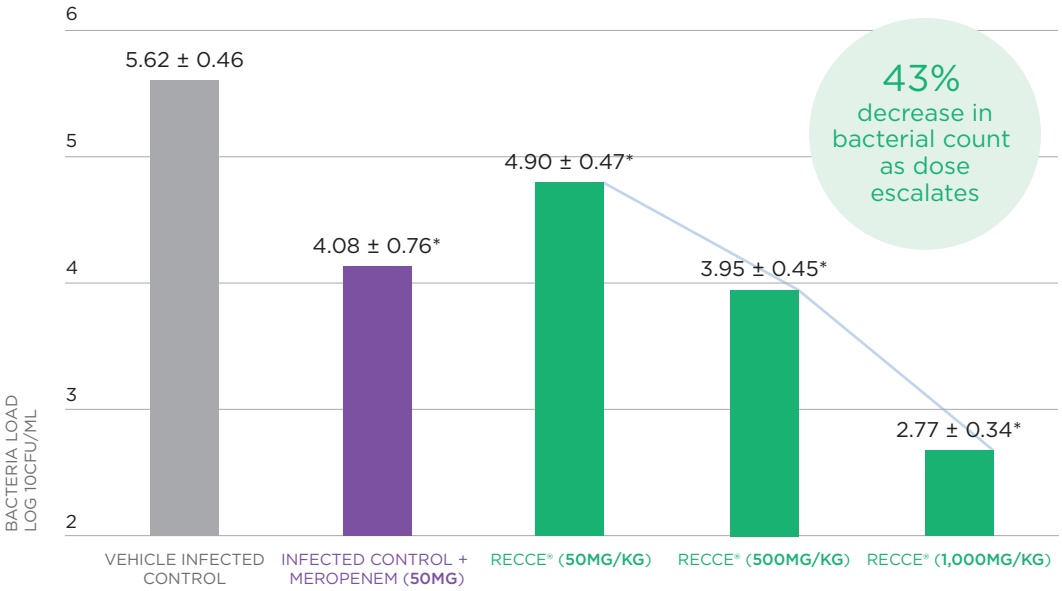
**Significantly lower than Day 1.*
***Significantly different from vehicle control.*
Trial conducted by independent clinical research organization.

In a mouse model study carried out by an independent contract research organization, RECCE® 327 demonstrated significant *in-vivo* antibacterial activity against *Neisseria gonorrhoeae (N. gonorrhoeae)*, a species of Gram-negative bacteria and the second most common sexually transmitted infection (STI) globally. The data demonstrated a dose-dependent decrease in bacterial load in infection as compared to the vehicle control and approved therapy.

In this study Meropenem, a broad spectrum carbapenem antibiotic, was used at its optimum dose as the recognized efficacy model. In practice however, Meropenem's high rates of bacterial resistance have recently led to restriction of its use strictly reserved for infections caused by resistant organisms.

Efficacy of RECCE® 327

Against *N. Gonorrhoeae* in Mice



**(p<0.05) significantly different from vehicle control.*

RECCE® 327 mg/kg dosing is based upon 'total administered solution'. A significant proportion of RECCE® 327 administered solution quoted includes inactive components such as diluent/water and stabilizing medium. The Active Pharmaceutical Ingredient (API) as is sometimes the quoted mg/kg of the comparative product/s, likely to dramatically benefit by way of reduction to the otherwise stated RECCE® figure.

Furthermore, previous *in-vitro* studies evaluating RECCE® 327 against *S. aureus, E. coli,* and *P. aeruginosa* bacteria showed no resistance, even after over 25 repeated exposures. RECCE® 327 continued to display the same clinically relevant kill-rates for standard bacteria and their superbug forms. This data suggests that RECCE® 327 may be more effective against a wider range of bacteria and may come without the toxicity concerns associated with current antibiotics. It also supports RECCE® 327's hypothesized universal mechanism of action against mutating bacteria.

Additional RECCE® 327 Formulations in Bacterial and Viral Diseases

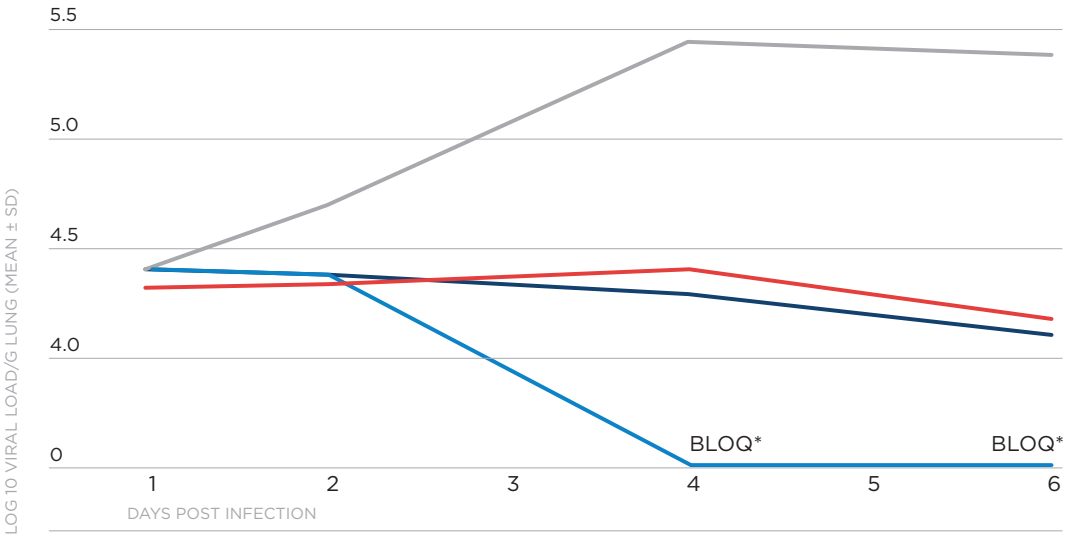
Recce Pharmaceuticals is continuing to develop its pipeline against other serious bacterial and viral diseases. Recce will leverage its versatile synthetic polymer platform, which are easily formulated for topical, nasal, oral or inhaled use to create additional anti-infectives against a range of infectious diseases.

As a new class, synthetic polymer drugs may be effective against other deadly superbugs, beyond those that are bacterial in origin, including viruses. In particular, Recce's 'master key' synthetic anti-infectives have exhibited efficacy against the Influenza A virus in mice. RECCE® 327 showed a significant dose-dependent decrease in the viral growth rate and viral load in lungs for mice infected with Influenza A following treatment with RECCE® 327 compared to the control group, and a group treated with an approved antiviral drug. At 1000mg/kg, the viral count fell below the limit of quantitation (BLOQ) on Days 4 and 6 post-infection.

Influenza A viruses are enveloped viruses and causative agents of respiratory disease. The genome of the Influenza A viruses comprises single-stranded ribonucleic acid (RNA) molecules – similar to that of coronaviruses, where the genome also comprises single-stranded RNA.

Efficacy of RECCE® 327

Against Influenza A Lung Infection in Mice



*BLOQ – Below Limit of Quantitation.

RECCE® 327 mg/kg dosing is based upon 'total administered solution'. A significant proportion of RECCE® 327 administered solution quoted includes inactive components such as diluent/water and stabilizing medium. The Active Pharmaceutical Ingredient (API) as is sometimes the quoted mg/kg of the comparative product/s, likely to dramatically benefit by way of reduction to the otherwise stated RECCE® figure.

Group	Day 1	Day 6	% Change
VEHICLE CONTROL	4.38	5.32	+19.308%
RIBAVARIN 66MG/KG	4.29	4.16	-3.08%
RECCE®327 500MG/KG	4.39	4.09	-7.08%
RECCE®327 1,000MG/KG	4.39	BLOQ*	-100%

Recce has developed a new compound RECCE® 529, focused on viral indications following background anti-viral research. Claims to RECCE® 529 have been lodged in a provisional Patent Family 4 submission and are expected to be built upon as independent COVID-19 study data becomes available.

RECCE® 327 and RECCE® 529 against COVID-19

The ongoing global pandemic highlights the critical need and importance of new treatments like RECCE® 529 to help reduce the spread and mortality rate of patients infected by SARS-CoV-2. As noted with past viral pandemics, a substantial amount of deaths are caused by secondary bacterial infections, often starting as pneumonia and progressing to sepsis.

In response to the pandemic, Recce is undertaking initial studies of RECCE® 529 to investigate its potential therapeutic effect against SARS-CoV-2, the virus that causes COVID-19. In collaboration with U.S. based company Path BioAnalytics, Inc. (PBA) and the University of Tennessee, this international research study will evaluate the anti-viral activity of RECCE® 327 and RECCE® 529 against SARS-CoV-2 in an *ex-vivo* respiratory model system.

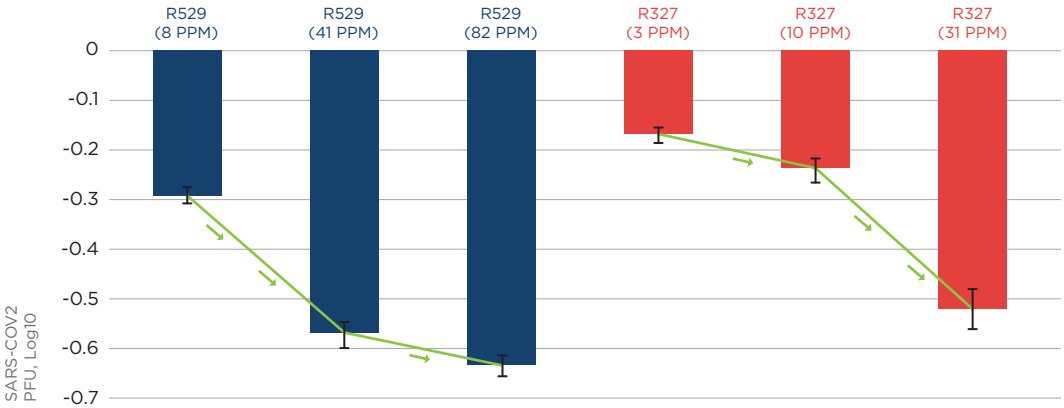
PBA's respiratory organoids are pseudo-stratified, differentiated 3D cell cultures derived from primary respiratory cells that replicate the airway physiology and are amenable to SARS-CoV-2 infection. Unlike conventional model systems, this organoid technology does not place selective pressure on viruses, thus maintaining an accurate representation of viral infection.

Recce's work with PBA has shown concentration-dependent reductions in SARS-CoV-2 (COVID-19) virus infection as compared to a control group for both RECCE® 327 and RECCE® 529 treated respiratory organoids. Based on these results, U.S. researchers have recommended that further studies are warranted, and Recce should advance research of both compounds. As such, Recce has secured testing of the compounds in an *in-vivo* COVID-19 infection animal model study. The method of administration in the study will be intranasal administration to target viral infection in the airways/lungs. In a separate study, RECCE® 327 and RECCE® 529 indicated an excellent toxicity profile with less than 0.25% effect on Vero (monkey) cells at the concentrations tested.

Concentration-dependent Reduction in Viral Infection

Relative Change over Baseline vs Control - 48hrs

Values reported as Mean ± SD



COVID Organoid Protocol: Organoids comprising human airway epithelial (HAE) cells were infected by inoculation with SARS-CoV-2 virus and incubated at 37 deg C with varying concentrations of R327 (H:31ppm, M:10ppm, L:3ppm) and R529 (H:82ppm, M:41ppm, L:8ppm) and viral load – measured by the number of PFUs (plaque-forming units of virus) – assessed at time points. The Control was polyethylene glycol (PEG) 200.

Further to Recce's advancements in the US, RECCE® 327 was selected to be in a SARS-CoV-2 Antiviral Screening Program to be conducted in Australia. The SARS-CoV-2 Antiviral Screening Program is a fee-for-service research program being conducted at a scientific Australian Government agency and a world class institute focused on infection and immunity.

Evaluation of RECCE 435® against *Helicobacter pylori*

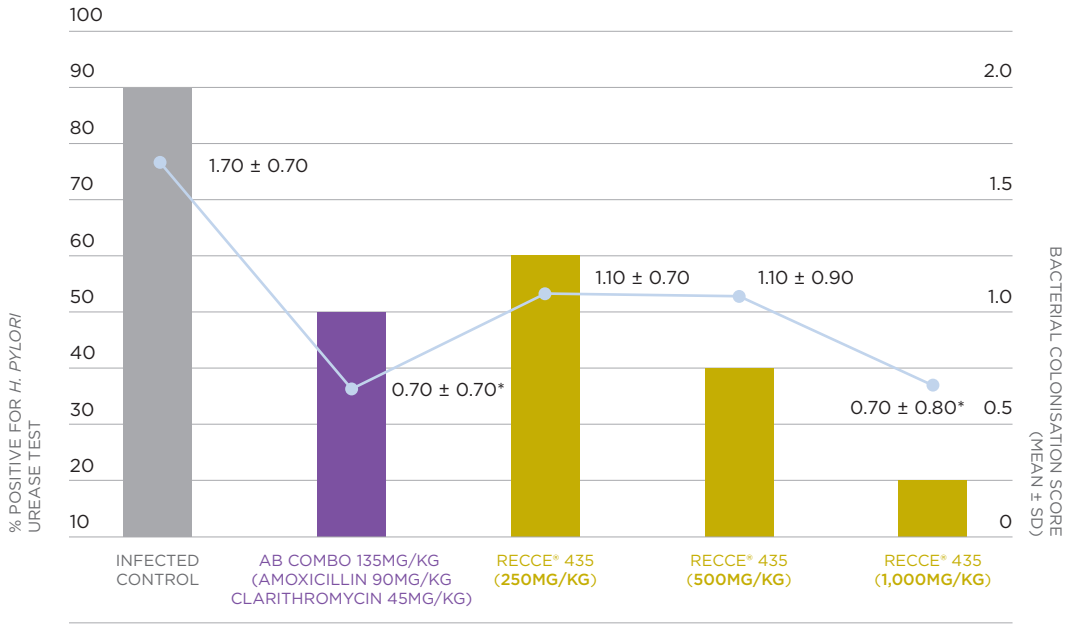
Recce Pharmaceuticals recently announced its new broad-spectrum synthetic polymer antibiotic formulated for oral use, RECCE® 435. This compound has shown positive efficacy against *Helicobacter pylori (H. pylori)* bacteria in rats treated with the new antibiotic, including a favorable toxicity profile in a related study.

Helicobacter pylori is a species of Gram-negative bacteria commonly infecting the lining of the stomach and upper digestive tract with particular prevalence in the neighboring Asia-Pacific region. There is no available first-line therapy that is curative in all patients at this time. *Helicobacter pylori* is a major cause of morbidity and mortality worldwide and is estimated that more than 50% of the global population is infected.[5]

Results from a study evaluating RECCE® 435 against *H. pylori* in mice showed dose-dependent efficacy with a significant reduction in bacterial load. Upon completion of the study, a urease test was carried out upon the stomach lining to confirm the presence of *H. pylori* in the subjects as measured by a urease diagnostic test. No signs of toxicity were observed at any dosage level throughout the efficacy study.

RECCE® 435 Oral Rat Study

Helicobacter pylori (H. pylori)



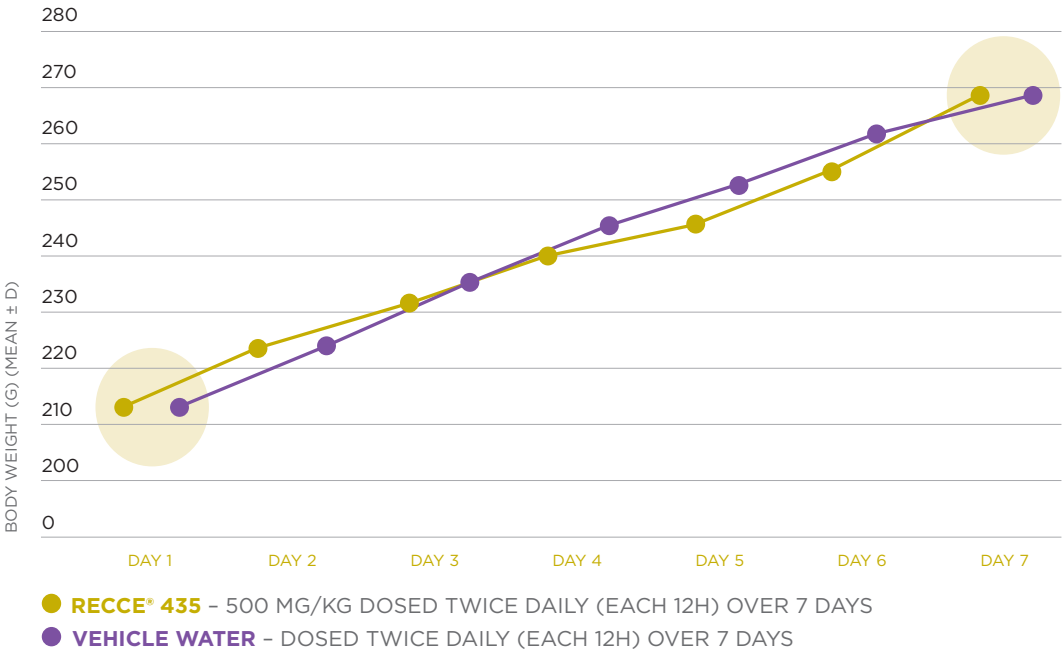
**significantly lower than infected control (p<0.05)*

RECCE® 435 mg/kg dosing is based upon 'total administered solution'. A significant proportion of RECCE® 435 administered solution quoted includes inactive components such as diluent/water and stabilizing medium. The Active Pharmaceutical Ingredient (API) as is sometimes the quoted mg/kg of the comparative product/s, likely to dramatically benefit by way of reduction to the otherwise stated RECCE® figure.

Most importantly, an additional independent study examining the safety of oral dosing of RECCE® 435 up to 500mg/kg was administered to groups of five mice each twice daily for seven days, compared to water-only administration. The data indicates their feeding habits, which contribute to weight gain, were not negatively impacted, supporting overall general and gastrointestinal health.

RECCE® 435 Oral Rat Study

Mean body weights of rats following oral administration with vehicle and RECCE® 435 group



RECCE® 435 – 500 MG/KG DOSED TWICE DAILY (EACH 12H) OVER 7 DAYS

VEHICLE WATER – DOSED TWICE DAILY (EACH 12H) OVER 7 DAYS

**significantly lower than infected control (p<0.05)*

RECCE® 435 mg/kg dosing is based upon 'total administered solution'. A significant proportion of RECCE® 435 administered solution quoted includes inactive components such as diluent/water and stabilizing medium. The Active Pharmaceutical Ingredient (API) as is sometimes the quoted mg/kg of the comparative product/s, likely to dramatically benefit by way of reduction to the otherwise stated RECCE® figure.

Moving forward, Recce has appointed Professor Philip Sutton, a global infectious disease expert with more than 30 years' experience, to their Clinical Advisory Committee and Head of the *H. pylori* development program. Professor Sutton currently leads the Mucosal Immunology Group at the Murdoch Children's Research Institute in Victoria, Australia with a specific interest in infections caused by the *H. pylori* bacterium due to its prominence and link to stomach ulcers and gastric cancer.

Manufacturing Recce's Synthetic Anti-Infectives

Recce's unique platform of anti-infectives are based on synthetic polymers that are wholly owned and manufactured in Australia.

Anti-infectives with a synthetic, polymer-based platform

Recce's anti-infectives are wholly synthetic and based on a patented polymeric structure that is 100% soluble in water at all pH levels. RECCE® anti-infectives can be formulated for IV, topical, nasal, oral, and inhaled use. This versatility is beneficial in developing the anti-infectives for indications beyond sepsis.

The polymer-based platform allows for the discovery and design of further novel anti-infectives by varying the compounds' composition. Recce's synthetic anti-infectives are more efficient to manufacture than current anti-infectives that are derived from naturally occurring sources.

Conventional methods that derive anti-infectives from natural sources rely on lengthy and large-scale manufacturing processes. This can involve cultivation of bacterial or viral cultures followed by several time-intensive purification stages. In contrast, Recce has an automated manufacturing process hour – producing 500 doses per automated manufacture output in less than one hour with a 99.9% product yield.

Recce has demonstrated its manufacturing quality and volume capabilities for RECCE® 327's first-in-human Phase I clinical trial.

First-in-Human Phase I Clinical Trial

Recce Pharmaceuticals has formalized a Phase I clinical trial agreement to conduct a first-in-human study of its lead compound RECCE® 327. The randomized, double blind, placebo-controlled single-ascending dose study will involve 48 healthy subjects to evaluate safety, tolerability, pharmacokinetic and pharmacodynamic properties of RECCE® 327.

The clinical trial will be conducted at CMAX Clinical Research, an independent trial facility located adjacent to The Royal Adelaide Hospital, centrally positioned in Adelaide South Australia. The clinical trial facility has consistently maintained world-class standards and meets international regulatory authority data entry and quality requirements, including the European Medicines Agency and U.S Food and Drug Administration (FDA). CMAX has more than 30,000 registered patient volunteers on file.

Summary

Without effective anti-infectives to treat bacterial and viral infections, lifesaving medical procedures such as surgeries may become risky to perform because of the potential of difficult-to-treat surgical site infections. Wholly owned and manufactured in Australia, Recce anti-infectives have the potential to address the increasing global threat posed by antibiotic resistance and emerging viral pathogens.

An estimated 700,000 people worldwide die each year from antibiotic resistant infections, many of which are 'ESKAPE' – the deadliest pathogens. If the current trends continue, superbugs will be the leading global cause of death by 2050. RECCE® 327 and RECCE® 435 represent one of the first new classes of synthetic antibiotics in over three decades that have the potential to continuously kill these pathogens. RECCE® 529 will be further investigated for efficacy and safety in animal model studies against common and emerging viral pathogens. RECCE® compounds have a universal mechanism of action that have been designed to empower physicians with an effective treatment, which can be used against a broad range of bacteria and viruses without developing resistance – even after repeated use.

Facts

US$100 Trillion

AMR could cost US$100 Trillion between now and 2050[4]

10 Million

If rates of AMR continue to rise the annual global death toll may reach 10 Million by 2050[4]

US$40k

Hospitals spend an additional up to US$40,000 to treat a patient infected by resistant bacteria[6]

2.8 Million

More than 2.8 Million antibiotic-resistant infections occur in the U.S. each year[7]

1 in 5

deaths globally (11 million) in 2017 were recorded due to Sepsis[2]

US$62 Billion

In 2019, the cost of sepsis care for inpatient admissions and skilled nursing facility admissions was more than US$62 billion[8]

48.7%

In ICU patients, approximately one-half (48.7%) of sepsis cases were acquired in the hospital[9]

1 in 3

patients who dies in a hospital has sepsis[3]

References

1 https://www.cdc.gov/flu/treatment/antiviralresistance.htm#:~:text=When%20an%20influenza%20virus%20changes,in%20viruses%20with%20reduced%20susceptibility
2 https://www.who.int/news-room/fact-sheets/detail/sepsis
3 https://www.cdc.gov/sepsis/clinicaltools/index.html#:~:text=Each%20year%2C%20at%20least%201.7,in%20a%20hospital%20has%20sepsis
4 The Review on Antimicrobial Resistance. 2015. Securing New Drugs for Future Generations: The Pipeline of Antibiotics. The Review on Antimicrobial Resistance, chaired by Jim O'Neill. Report commissioned by the UK Prime Minister. May 2015.
5 https://www.mja.com.au/journal/2016/204/10/epidemiology-clinical-impacts-and-current-clinical-management-helicobacter
6 https://www.oecd.org/health/health-systems/AMR-Policy-Insights-November2016.pdf
7 CDC's Antibiotic Resistance Threats in the United States, 2019 (2019 AR Threats Report).
8 https://www.healthleadersmedia.com/clinical-care/new-data-sepsis-prevalence-and-costs-astonished-dhhs-researchers
9 https://apps.who.int/iris/bitstream/handle/10665/334216/9789240010789-eng.pdf

recce.com.au