EDISON

Recce Pharmaceuticals

Initiation of coverage

Seeking a breakthrough in sepsis

Healthcare

8 March 2023

Price	**A$0.59**
Market cap	**A$105m**
	US$0.66/A$
Net cash (A$m) at 31 December 2022 (excludes A$4.3m R&D tax rebate cash receipt received in January 2023)	1.85
Shares in issue	178.3m
Free float	56.4%
Code	RCE
Primary exchange	ASX
Secondary exchanges	Frankfurt: R9Q, OTC: RECEF

Recce Pharmaceuticals is developing a novel class of broad-spectrum synthetic anti-infective drugs to which, so far, all tested bacteria have been unable to develop resistance. This could be a very desirable trait given widespread concerns about antimicrobial resistance (AMR). The lead indication for Recce's synthetic polymer antibiotic, Recce 327 (R327), is sepsis, a substantial area of unmet need with significant mortality and high costs of care. A Phase Ib/IIa multiple-dose study of an intravenous (IV) R327 formulation in healthy subjects is planned to start in H1 CY23. The company is also assessing other infection indications, such as complicated urinary tract infections (UTIs). A topical (spray-on) formulation of R327 is also being assessed in human trials for burn wound infections, and a new study for diabetic foot infections is expected to start shortly. We value Recce at A$497m, or A$2.79/share.

Year end	Revenue (A$m)	PBT* (A$m)	EPS* (A$)	DPS (A$)	P/E (x)	Yield (%)
06/21	1.9	(13.5)	(0.09)	0.0	N/A	N/A
06/22	3.1	(11.0)	(0.06)	0.0	N/A	N/A
06/23e	6.2	(17.5)	(0.10)	0.0	N/A	N/A
06/24e	5.9	(42.0)	(0.23)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding amortisation of acquired intangibles, exceptional items and share-based payments.

Broad-spectrum anti-resistant anti-infectives

Preclinical studies using lead candidate R327 have shown broad-spectrum activity against a wide range of gram-positive and gram-negative bacteria as well as COVID-19 and influenza. R327's lead indication is the treatment of sepsis and bacteremia (ie the presence of bacteria in circulating blood). Sepsis is the United States' most expensive condition in aggregate to treat in the hospital, costing the healthcare system US$57bn in inpatient costs, according to a recent review in *Critical Care Medicine*. This includes about 1.7 million sepsis cases in the US (49.8 million globally) and 270,000 deaths in the US (11 million globally).

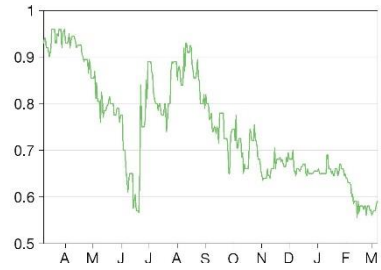
Robust clinical programme expected in CY23

Recce's Phase I single ascending dose study in Australia of the IV formulation of lead candidate R327 in healthy volunteers showed favourable safety in dosing up to 6,000mg (in a one-hour infusion). The company expects to start a multiple ascending dose study in H1 CY23, as well as a study in UTIs. A Phase I/II study in Australia of a spray-on topical R327 formulation is ongoing for the treatment of infected burn wounds, and Recce intends to start dosing in a Phase II study in H1 CY23 of the topical formulation in diabetic foot infections.

Valuation: A$497m or A$2.79/share

We value Recce at A$497m or A$2.79/share using a risk-adjusted NPV with a 12.5% discount rate, with IV R327 in sepsis being the lead value driver. We believe the novel anti-infective platform has wide potential in several indications. We note significant additional funding (modelled at A$220m, including an estimated requirement of c A$20m in H223) will be needed to advance R327 to commercial stage, which we project in FY28, and ongoing profitability.

Share price performance



%	1m	3m	12m
Abs	(1.7)	(8.5)	(37.9)
Rel (local)	0.3	(10.2)	(39.9)
52-week high/low		A$0.97	A$0.56

Business description

Recce Pharmaceuticals is an Australian company developing its novel, broad-spectrum synthetic polymer anti-infective drugs for the treatment of several infectious diseases, including sepsis (Phase II-ready), burn wound infections (Phase I/II) and urinary tract infections.

Next events

Start Phase Ib/IIa R327 (IV) multiple dose study in healthy subjects	H1 CY23
Start Phase II R327 (IV) study in urinary tract infections	H1 CY23

Analyst

Pooya Hemami CFA +1 646 653 7026

healthcare@edisongroup.com

Edison profile page

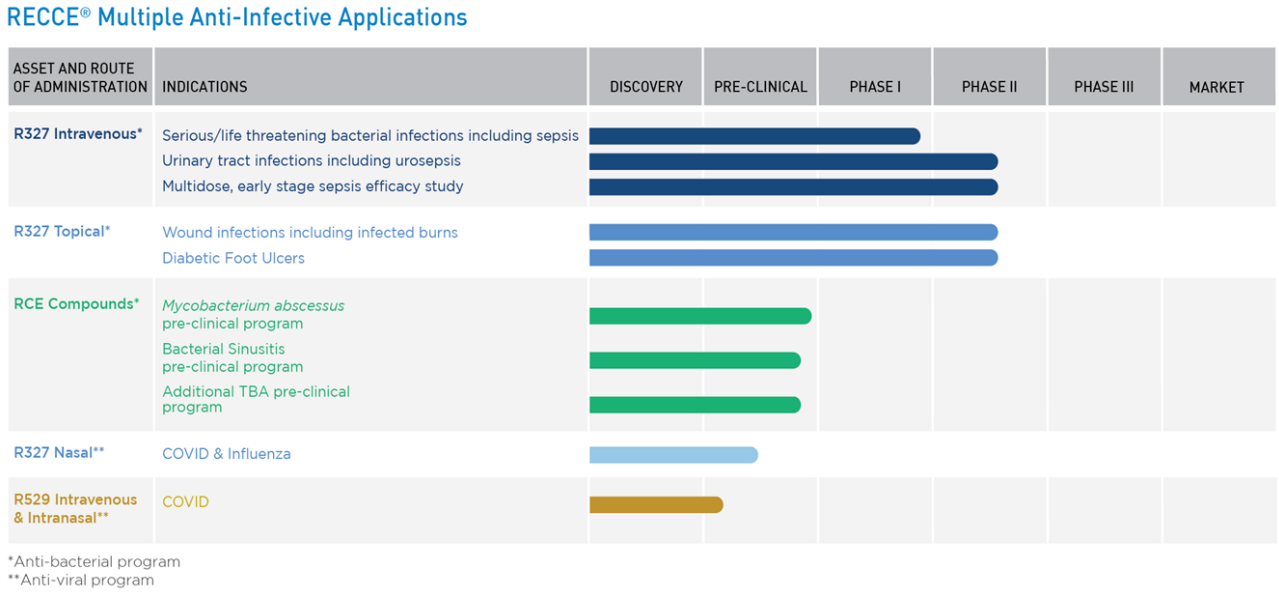
Investment summary

Company description: Novel, synthetic, potentially resistance-free anti-infective drugs

Recce Pharmaceuticals is an Australia-based, clinical-stage company developing a new class of novel anti-infective drugs (synthetic polymers) for the treatment of antibiotic-resistant bacteria and viral pathogens. Its lead pipeline candidate R327 is an IV formulation anti-infective being developed to treat life-threatening infections, including those that are antibiotic-resistant, with an initial focus on sepsis, one of the deadliest and most costly indications (at least directly) for the healthcare system. The drug has a novel, multifaceted mechanism of action (MoA) that has allowed it to show sustained effectiveness against a wide range of bacteria and viruses in preclinical models with no evidence of bacterial resistance observed to date. The company's internal testing showing no resistance formation even after multiple generations of bacterial replication could be a strong competitive advantage given widespread concerns about AMR. To our knowledge, R327 is the only clinical-stage antibiotic drug candidate being developed specifically for sepsis (although currently approved antibiotics are often used 'off-label' to treat sepsis).

Antibiotic treatment is generally considered the backbone of treatment for sepsis, with early treatment widely recognised as essential for patient recovery. However, drug-resistant bacteria, referred to as superbugs, along with physicians commonly being unable to identify the specific pathogen, can make early antibiotic treatment difficult, and delayed diagnosis or treatment is associated with increased mortality risk. Treatment with incorrect antibiotics can adversely affect patient outcomes and therefore a safe and broadly effective antibiotic for sepsis that can potentially be administered earlier, or with less fear of administering the wrong treatment, is sorely needed.

Exhibit 1: Recce Pharmaceuticals' pipeline



Source: Recce Pharmaceuticals

The company also recently began exploring IV R327 for complicated UTIs, and intends to begin a multi-dose study for complicated or resistant UTIs in H1 CY23. Approximately 25% of sepsis cases are reported to start in the urogenital tract.

Recce's secondary pipeline candidate is a spray-on topical formulation of R327, currently in a proof-of-concept Phase I/II clinical trial for the treatment of gram-negative and gram-positive burn

wound infections. The topical R327 formulation is also being advanced in diabetic foot infections, where the company received regulatory approval in Q4 CY22 to start an Australia-based Phase I/II study in diabetic foot infections, and it plans to start enrolment in H1 CY23.

The company also has an oral polymer formulation in preclinical development called R435. Lastly, R327 and a newer formulation, R529, are being assessed as anti-viral treatments in preclinical/research stages for treating COVID-19 and influenza, both as IV and nasal formulations.

The company was founded by its technology's inventor, Dr Graham Melrose, in 2008 and listed on the ASX in 2016. Dr Melrose, former Australasia head of research at Johnson & Johnson (J&J), is one of the company's largest shareholders.

Valuation: A$497m or A$2.79/share

Our valuation of Recce Pharmaceuticals at A$497m or A$2.79/share is based on a risk-adjusted net present value (rNPV) of the IV R327 formulation in sepsis and in complicated/recurrent UTIs, and of the topical spray formulation of R327 in burn wound infections and mild diabetic foot infections. We expect the company to commercialise R327 in the United States, Europe and Australia beginning in CY28 (for sepsis and burn wound infections, with remaining indications' market entry anticipated in CY29). Most of the value in our model is ascribed to the sepsis indication given the substantial unmet need in this area and that many of the remaining targeted indications are more manageable with a variety of other antimicrobial products; the pricing power may not be as robust for the topical indications, in particular. As per usual Edison policy, we do not assign value to the company's preclinical programmes. We are optimistic on R327's potential given its current characteristics (does not appear to promote resistant strains, broad spectrum, tolerable, rapidly and irreversibly bactericidal). A pharma partnership for any of Recce's pipeline candidates or transition into the clinic for additional indications could add value to our outlook.

Financials: Funding needed to advance pipeline

The company reported A$1.85m in net cash at 31 December 2022 and in January 2023, the company received A$6.2m in cash proceeds, with A$4.3m resulting from an Australian government R&D tax credit rebate, and an additional A$1.9m consisting of an advance payment from Radium Capital (which corresponds with a portion of the anticipated R&D tax credit to be received for the FY23 activities). Altogether, we model that it will raise a total of A$20m in H223 to fund its pipeline. Expenditures have increased as the company has progressed clinical development, with its operating cash burn rate increasing from A$9.0m in FY22 to A$10.2m in H123. We expect Recce's cash needs will expand as it funds clinical trials for its four targeted clinical-stage R327 indications. As is customary in the drug development sector, clinical trial costs are expected to rise as a drug candidate advances to later-stage development, given the need to recruit larger numbers of patients. We expect the company to benefit from Australia's 43.5% R&D refundable tax credit, where, unlike most Australian development-stage companies, Recce has been granted the ability to apply this tax credit to overseas R&D activities. Altogether, we forecast operating cash burn to rise to A$42m in FY24. We expect Recce will need to raise a further A$200m by FY28 before becoming sustainably cash flow positive. As per usual Edison methodology, we model these raises as illustrative debt.

Sensitivities: Sepsis is a difficult indication

Recce is subject to near-term and long-term clinical development risks, regulatory risks and commercial risks with physician adoption, as well as competitive risks and funding risks typical of biotechnology companies in this stage of development. We highlight that substantial funding (estimated at A$220m) will be needed in our view to bring all four targeted indications to market and challenges to obtaining funding may result in development delays and/or significant dilution (if raises are conducted via equity, and particularly if pricing terms are not favourable to existing

shareholders). In particular, we estimate that the amount of funding required exceeds the company's current market capitalisation and note that if our projected funding needs are entirely met through equity issuances at the prevailing market price (A$0.59/share) our current per share valuation would be revised to A$1.30.

Specifically with respect to sepsis, drug development has been highly challenging given the complex and multi-faceted nature of the condition (involving both infection and inflammation factors), resulting in many drug development failures; there have been no FDA-approved drugs aside from vasoconstrictor Giapreza (angiotensin II for septic shock) and Eli Lilly's withdrawn drotrecogin alfa. However, many of these clinical failures have been in the context of anti-inflammatories to curtail the inflammatory response, as opposed to the underlying infection, and represent an entirely different approach to sepsis compared with R327's anti-infective mechanism, which, if it confirms the broad spectrum of activity shown to date and lack of AMR, has the potential to reach a breakthrough in this challenging area.

Framing the Recce opportunity

The frightening past reality of infectious disease being a common cause of death is at risk of coming back in the coming decades if nothing is done to combat microbes' development of resistance against common antibiotics, as very few new classes of antibiotics have been developed in the past few decades. Natural selection processes drive antibiotic resistance; the use, misuse and overuse of antibiotics in inpatient and outpatient settings as well as common usage in animals for food production hastens the development of antibiotic resistance. The most dangerous of the resistant microbes are those referred to as superbugs, which can arise in the hospital setting and resist multiple antibiotics. Superbugs in the hospital present a sobering risk for surgical procedures.

AMR is a significant healthcare issue and is estimated to kill 700,000 people around the globe annually, and this amount is predicted by a United Nations interagency group to reach 10 million annually in 2050 if nothing is done to combat AMR. Additionally, a 2019 Centers for Disease Control and Prevention (CDC) report estimated that there were 2.8 million antibiotic-resistant infections causing 35,000 deaths annually in the United States.

AMR infections cost the United States' healthcare system billions of dollars every year, and to help stimulate R&D in anti-infectives, governments have helped subsidise antibiotic research and provided incentives, such as the qualified infectious disease product (QIDP) designation in the United States, which provides eligible anti-infective drug candidates expedited (priority) FDA review and extended market exclusivity if approved.

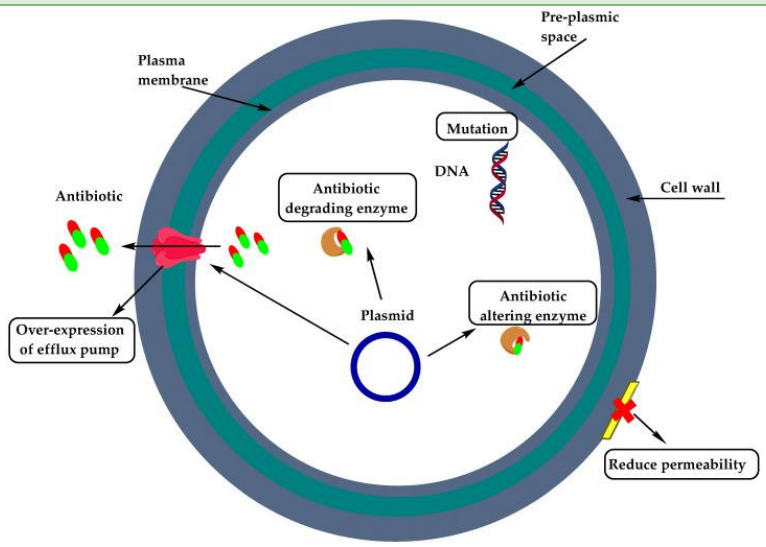
New antibiotics approvals dwindling

Pew Charitable Trust outlined the shortage of new classes of antibiotics that have been discovered and patented within the last 40 years. Most antibiotic drugs (since the first such molecules were discovered in the 20th century) were originally developed from compounds found in nature – soil particularly. The vast majority of new antibiotic approvals in recent decades have been new molecules falling within existing drug classes or acting against established bacterial site targets. According to a 2022 report by the Biotechnology Innovation Organization, the 2012 approval of bedaquiline (Sirturo, J&J), which inhibits ATP synthase, represented the first novel target approval in more than 30 years.

How bacteria develop antibiotic resistance

There are various mechanisms by which bacteria can become resistant. Gram-positive bacteria have two primary resistance mechanisms: resistance developed by learning to degrade an antibiotic enzymatically, and resistance developed by decreasing affinity or susceptibility of the antibiotic's target site. Secondary resistance mechanisms include a bacterium decreasing its membrane permeability or increasing the number of efflux pumps whereby a bacterium can jettison an antibiotic.

Exhibit 2: Gram-positive bacterial resistance mechanisms



Source: Jubeh, B., Breijyeh, Z., & Karaman, R. (2020). Resistance of Gram-Positive Bacteria to Current Antibacterial Agents and Overcoming Approaches. *Molecules, 25*(12), 2888.

Recce's potential solutions, introducing R327

Recce's approach to delivering novel anti-infective compounds to help address AMR and challenging infectious indications such as sepsis lie within its synthetic polymer technology platform, resulting in anti-infective drug candidates. Recce's primary patent describes the compound as a 'copolymer comprising an acrolein derived segment or a polyacrolein oligomer segment and a polyalkylene glycol oligomer segment, the copolymer having a molecular weight of no more than 1500 Daltons'.

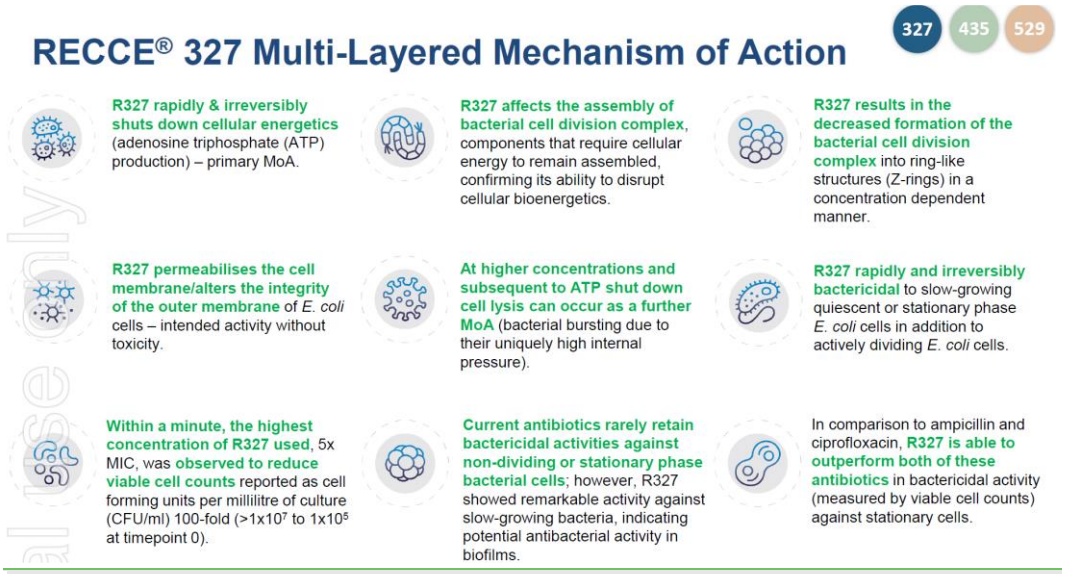
Recce cites its fully synthetic chemistry approach for its anti-infective compounds as a competitive advantage, given the resulting robust potential controls in production as well as the advantages in the chemistry itself (versus natural products) leading to AMR resilience. Most antibiotics currently in use were discovered as natural compounds (eg isolated from actinomycetes, including aminoglycoside, macrolide, tetracycline and amphenicol class antibiotic drugs) and produced via fermentation, and many penicillin derivatives (eg ampicillin) are considered semi-synthetic. On the other hand, fully synthetic antibacterials reflect a small fraction of currently approved drugs, with the fluoroquinolone class (eg ciprofloxacin, levofloxacin, moxifloxacin etc) and sulfonamide antibiotics considered synthetic drugs. Altogether, natural products have been the starting points for historical antibiotics discovery, but making specific chemical adjustments (ie to try to overcome AMR) to structurally elaborate natural products becomes increasingly difficult, and may have played a role in the slowdown in recent years in antibacterial drug discovery by this route. The synthetic approach, such as employed by Recce, may enable the design of complex structures (potentially resulting in novel MoAs that combat AMR) that may not be readily achievable with natural or semisynthetic antibiotics.

Multiple mechanisms of action appear to provide protection against AMR

As opposed to many antibiotics that generally have a single MoA, R327 functions in multiple ways. These have been detailed in several preclinical studies and the various mechanisms working in tandem are believed by management to be what allows R327 to kill and 'keep on killing' even resistant strains of bacteria, growing and nongrowing, including all ESKAPE pathogens.[1]

[1] Most severe hospital-acquired infections are caused by a group of six multi-drug-resistant bacteria collectively referred to as 'ESKAPE' pathogens, which are particularly virulent due to their AMR properties. These include: *Enterococcus faecium* (*E. faecium*), *Staphylococcus aureus* (*S. aureus*), *Klebsiella pneumoniae* (*K. pneumoniae*), *Acinetobacter baumannii* (*A. baumannii*), *Pseudomonas aeruginosa* (*P. aeruginosa*) and *Enterobacter* species.

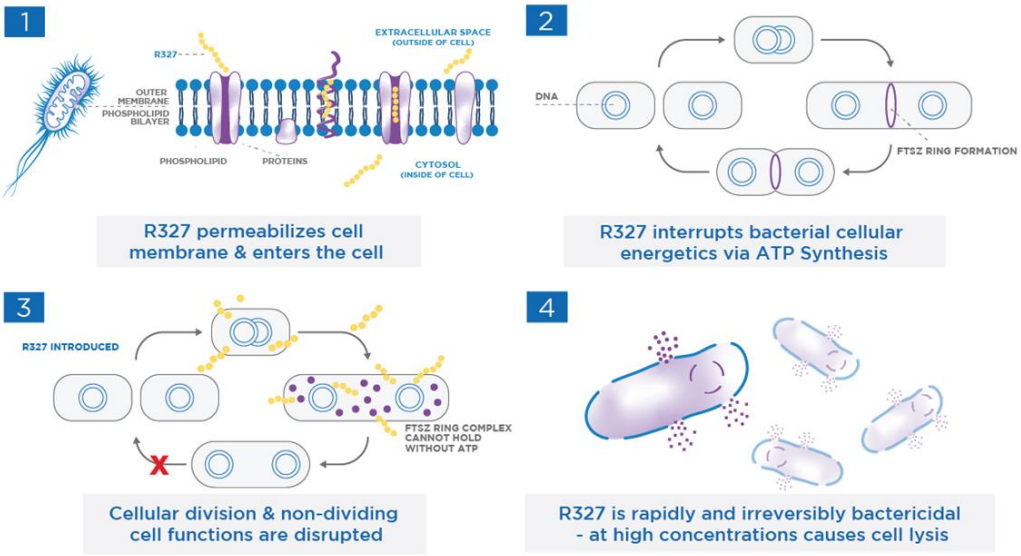
Exhibit 3: R327's multiple mechanisms of action



Source: Recce corporate presentation, January 2023

Exhibit 3 summarises the multiple MoAs whereby R327 can exert its effects. Among these, the primary identified and proposed antibacterial mechanisms for R327 involve disrupting cellular ATP production, halting cell division and directly disrupting the bacterial cell wall, causing lysis (which itself refers to the destruction of the cell following damage to its outer membrane). The drug permeabilises the bacterial cell membrane and can enter the cell, interrupting bacterial ATP synthesis, thus interrupting its source of energy. This in turn prevents cellular division by preventing the assembly of the bacterial cell division complex (which would be required for cellular replication).

Exhibit 4: Summary of R327 cell division disruption and lysis mechanisms of action



Source: Recce Pharmaceuticals

Favourable demonstration of inhibition of cellular replication

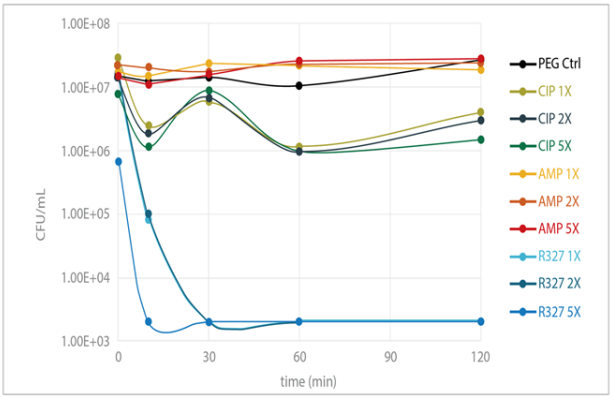
In R327's preclinical testing, *E. coli* isolates were tested with the minimum inhibitory concentration (MIC), and five times that concentration, of R327, resulting in only 22% (1x MIC) and 17% (5x MIC) of the cells containing FtsZ rings after 30 minutes. Tubulin-like protein FtsZ is generally required for bacterial cell division. FtsZ rings form from FtsZ filaments when bacteria are in the process of

dividing, and these rings are critical for division. The remainder of the cells did not contain full FtsZ rings following R327 treatment, and were therefore believed to be incapable of replicating further. The proportion of cells without FtsZ rings were even more pronounced at 60 minutes, suggestive of continued and expanded inhibition against cellular division.

Activity against non-dividing bacterial cells

A subsequent study (see Exhibit 5) investigated the efficacy of R327 against nondividing or stationary-phase *E. coli*. The drug outperformed ciprofloxacin (CIP) and ampicillin (AMP) at all relative dose levels, rapidly and irreversibly reducing viable bacterial colony forming units (CFU) to less than 1/100th of baseline.

Exhibit 5: In vitro change in *E. coli* CFU versus time



Source: Recce Pharmaceuticals

These studies indicate that R327 may exert its ATP-limiting effects on bacteria regardless of their dividing state, likely by interfering with protein synthesis, which gives confidence in the drug's potential ability to clear up infections. To date and to our knowledge, the drug has not failed to show activity against any form of bacteria.

Bactericidal activity at high concentrations

At higher tested concentrations, R327 is bactericidal (ie kills bacteria) and causes cell lysis to bacteria but not animal cells or fungi. The drug works to disrupt the bacterial cell membrane activity through nonspecific hydrophobic interactions (ie forces relating to the repulsion of water) between R327 (an acrolein polymer as stated above) and the bacterial cell membrane itself. The drug is not known to bind specifically or with high affinity to any bacterial cell wall component (recall that unlike animal cells, most bacterial cells contain a cell wall). However, these nonspecific R327 hydrophobic interactions mildly disrupt the bacterial cell wall and are bactericidal. The main reason this interaction is bactericidal without affecting fungi or animal cells is because bacterial cells have high internal pressure. This is referred to as the Turgor pressure, which can vary between bacteria types, anywhere from 5–30 atm (1 atm being atmospheric pressure) for gram-negative to gram-positive bacteria. The bacterial wall is what protects the membrane, which pushes up against it, from bursting due to this pressure. When the wall's integrity is compromised, the cell can burst.

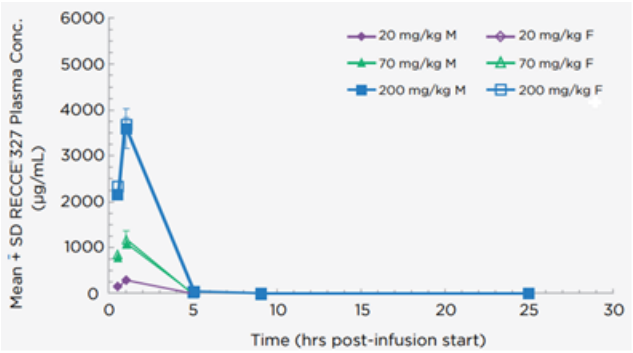
Toxicology studies

Toxicology trials conducted to date have not shown any stimulation of the immune response, which is critical in sepsis treatment. R327's selective membrane interaction with bacterial cells has been verified by two independent US laboratories, both testing on whole human blood with no significant hemolysis observed.

Additionally, pharmacokinetic analyses conducted in rats and dogs indicate that IV-infused R327 is cleared from the bloodstream within hours (likely well after exertion of its anti-infective effects). This

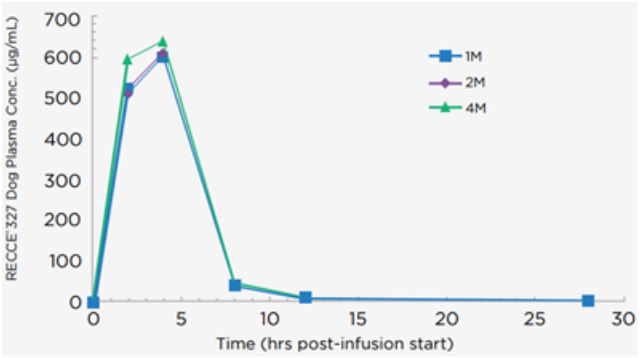
likely lowers the likelihood of toxic build-up or systemic toxicity. In-vitro studies of cell line assays have concluded that R327 does not promote mutation across a wide range of concentrations. Specific metabolism studies following clearance from the bloodstream will be conducted as part of the company's current preclinical preparation for investigational new drug (IND)-enabling studies (needed prior to the start of a US study).

Exhibit 6: R327 blood clearance (bolus)



Source: Linnaeus Bioscience, Recce Pharmaceuticals

Exhibit 7: R327 blood clearance (four-hour infusion, 70mg/kg)



Source: Linnaeus Bioscience, Recce Pharmaceuticals

Bacterial rates of killing

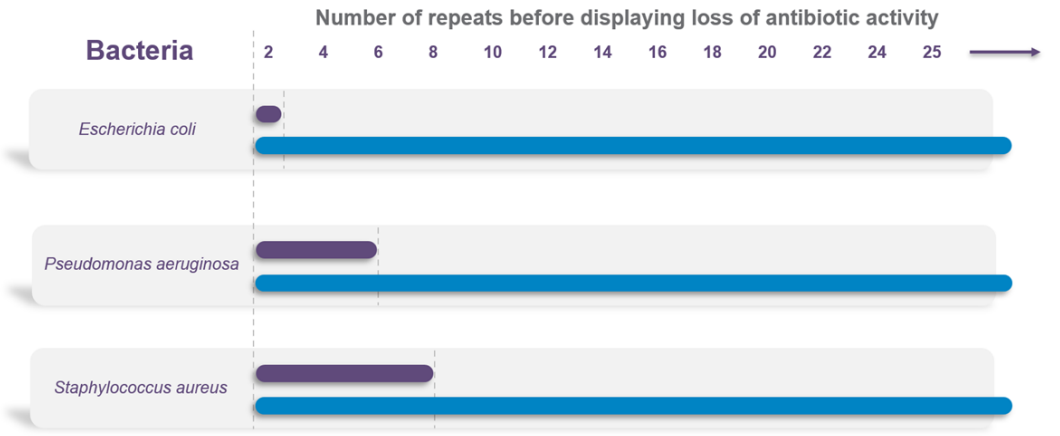
R327 has demonstrated in-vitro rates of killing various bacteria within the amount of time it takes to clear from the bloodstream (see Exhibits 6 to 8), suggesting potential use for the treatment of sepsis or bacteremia infections.

Exhibit 8: Rates of killing of bacteria (10^6 CFU/mL) by RECCE antibiotics (1,000ppm)

	RECCE 327	RECCE 355
S. aureus	1-3 hours	20-60 mins.
S. pyogenes	20-60 mins.	20-60 mins.
E. faecalis	1-3 hours	-
E. coli	20-60 mins.	-
P. aeruginosa	3-24 hours	3-24 hours
C. difficile	-	20-60 mins.
Superbugs		
MRSA (S. aureus)	1-3 hours	20-60 mins.
VRE (E. faecalis)	1-3 hours	-
K. pneumoniae	20-60 mins.	-
S. aureus (see below)	1-3 hours	20-60 mins.
E. coli (see below)	20-60 mins.	20-60 mins.
P. aeruginosa (see below)	3-24 hours	20-60 mins.

Source: Recce Pharmaceuticals

Exhibit 9: Generations of bacteria tested without resistance, R327



Source: Recce Pharmaceuticals. Note: Purple line represents an unspecified commercial antibiotic cited by Recce that generates more than US$10bn in revenue; blue line represents R327, for which the company specifies that it did not demonstrate a loss of antibiotic activity even after 25 repeats.

One of the strongest attributes, in our view, is that Recce has not observed resistance of any bacterial strain to R327. Exhibit 9 shows the results of an experimental comparison between R327 and a commercial antibiotic, whereby repetitive use of the competing antibiotic generated resistant strains of three different bacteria within eight generations of bacteria but R327 did not generate resistant strains even after 25 generations of bacteria.

Sepsis pathophysiology, epidemiology and treatment overview

Given the drug's promise in treating preclinical bacteremia (the presence of viable bacteria in the circulating blood) and a broad range of bacteria, the company is pursuing sepsis, a difficult clinical indication that can arise from a variety of pathogens, as its lead indication. Sepsis is mainly caused by bacteremia, and most studies show that gram-positive bacteria are the predominant cause. *S. aureus* (methicillin-resistant), *Streptococcus pyogenes* (*S. pyogenes*), *Klebsiella spp.*, *E. coli* and *Pseudomonas aeruginosa* (*P. aeruginosa*) are among the most frequently isolated bacteria in sepsis cases. Fungi only account for 19% of cases, according to a study in *Virulence*.

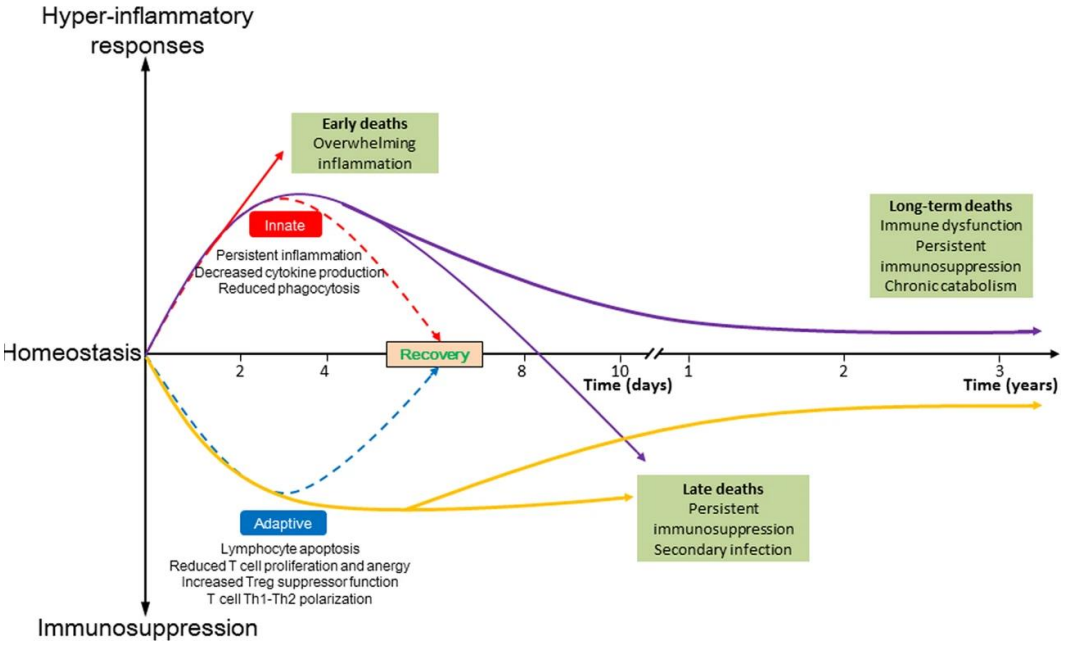
Sepsis is the body's distressed response to infection. More specifically, it is the excessive systemic inflammation (immune response) set forth as a defence mechanism against a significant infection, whereby the inflammatory response may cause damage to the host.

The underlying mechanisms by which sepsis develops and evolves are complex. As a brief overview, the systemic immune response to a bacterial infection causes activation of various immune cells and production of inflammatory agents including cytokines due to pathogen associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs) and lipopolysaccharides (LPS) produced by the bacteria. In a normal infection, the immune stimulation is fairly quickly resolved. However, in sepsis, the stimulus is far greater and a persistent activated and suppressive immune state can coexist.

This immune activation can go on to damage the host and also exhaust the immune system and cause mass immune cell death, whereby the patient is then left immunocompromised – in a phase of prolonged immune suppression with depleted and dysfunctional numbers of immune cells (natural killer cells, T-cells, macrophages, neutrophils, etc). This leaves the patient susceptible to (what would normally be) mild secondary infections. Exhibit 10 shows various host inflammatory responses to infection, consisting of an immune hyperinflammatory reaction shortly followed by a compensatory and concurrent suppressive response; instead of balance, this can result in both tissue damage from inflammation as well as susceptibility to infection and immune exhaustion due to the suppressive immune response. In some cases, patients will succumb to secondary

infections, while in other cases the systemic inflammatory and immunosuppressive responses persist, failing to resolve, which can cause morbidity and mortality due to fibrosis and organ damage. While infection is the underlying cause of disease and proper antibiotic treatment remains a cornerstone of initial sepsis treatment, a runaway inflammatory response may be untreatable with an antibiotic (which would not directly suppress or control the inflammatory response).

Exhibit 10: Dysfunctional septic inflammatory response



Source: Cao, C., Yu, M. & Chai, Y. Pathological alteration and therapeutic implications of sepsis-induced immune cell apoptosis. *Cell Death Dis* **10,** 782 (2019).

According to the CDC, at least 1.7 million American adults develop sepsis annually, with 270,000 of them dying of the acute disease, and one in three people who die in a hospital have sepsis. The underlying infection or the sepsis itself starts outside the hospital in 87% of cases.

Treatment and eradication of the underlying insult (pathogen) is considered critical to preventing or reducing the systemic overactivation of the immune system, as immune-mediated therapies such as NF-κB inhibitors, interleukin antagonists and steroids have had mixed results in studies assessing them for sepsis treatment, though these failures may be due to the fact that the immune response is both beneficial and detrimental, and therapies that aim to restore homeostasis rather than simply suppress the immune system may be required. In fact, focus has recently been shifted to the persistent immunosuppressive phase as a primary cause of sepsis patient mortality. Altogether, antibiotics are the cornerstone of sepsis treatment and many other treatment classes, many of which are inflammation-related, have failed to show benefit, as shown in Exhibit 11.

Exhibit 11: Sepsis therapy – a catalogue of failures

Target	Strategy	References
Lps/Endotoxin	HA-1A	Ziegler et al., 1991
	E5531	Bunnell et al., 2000
	Anti-CD14	Reinhart et al., 2004
	Eritoran	Opal et al., 2013
	Polymyxin B conjugate	Payen et al., 2015
Endocrinopathy	Methylprednisolone	Bone et al., 1989
	Vasopressin	Ohsugi et al., 2016
Hypercoagulability /Disseminated Intravascular Coagulation (DIC)	Activated Protein C	Bernard et al., 2001
	Anti-thrombin	Warren et al., 2001
	Heparin	Zhang and Ma, 2006
	Thrombomodulin	Hagiwara et al., 2016
Cytokines	Anti-TNF-α	Tracey et al., 1987
	IL-1 receptor Antagonists	Fisher et al., 1994
	Soluble TNF-α receptor	Borrelli et al., 1996
	Diacerhein	Calisto et al., 2012
Eicosanoids	Ibuprofen	Bernard et al., 1997
Nitric Oxide	L-NMMA	Petros et al., 1994
Oxidat1ve Stress	Statins	Patel et al., 2012
	Selenium	Sakr et al., 2014
Nf-Kb Transcription	Curcumin	Zhong et al., 2016
Apoptosis	Caspase inhibitors	Weber et al., 2009

Most, if not all, were targeting inflammation including caspase inhibitors. Caspases do have a central role in inflammation (Mandal et al., 2018).

Source: Nedeva, C., Menassa, J., & Puthalakath, H. (2019). Sepsis: Inflammation is a necessary evil. *Frontiers in Cell and Developmental Biology*, *7*.

The 2021 Surviving Sepsis Campaign (SCC) guidelines recommend that the administration of intravenous broad-spectrum antibiotics should be initiated within an hour if sepsis is suspected, or if the potential sepsis incident is without shock, rapid investigation is recommended with antibiotic administration within three hours if the concern for infection persists. Studies in septicaemia and septic shock show that delayed antibiotic administration is associated with detrimental outcomes including increased mortality,[2, 3, 4, 5] while inappropriate antibiotic selection has a detrimental outcome for patients.

Other treatment recommendations include the use of vasopressors to improve arterial pressure, administration of crystalloid fluids for resuscitation (plus albumin in patients who have received large volumes), additional corticosteroids in the case of ongoing need for vasopressors, and ventilation in the case of sepsis-induced acute respiratory distress syndrome (ARDS). However, front and centre of the treatment strategy is antimicrobial administration. An article (2020) in the *Journal of Thoracic Disease* states: 'One of the main concerns on the management of patients with

[2] Ferrer, R. et al. (2014). Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour. *Critical Care Medicine*, *42*(8), 1749–1755. https://doi.org/10.1097/ccm.0000000000000330

[3] Liu, V. X. et al. (2017). The timing of early antibiotics and hospital mortality in sepsis. *American Journal of Respiratory and Critical Care Medicine*, *196*(7), 856–863. https://doi.org/10.1164/rccm.201609-1848oc

[4] Kumar, A. et al. (2006). Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock*. *Critical Care Medicine*, *34*(6), 1589–1596. https://doi.org/10.1097/01.ccm.0000217961.75225.e9

[5] Kumar, A. (2009). Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. *Chest*, *136*(5), 1237–1248. https://doi.org/10.1378/chest.09-0087

sepsis and septic shock is the augmentation of antimicrobial efficacy, while preventing the emergence of resistant strains during treatment.'

R327's resistance to AMR and broad-spectrum activity could be key in sepsis

In our opinion, R327 appears to show the properties needed for having a solid chance of being the best 'one-size-fits-all' antimicrobial for sepsis given its properties of not having shown resistance to date (according to management), demonstrating broad antimicrobial activity, and being robustly bactericidal. With potentially little need to identify specific bacteria as all that have been tested to date have been destroyed rapidly by R327 according to the company's internal studies, the antimicrobial can potentially be administered more immediately without needing to wait for confirmation of the causative bacterial strain.

These attributes are of utmost importance in sepsis as inappropriate antibiotic selection is common (32%) and this was found by Leibovici et al. to increase mortality compared to appropriate antibiotic use (34% versus 18%). Additionally, it is common (~50% or greater) that no pathogen is identified. Various studies show that every hour that a patient with sepsis goes without antibiotics, the chances of mortality increase (range: 2–10% increase in mortality per hour), and so does the increase in morbidity in lieu of mortality, including expensive sequelae such as acute lung injury, acute kidney injury, multi-organ dysfunction (or worsening thereof) and increased patient length of stay. Hence, if the current safety profile is confirmed in future studies, clinicians may potentially use R327 without fear of inappropriate antibiotic administration or added risk of nephrotoxicity (often associated with combination antibiotic treatment), which can cause deleterious effects and increase the probability of mortality significantly.

Considerations of an antibacterial approach in sepsis

Recce's primary reason that R327 can improve patient outcomes with septicaemia is that, for every hour left untreated, the risk of mortality increases for these patients. However, in some sepsis cases, even if the pathogen is removed, the hyperinflammatory response may fail to resolve. For example, even if the bacterial pathogen is removed or inactivated (through antibiotic treatment or immune response), there is the risk that endotoxins or exotoxins released by the bacteria can provoke or worsen inflammatory reactions and damage bodily organs. Managing the effects of such toxins may be as important as eliminating the sepsis-causing bacteria in such cases.

R327 Phase I safety study of IV formulation

Recce conducted an in-human single dose-escalation study of the IV R327 formulation, with the initial design planned to enrol 80 healthy subjects with dosing up to 16,000mg (eight potential cohorts) over the course of 60 minutes, though this likely represents a dosing range much higher than required to eliminate infections, according to preclinical studies. In August 2022, the company reported that the drug was well-tolerated at a one-hour IV dose up to 6,000mg with no serious adverse events in a cohort of 10 patients at that dosing range. The company notes that the 6,000mg dose represents a 120-fold increase over the lowest dose cohort (50mg) of the trial, and to date over 60 healthy volunteers have been safely dosed with IV R327 in this Phase I study.

The study was conducted at Adelaide's CMAX clinical trial facility, and its primary endpoint was the safety and tolerability of R327, including the nature, frequency and severity of adverse events by treatment, laboratory safety parameters (serology, haematology, biochemistry and urinalysis), blood pressure and other vital signs (heart rate, respiration and temperature), physical examination and 12-lead electrocardiogram (ECG). Previously, minimal toxicity was detected at 4,000ppm (mg/kg) when dosing R327 in vero cells. The company indicated that 36 subjects have been dosed to date

in the first four arms, 1,000mg and below, with 10 subjects having subsequently been dosed in each of the 2,000mg, 4,000mg and 6,000mg arms (thus an estimated 66 subjects dosed to date). A key finding from this study was that R327's primary route of elimination was through the kidneys to the ureters and bladder, and that concentrations of R327 in the urine were c 15x higher than in the blood plasma. This has prompted the company to start investigating IV R327 UTIs (as discussed below) and to narrow in on urosepsis (sepsis that has been preceded by or was caused by UTIs) as the initial gateway to treating sepsis.

The company now plans to start a Phase Ib/IIa multiple-dose study in healthy volunteers in H1 CY23, assessing the drug's safety, tolerability and pharmacokinetics. Study completion is aimed for H2 CY23 and we expect the company to submit an IND application to the US FDA in Q4 CY23 and start a multiple-dose Phase II efficacy study in urosepsis in CY24. About 25% of sepsis cases are believed to originate in the urinary tract. While this planned Phase II efficacy study will concentrate on urosepsis, we assume that if results are positive, the pivotal Phase III programme (and overall commercial sepsis programme) will include all forms of sepsis. We anticipate the IV drug formulation to start pivotal Phase III sepsis studies (in Europe and the United States) in 2025 and, if approved, be commercialised in 2028.

Sepsis: Cost of care

Patient costs for sepsis in the United States were reviewed in *Critical Care Medicine* (2018). The average patient cost is US$21,568 (2010–16), with present-on-admission (POA) sepsis costing US$18,023 and non-POA costing US$51,022 and outliers increasing the average cost significantly. Thus, the average patient costs are in the tens of thousands of dollars and this provides a benchmark for R327 pricing power. We assume US$5,500 per patient per treatment course in the United States for R327 at launch, with a sales launch beginning in 2028 and a peak market penetration of 12.5% in 2032 (c 220,000 out of 1.7 million patients in the United States).

R327 for complicated UTIs

Given the high concentration of R327 in the kidneys as shown in the single ascending dose IV safety study above, UTIs present a natural application for R327, in our view. UTIs are the most common outpatient infections, with a lifetime incidence estimated at 50–60% among adult women. The prevalence increases with age, with women over 65 having about double the rate of that of the overall female population. UTIs can include cystitis, lower urinary tract and bladder infections and upper urinary tract and kidney infections. Simple UTIs are commonly treated with antibiotics such as trimethoprim/sulfamethoxazole, cephalexin, ceftriaxone and/or amoxicillin, but the most common bacterial cause of UTI (*E. coli*) is increasingly resistant to many of these drugs. Complicated UTIs, or cUTIs, are estimated to lead to about 626,000 hospital admissions per year in the United States, reflecting nearly 2% of all hospital admissions, and 80% of such UTIs are not believed to be related to the use of catheters. Recently approved drugs for treating cUTIs include Vabomere (meropenem/vaborbactam, Melinta Therapeutics, US$33m in 2021 sales), Zerbaxa (ceftolozane/tazobactam, Merck, US$130m in 2020 sales across all indications, although sales were voluntarily suspended for most of CY21 due to a product recall on sterility concerns) and Zemdri (plazomicin, Cipla Therapeutics following bankruptcy of developer Achaogen, US$86m in 2021 sales). We note that in September 2022, GSK entered into a licence agreement with Spero Therapeutics to obtain global rights (excluding Japan and certain Asian countries) to Spero's late-stage antibiotic candidate, tebipenem HBr, currently in development for cUTI. GSK paid US$66m upfront and purchased US$9m in Spero shares, and Spero will be entitled to up to US$150m in pre-commercial milestones, up to US$225m in commercial milestones, and tiered low single-digit to low double-digit royalties on net sales. Spero remains responsible for funding and the execution of the remaining Phase III trial of tebipenem HBr.

In preclinical (rat) models, Recce previously demonstrated R327's in vivo activity against *E. coli* in kidney and UTI models. This also supports R327's ability to potentially treat infection pre-urosepsis. Additionally, R327 demonstrated dose-dependent activity against *Neisseria gonorrhoeae* in female rat reproductive organs. Gonorrhoeae has developed resistance to all antibiotics classes (or types) except for one; these results further prove R327's broad-spectrum antibiotic capabilities.

We anticipate that IV R327 will be advanced for complicated and recurrent UTIs and, if used successfully, may potentially prevent the development of urosepsis in such cases. Assuming positive clinical development, we anticipate R327 will be positioned as a first-line IV treatment for already hospitalised (inpatient) cUTI patients (ie those at the highest risk), and potentially patients believed to be at high risk of requiring hospitalisation. The company also believes that a single infusion of R327 could be considered for those with highly recurrent UTIs, such as patients who may have over six UTI episodes per year.

Recce recently announced that it is starting a Phase I/II study of IV R327 using a faster infusion rate (15 minutes and 30 minutes) across three cohorts of healthy male and female subjects (total planned enrolment of 12 subjects). Like the completed Phase I IV study described above, this study will take place at the CMAX clinical research facility. Plasma and urine samples will be taken to assess R327's antibacterial effect in the urine on various bacterial strains. Subsequently, the company plans to start a Phase II study of the IV formulation in UTI patients in H2 CY23. The first portion of this Phase II efficacy study in UTI subjects will be a single-dose efficacy study and it will be followed by a multiple ascending dose portion.

We model that the R327 UTI programme will start Phase III pivotal studies in CY25 and conservatively assume it could reach regulatory approval in CY29. An earlier timeline to approval is possible, but we assume the company will dedicate greater attention to the sepsis programme, which we believe faces a less crowded marketplace than the UTI indication. We also assume an average net price per treatment course of US$5,500 in the United States at launch. We conservatively assume that the product at peak (2033) will be used in about 32,000 US patients (representing c 5% of US cUTI cases), leading to US$190m in net US sales, but may revisit our assumptions as the programme advances in the planned clinical stages and should the company demonstrate additional differentiation characteristics during product development.

R327 (spray-on) Phase I/II burn wound infection study

Recce is also developing a topical spray-on formulation of R327, initially targeted for the treatment of burn wound infections. Burns are considered tissue damage resulting from heat, radiation (commonly overexposure to the sun), or chemical or electrical contact. Burns can either be minor medical injuries or they can be life-threatening injuries. Generally, the primary serious burn treatment objectives are controlling pain, removing dead tissue, preventing infection, reducing scarring risk and regaining function.

Infection is the primary driver of morbidity and mortality in burn patients, but the diagnosis and management of burn wound infections can be difficult due to many physiologic features unique to burn injury. A variety of factors can put a patient at risk of developing a burn wound infection, with patients with particularly severe burns at higher risk of infection and/or burn wound sepsis. In contrast to other types of injury such as lacerations or blunt force trauma, burn wounds cause metabolic and inflammatory alterations resulting in a state of immunosuppression, which puts the patient at higher risk of complications such as infection, with about 61% of burn wound deaths caused by infection. Infections resulting from burn wounds can either be topical/local (eg burn wound impetigo, or cellulitis, which is treated systemically but topical drugs may be also used) or systemic (such as bacteremia, UTI, sepsis or pneumonia). About 500,000 people in the United States seek medical treatment for burns annually, with 40,000 admitted to a hospital for specialised

treatment consisting of a combination of treatment strategies. Treatment of burn wounds and resulting infection or sepsis includes wound cleansing, debridement, topical or systemic antimicrobial therapy and, in severe cases, skin grafts from uninjured parts of the body or allografts produced by a variety of companies like MiMedx (Nasdaq: MDXG) or spray-on skin cells expanded from a patient sample produced by the Recell system distributed by Avita Medical (Nasdaq: RCEL). Notably, Professor Fiona Wood, an investigator in Recce's Phase I/II burn wound trial, developed Avita's Recell technology for wound healing. Often when patients present with a burn wound, first-line therapy intended to prevent subsequent infection includes a topical anti-septic product such as chlorhexidine gluconate or silver nitrate, or topical antibiotics such as silver sulfadiazine, bacitracin or mupirocin.

Data are scarce regarding the prevalence of wound infection among hospitalised burn victims. According to the two American Burn Association analyses of over 200,000 cases, the rates of burn wound infections and cellulitis in hospitalised burn patients seeking burn wound care is between c 2.5% and 3.4%. This excludes systemic infection cases (occurring in c 7% of burn wounds), which require systemic medications and where we do not view topical drugs as a significant contributor.

R327 topical data to date

Recce's preclinical topical burn study in rats showed significant antibacterial activity against MRSA (methicillin-resistant *Staphylococcus aureus*): data demonstrated reduced bacterial load and higher percentage of wound closure with increasing doses of R327 compared to Soframycin. A separate human skin model showed the antibiotic was non-irritating, even at high concentrations. Subsequently the product candidate advanced to human trials.

The non-randomised, ongoing Phase I/II R327 spray formulation study is enrolling up to 30 patients with clinical signs and symptoms of local burn wound infection. Over a 14-day treatment period, 10 patients will receive R327 daily, and 20 patients in a separate cohort will receive the antibiotic drug three times per week. This Phase I/II trial is being conducted at Fiona Stanley Hospital and is sponsored by the West Australian health department, with further updates anticipated over CY23. The drug showed its broad-spectrum activity in the clinical setting with visible infection reduction within 24 hours of dosing in all patients, according to the company's Phase I/II interim results announcement on 7 December 2021. Further, all acute infections were cleared within five days and all chronic infections were cleared within seven days. As such, the treatment duration was reduced from 14 days to five days for acute infections and seven days for chronic infections, to better fit the faster-than-anticipated clearance of infections shown in the interim data. The drug's activity was demonstrated across gram-positive (*S. aureus* and *Staphylococcus lugdunensis*) and gram-negative bacteria (*P. aeruginosa, Klebsiella pneumoniae, Morganella morganii, Proteus vulgaris, Proteus mirabilis*), some of which were classified as multi-drug resistant and difficult to treat due to biofilms, using patient swab samples.

Current treatment approaches for local burn infections

Once a local infection is confirmed, treatment options include a variety of topical antimicrobial or antibacterial agents cited above, such as creams (eg bacitracin, mupirocin and silver sulfadiazine) and water-based solutions (eg mafenide acetate and silver nitrate). Silver dressings are generally advantageous with respect to application frequency as silver ions are released into the wound bed over time, but each therapy carries its own risk profile. Silver-based topical wound therapies have been associated with either delayed or incomplete re-epithelialization, as well as grey stained scars, hypersensitivity, neutropenia and ineffectiveness due to limited penetration of the burn eschar/scab or due to inactivity against specific pathogens. Additionally, a range of contact layers and dressings have been studied or are under development, including those using extended-release antibiotics, silver gels, antimicrobial carbon fibre and/or honey.

R327's profile could be desirable in the inpatient or outpatient burn wound infection setting due to the external application, currently demonstrated safety profile and shown resilience to date against the formation of drug-resistant strains. Given the availability of alternate therapies for burn wounds and the reduced morbidity risk as a whole versus sepsis or cUTI, our model assumes a lower price point (net US$1,500 per treatment course) at US launch than for the IV R327 indications above.

Topical R327 for diabetic foot infections

In October 2022, Recce announced that it is expanding topical R327 development to include mild diabetic foot infections (DFIs), and in December 2022, it received Australian approval to start a Phase I/II study at Sydney South West's Limb Preservation and Wound Research Unit. The study will assess R327 in this indication in up to 32 patients, with the first enrolment planned for H1 CY23.

Diabetic foot ulcers are frequent complications of patients who have diabetes mellitus, if the condition is not adequately controlled. Approximately 37 million people have diabetes in the United States, and among them about 2–4% will obtain foot ulceration each year, of which 50–60% will result in DFIs, the leading cause of foot morbidity in diabetic patients. About 20% of moderate to severe DFIs lead to amputation. Recce believes that topical R327 can potentially be useful in mild DFIs (as more advanced cases require systemic antibiotics). While current literature suggests that topical application of antimicrobials may have merit in many cases (such as patients who do not tolerate oral antibiotics), there is limited high-quality evidence on the appropriate indications, dosages and pharmacokinetics, and consequently, current treatment guidelines do not encourage the use of any currently approved topical antibiotic for treating mild DFIs. Hence, there is a considerable opportunity should topical R327 in a controlled setting demonstrate clinical benefit (such as the prevention of DFI progression or recurrence), although we remain cognisant of the historical challenges of topical drugs in this indication and hence assign a modest probability of success for topical R327 in DFI until proof of concept is shown in clinical trials.

If the current Australian Phase II study is successful, we assume that the company will pursue a second Phase II study in CY24 that would include multiple sites (including the United States or Europe) before starting a Phase III pivotal programme in CY25, which we model can lead to launch in CY29. We estimate that the annual incidence of mild DFIs that can be potentially treated with a topical product would be approximately 150,000 a year and at peak, topical R327 could potentially be used in about 25% of such cases. As with burn wound infections, we believe the morbidity risk in this indication (mild DFI) is lower than the cUTI or sepsis indications sought by IV R327 and we assume an average net per-course pricing of approximately US$1,500 at launch (versus our higher assumed pricing for the IV indications described above), resulting in estimated peak global (US and Europe) sales of US$102m in 2033.

Preclinical programmes

Recce has a number of preclinical programmes that could be value drivers in the future, but are not included in our valuation analysis at this early stage (as per Edison policy).

Additional bacterial conditions under preclinical evaluation

Recce is conducting preclinical work on three bacterial indications with unmet need. *Helicobacter pylori* is a gram-negative bacterium that typically is found in the stomach, and *H. pylori* infection is the leading risk factor/cause for peptic ulcers and stomach cancer. Prevalence rates of this bacteria vary greatly with estimations for various populations ranging from under 15% to over 85%, with a total of about two-thirds of the world population infected with the bacteria. The company is assessing the feasibility of its antimicrobial compounds for *H. pylori* infections and ulcers.

Mycobacterium abscessus is another strain under preclinical-stage investigation, as it can cause skin and soft-tissue infections (SSTIs) and is a significant cause of severe lung infections in individuals with chronic lung diseases such as cystic fibrosis. *M. abscessus* is viewed as one of the most drug-resistant non-tuberculosis mycobacteria and current treatment guidelines recommend 18 months of multidrug therapy.

The company is also assessing R327 and its compounds for bacterial sinusitis and rhinosinusitis, and has shown improvements in *Streptococcus pneumoniae* colonisation in preclinical models associated with this strain. Sinusitis is very common, with c 30 million people diagnosed with the condition each year in the United States, and while there is a wide range of estimates of which proportion is related to bacterial origin, a recent meta-analysis estimated that c 50% of sinusitis cases are due to bacteria. While the large majority of cases can be well-managed with supportive therapy and/or existing antibiotics, we believe there can be unmet need in patients with immune deficiencies and anticipate that this could be an area that Recce is assessing.

COVID-19

In July 2020, R327 was selected for the Priority 1 Candidate Group for antiviral testing in the SARS-CoV-2 Antiviral Program run by an Australian government agency responsible for scientific research, and The Peter Doherty Institute for Infection and Immunology, which helped initiate the company's COVID-19 studies. The studies showed minimal toxicity and antiviral effectiveness in vero cells, and further, recently reported studies in Syrian golden hamsters confirmed the antiviral effect.

COVID-19 may be an attractive indication for R327, but recent developments of efficacious EUA-authorised oral antivirals, such as Pfizer's Paxlovid (nirmatrelvir, a 3CL protease inhibitor plus ritonavir for PK enhancement), other 3CL protease inhibitors, Merck's molnupiravir (EUA approved, targets RdRp for lethal mutagenesis), Gilead's IV remdesivir (inpatient and outpatient, RdRp) as well as inhaled remdesivir and others make the field a crowded and relatively well-addressed space despite the market being so new and drugs not being widely available yet. Outpatient antiviral solutions could reduce hospitalisation rates significantly even in the face of COVID-19 becoming endemic.

Still, patients will present at the hospital with severe disease, as is the case with influenza despite available vaccines and antivirals. R327 may potentially offer a better path forward to eliminate unnecessary antibiotic use in hospitalised COVID-19 patients by simultaneously acting as an antiviral and antibiotic; this is the aspect that may potentially set R327 apart from other antivirals: the clinical management of severely ill patients. It is well known that remdesivir is contraindicated in patients with compromised kidney function and that additional drugs can put stress on patients with or at risk of organ dysfunction. Regardless, these patients are routinely administered antibiotics despite being hospitalised from a viral infection (SARS-CoV-2), to prevent bacterial superinfection that would likely be lethal to the patient. The *Lancet Microbe* published an antibiotic overuse study in COVID-19 patients, where in over 48,000 patients, 85% were given antibiotics; however, subsequent testing revealed that only 13% had bacterial infections. Inappropriate antibiotic use in this case may also have a negative impact on the patient. Aside from that, the COVID-19 antiviral field is crowded and solutions like Paxlovid may be difficult to compete against.

Influenza A

R327 was also tested to treat Influenza A in mice (in vivo) and showed dose-dependent reduction in viral load compared to control, with a 1,000mg/kg daily dose (for five days) reducing the viral load below the limit of quantitation on days four and six of treatment.

Antibiotic competition

Recce refers to R327 and its pipeline candidates as anti-infectives (as it believes there is also antiviral drug activity) although their current lead programmes (sepsis, burn wound infections) are primarily geared towards demonstrating their antibacterial properties. There are a broad range of antibiotics in development for various indications to add to the already available arsenal of antibiotics, of which combinations are used for sepsis commonly. None of the recently FDA-approved antibiotics (2017–20) have conclusive broad-spectrum activity against all priority pathogens. In development, new anti-infective therapies include antibiotics, antibody therapies, bacteriophage or phage enzyme therapies, microbiome therapies, vaccines and traditional small molecule agents, and as such the field is crowded, but we are unaware of any therapy that has demonstrated an inability to promote any bacterial resistance (to date) while acting as a bactericidal against a broad range of pathogens. That being said, it is important to realise that there is a wide range of available antibiotics for the treatment of infections from burn wounds to sepsis, and there are more (292 according to the World Health Organization 2020 report) in the global pipeline.

Exhibit 12: Antibiotics in Phase III development or FDA approved, 2017–20

Antibiotic	Stage	Company	Category
Benapenem	Phase III	Sihuan Pharmaceutical	Carbapenem
Cefepime + taniborbactam	Phase III	Venatorx Pharmaceuticals Inc/Global Antibiotic Research and Development Partnership (GARDP) (Everest Medicines II licensee)	β-lactam (cephalosporin) + β-lactamase inhibitor (cyclic boronate)
Cefilavancin	Phase III*	R-Pharm	Glycopeptide-β-lactam (cephalosporin) hybrid
EMROK/EMROK O	Phase III	Wockhardt	Fluoroquinolone
Exblifep (cefepime + enmetazobactam)	Phase III	Allecra Therapeutics	β-lactam (cephalosporin) + β-lactamase inhibitor (penicillanic acid sulfone)
Gepotidacin (GSK2140944)	Phase III	GlaxoSmithKline	Triazaacenaphthylene
Ridinilazole	Phase III	Summit Therapeutics	Bis-benzimidazole
Sulbactam + durlobactam	Phase III	Entasis Therapeutics	β-lactam (sulbactam)+ β-lactamase inhibitor (diazabicyclooctane)
T-4288 (solithromycin)	Phase III	Toyama Chemical Co	Macrolide
Tebipenem/tebipenem pivoxil hydrobromide	Phase III	Spero Therapeutics	β-lactam (carbapenem)
WCK 5222 (cefepime + zidebactam)	Phase III*	Wockhardt	β-lactam (cephalosporin) + β-lactamase inhibitor (diazabicyclooctane)
Zevtera (ceftobiprole)	Phase III	Basilea Pharmaceutica International	β-lactam (cephalosporin)
Zoliflodacin (ETX0914)	Phase III	Entasis Therapeutics Inc./Global Antibiotic Research and Development Partnership (GARDP)	Spiropyrimidinetrione
Delafloxacin (Baxdela)	Approved (2017)	Melinta Therapeutics	Fluoroquinolone
Vabomere	Approved (2017)	Melinta Therapeutics	Carbapenem, β-lactamase inhibitor
Ozenoxacin	Approved (2017)	Medimetriks Pharmaceuticals	Quinolone
Plazomicin (Zemdri)	Approved (2018)	Achaogen, Inc.	Aminoglycoside
Eravacycline (Xerava)	Approved (2018)	Tetraphase Pharmaceuticals (La Jolla)	Flourocycline
Sarecycline (Seysara)	Approved (2018)	Paratek Pharmaceuticals	Tetracycline
Omadacycline (Nuzyra)	Approved (2018)	Paratek Pharmaceuticals	Tetracycline
Rifamycin (Aemcolo)	Approved (2018)	Cosmo Pharmaceuticals	Ansamycin
Imipenem, cilastatin, relebactam (Recarbrio)	Approved (2019)	Merck & Co.	Combination
Pretomanid/nitroimidazole + bedaquiline and linezolid	Approved (2019)	TB Alliance	Combination
Lefamulin (Xenleta)	Approved (2019)	Nabriva Therapeutics	Pleuromutilin
Cefiderocol (Fetroja)	Approved (2019)	Shionogi & Co	β-lactam (cephalosporin)

Source: PEW Research Center, Edison Investment Research

In-house manufacturing capabilities

Recce has built a wholly owned manufacturing facility in Australia, designed to pharmaceutical specification for complete control of its processes. The facility's process is reproducible and has a chemistry, manufacturing and controls (CMC) data package and currently has demonstrated scale

up for enough supply for its Phase I and II studies. In order to produce commercial volumes, the company may need to expand its production capacity or rely on third-party contract manufacturing partners. As stated previously, Recce cites the synthetic nature of its anti-infective compounds as a competitive advantage, given that that it has robust control of all steps in manufacturing leading to potentially robust quality control and, when scaled, effective control on COGS.

Intellectual property and market exclusivity

Recce's patent portfolio contains over 40 patents and patent applications in key nations and geographical healthcare markets, including the United States, Europe, Japan, China and Australia.

Exhibit 13: Recce patent family summary

Filed	Patent Family 1	Expiry	Patent Family 2	Expiry	Patent Family 3	Expiry
Australia	✓	2028	✓	2037	Accepted	2037
USA	✓	2029	✓	2037	✓	2037
Europe	✓	2028	✓	2037	✓	2037
Germany	✓	2028	✓	2037	✓	2037
Spain	✓	2028	✓	2037	✓	2037
France	✓	2029	✓	2037	✓	2037
UK	✓	2028	✓	2037	✓	2037
Italy	✓	2028	✓	2037	✓	2037
Sweden	✓	2028	✓	2037	✓	2037
Japan	✓	2028	✓	2037	✓	2037
China	✓	2028	Pending	2037	✓	2037
HK	Pending	2028	Pending	2037	✓	2037

Source: Recce Pharmaceuticals reports

Recce's 'Patent Family 1' covers antimicrobial polymers and their compositions, including the manufacturing process and use of the polymer in treatment of diseases. 'Patent Family 2' covers the copolymer for use in the method of treatment of a parenteral infection, including the method of manufacture, administration and application to treat a broad range of common human infections. 'Patent Family 3' is the same type of patient family (method of use) as 'Patent Family 2' but it covers the use of the company's copolymers as antiviral agents and the method for treatment of viral infections, including a broad range of viral infections, particularly parenteral viral infections.

R327 has also been granted Qualified Infectious Disease Product designation by the US FDA, which comes with an additional five-year exclusivity that adds onto exclusivity granted for a new chemical entity (NCE). Thus, R327 qualifies for 10-year exclusivity post approval. Thus, regardless of patent life, the product will at least have an initial 10-year market exclusivity.

Sensitivities

Recce is subject to near-term and long-term clinical development risks, regulatory risks, commercial risks with physician adoption, as well as competitive risks and funding risks, typical of biotechnology companies in this stage of development. While our model accounts for future financings as illustrative debt, funding could be highly dilutive if done through equity. The amount of dilution would depend on market conditions at the time of the raise, but raising capital when the share price is well below our valuation (or when market conditions are not optimal) could lead to significant dilution. We forecast the company will need to raise an additional A$220m before becoming cash flow positive in 2029, starting with A$20m in H223. In particular, we estimate that the amount of funding required exceeds the company's current market capitalisation and note that if our projected funding needs are entirely met through equity issuances at the prevailing market price (A$0.59/share), our current per-share valuation would be revised to A$1.30. Any challenges to obtaining funding could also lead to development delays.

Specifically with respect to sepsis, even if R327 is successful, the potential of improved screening diagnostics to allow physicians to potentially more quickly identify specific pathogens in the context of sepsis could allow physicians to administer other antibiotics (known to target the identified pathogen) instead of R327 for sepsis patients. Additionally, sepsis remains a complex condition with a very challenging road to drug approval. No drug has obtained approval specifically for sepsis aside from an Eli Lilly drug now withdrawn from the market following a lack of efficacy in a post-marketing study and angiotensin II, a vasoconstrictor to treat low blood pressure in septic shock.

Our Recce valuation is highly dependent on our pricing assumptions for IV R327 in sepsis and cUTI indications. Given the severity and potential morbidity of the above conditions (particularly sepsis) and the current pricing for high-value IV antibiotics (eg an eight-day course of Vabomere costs c US$8,000), we believe our US$5,500 at launch US market pricing assumption per average treatment course for IV R327 is reasonable, but as a sensitivity, we note that using a lower US$3,500 pricing level would reduce our valuation to A$280m (or A$1.57/share).

With regards to R327 and burn wound infections and DFIs, the number of inexpensive topical antibiotics and antimicrobials available could make this a crowded market and may limit the pricing power and market share of topical R327 in this indication. As it relates to DFIs, concerns have been raised in the literature as to the effectiveness of using topically administered drugs for the indication and topical R327 will need to demonstrate effective penetration and targeting to overcome such concerns.

Valuation

We value Recce at A$497m, or A$2.79/share, based on an rNPV methodology applying a 12.5% discount rate. Our model forecasts a Recce-led US and European Union sales launch in CY28 for IV R327 (in sepsis) and topical R327 (in burn wounds), followed by introductions in CY29 for IV R327 in complicated and recurrent UTIs and for topical R327 in DFIs. We await further pipeline advancement prior to including additional territories such as Australia in our forecasts. With our estimated US and EU sales totalling A$3.66bn in FY32, sepsis is the lead driver of our valuation, reflecting c 87% of the pipeline value excluding corporate costs and cash. We model peak gross margins of 92.5% in sepsis and EBIT margins of 71%. As stated above, the potential addressable market for sepsis is substantial, with over 1.7 million US cases annually, and our forecasts assume 12.5% peak market share, as we anticipate many sepsis cases will continue to be treated with alternative approaches, even if R327 is clinically successful, given entrenched treatment patterns and the complex and multifaceted pathophysiology of the condition. The complex nature of the

condition, and lack of success for nearly all attempted treatment candidates, underlie our modest probability of success (PoS) estimate of 15% in sepsis.

We assume R327 IV formulation average net pricing per treatment course at launch of US$5,500 per patient in the United States and US$3,300 in the EU. Factors supportive of elevated pricing include the current pricing of daptomycin and linezolid and the immense healthcare costs associated with sepsis.

We also model significant opportunities for complicated and recurrent UTIs, with FY32 sales estimated at c US$256m (peak FY35 revenue of c US$360m), and the demonstration of proof-of-concept in currently planned clinical studies would likely raise our PoS estimate (currently 15%) and overall programme valuation.

For burn wounds, we take into account the ability of inexpensive antimicrobials to perform well as prophylactics as well as the mortality and morbidity risks associated with wound infections that may result in complications, while benchmarking to other antibiotics in the acute bacterial skin and skin structure infections categories (omadacycline, delafloxacin) as well as the price of other burn wound care spray-on products (Recell). We assume a launch price of US$1,500 in the United States and US$900 in the EU as a price per treatment course for R327 in spray formulation.

We forecast the total costs of running the planned multiple-dose IV R327 study, a subsequent Phase II efficacy urosepsis trial and two multinational Phase III sepsis trials will total between A$55m and A$60m before the end of FY27. Notably, through Australia's R&D tax incentives, the company's R&D expenses could be eligible for up to a 43.5% rebate from the Australian government, which we model in our forecasts.

Our valuation does not include commercialisation of Recce's products in other jurisdictions excluding the United States and Europe, and as such, efforts or partnership developments in other regions could add upside to our models. We do not ascribe value to Recce's preclinical programmes at this time.

Exhibit 14: Recce Pharmaceuticals rNPV valuation

Product	Indication	Launch	Sales (A$m) in 2032	NPV (A$m)	Probability of success	rNPV (A$m)	rNPV/basic share (A$)
R327 (IV)	Sepsis	2028	3,657	3,542	15%	510	2.86
R327 (IV)	Complicated UTI	2029	381	324	15%	39	0.22
R327 (topical)	Burn wounds	2028	271	193	20%	28	0.16
R327 (topical)	Diabetic foot infections	2029	126	91	15%	7	0.04
Corporate costs				(88.3)		(88.3)	(0.50)
Estimated net cash at 31 December 2022				1.8		1.8	0.01
Total equity value						497.4	2.79

Source: Edison Investment Research

We also highlight that our rNPV valuation does not factor in the potential strategic value of a strong anti-infective platform and/or what a potential treatment for sepsis may offer to other biopharma industry participants. We highlight for illustrative purposes that in 2014, Merck acquired Cubist Pharma for US$9.5bn in enterprise value, with Cubist at the time having been commercialising daptomycin for *S. aureus* bacteremia and complicated skin and skin structure infections and having a deep anti-infective pipeline including ceftolozane/tazobactam for cUTI (subsequently FDA approved). Hence, while we do not ascribe any specific value for this, a take-out or M&A offer for Recce or parts of its technology could potentially be higher than our rNPV valuation.

Financials

The company reported A$1.85m of gross cash at 31 December 2022. In January 2023, the company received A$6.2m in cash proceeds, with A$4.3m resulting from an Australian government R&D tax credit rebate, and an additional A$1.9m consisting of an advance payment from Radium

Capital. The advance payment corresponds to a portion of the upcoming R&D tax credit the company expects to receive for the FY23 year's activities. Altogether, we model that Recce will raise A$20m in H223 to fund its pipeline.

Expenditures have increased as the company has progressed clinical development, with its operating cash burn rate increasing from A$9.0m in FY22 to A$10.2m in H123. We expect Recce's cash needs will expand as it funds clinical trials for its four targeted clinical-stage R327 indications. While we expect the company to benefit from Australia's 43.5% R&D refundable tax credit, we forecast operating cash burn to rise to A$18m in FY23 and A$42m in FY24 (and A$65m in FY25). The driver for these costs will be the large-scale Phase II or Phase III studies required for each of the four sought indications.

Depending on the availability of capital, the company may decide to prioritise certain programmes over others, which may affect the timing of launches in non-prioritised indications and affect our overall valuation. Our current funding model assumes the company will advance all four programmes in parallel. However, if the company in the future prioritises sepsis (and/or urosepsis) and cUTIs and puts its remaining development programmes on hold until the initial R327 commercial approval, this would reduce its overall funding need as it could subsequently apply post-launch commercial revenue towards resuming R&D and product development activities in the remaining sought indications. In addition, partnerships and/or non-dilutive forms of funding (such as third-party sponsorship of clinical trials) could also reduce the future funding need, although these are not specifically included in our forecasts.

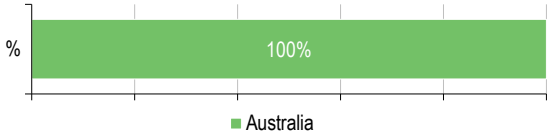
Altogether, we view sepsis as the primary driver of the company's valuation and expect the company will prioritise the sepsis (and/or urosepsis) and cUTI indications. Assuming the company will continue to develop all four planned clinical-stage indications, we expect Recce will need to raise a further A$200m by FY28 before becoming sustainably cash flow positive. As per usual Edison methodology, we model these raises as illustrative debt. We note that the company has an at-the-market (ATM) equity financing facility with Acuity Capital, expiring in January 2026, that provides it with up to A$20m of standby equity capital. Recce is not required to use the ATM and it may terminate the ATM at any time without cost or penalty.

Revenues for Recce are comprised mostly of R&D tax incentive rebates from the Australian government. The company recently reported that it received A$6.2m in R&D cash receipts (which we expect to be recognised in H223).

Exhibit 15: Financial summary

A$000s	2020	2021	2022	2023e	2024e
Year end 30 June	IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS					
Revenue	1,122	1,857	3,085	6,219	5,932
Cost of Sales	0	0	0	(0)	(0)
Gross Profit	1,122	1,857	3,085	6,219	5,932
Sales, General & Administrative	(3,136)	(9,511)	(7,677)	(9,650)	(9,450)
Net Research & Development	(2,071)	(5,657)	(6,285)	(13,636)	(37,879)
EBITDA	(4,085)	(13,311)	(10,878)	(17,067)	(41,397)
Depreciation & amortisation of intangible assets	0	0	0	0	0
Depreciation, amortisation & other	(201)	(296)	(188)	(197)	(255)
Normalised Operating Profit (ex. amort, SBC, except.)	(4,231)	(8,389)	(10,809)	(17,264)	(41,652)
Operating profit before exceptionals	(4,286)	(13,607)	(11,065)	(17,264)	(41,652)
Exceptionals including asset impairment	0	0	0	0	0
Other	0	0	0	0	0
Reported Operating Profit	(4,286)	(13,607)	(11,065)	(17,264)	(41,652)
Net Finance income (costs)	(31)	94	79	(243)	(338)
Profit Before Tax (norm)	(4,317)	(13,513)	(10,986)	(17,508)	(41,990)
Profit Before Tax (FRS 3)	(4,317)	(13,513)	(10,986)	(17,508)	(41,990)
Tax	0	0	0	0	0
Profit After Tax and minority interests (norm)	(4,317)	(13,513)	(10,986)	(17,508)	(41,990)
Profit After Tax and minority interests (FRS 3)	(4,317)	(13,513)	(10,986)	(17,508)	(41,990)
Average Basic Number of Shares Outstanding (m)	127.2	155.4	174.1	177.6	178.8
EPS - normalised (A$)	(0.03)	(0.09)	(0.06)	(0.10)	(0.23)
EPS - normalised and fully diluted (A$)	(0.03)	(0.09)	(0.06)	(0.10)	(0.23)
EPS - (IFRS) (A$)	(0.03)	(0.09)	(0.06)	(0.10)	(0.23)
Dividend per share (A$)	0.0	0.0	0.0	0.0	0.0
BALANCE SHEET					
Fixed Assets	505	501	439	417	210
Intangible Assets	0	0	0	(101)	(357)
Tangible Assets	505	501	439	518	567
Investments in long-term financial assets	0	0	0	0	0
Current Assets	2,739	21,181	12,185	14,282	7,498
Short-term investments	0	0	0	0	0
Cash	2,682	20,873	11,582	13,970	7,187
Other	57	308	603	311	311
Current Liabilities	(885)	(1,078)	(2,447)	(1,168)	(1,168)
Creditors	(885)	(1,078)	(2,447)	(1,168)	(1,168)
Short term borrowings	0	0	0	0	0
Long Term Liabilities	(46)	(100)	(115)	(20,233)	(55,233)
Long term borrowings	0	0	0	(20,000)	(55,000)
Other long term liabilities	(46)	(100)	(115)	(233)	(233)
Net Assets	2,313	20,504	10,061	(6,703)	(48,693)
CASH FLOW STATEMENT					
Operating Income	(4,286)	(13,607)	(11,065)	(17,264)	(41,652)
Movements in working capital	253	144	1,532	126	0
Net interest and financing income (expense)	(31)	94	79	(243)	(338)
Depreciation & other	201	296	188	197	255
Taxes and other adjustments	55	5,218	256	(850)	(0)
Net Cash Flows from Operations	(3,807)	(7,856)	(9,010)	(18,035)	(41,735)
Capex and capitalised expenditures	(6)	(76)	(40)	(44)	(49)
Acquisitions/disposals	0	0	0	395	0
Interest received & other investing activities	0	0	0	0	0
Net Cash flows from Investing activities	(6)	(76)	(40)	350	(49)
Net proceeds from share issuances	6,980	26,338	287	73	0
Net movements in long-term debt	0	0	0	20,000	35,000
Dividends	0	0	0	0	0
Other financing activities	(888)	(215)	(528)	0	0
Net Cash flows from financing activities	6,092	26,123	(240)	20,073	35,000
Effects of FX on Cash & equivalents	0	0	0	0	0
Net Increase (Decrease) in Cash & equivalents	2,279	18,191	(9,291)	2,388	(6,784)
Cash & equivalents at beginning of period	403	2,682	20,873	11,582	13,970
Cash & equivalents at end of period	2,682	20,873	11,582	13,970	7,187
Closing net debt/(cash)	(2,682)	(20,873)	(11,582)	6,030	47,813
Lease debt	83	127	75	127	127
Closing net debt/(cash) inclusive of IFRS 16 lease debt	(2,599)	(20,746)	(11,507)	6,157	47,941
Free cash flow	(3,813)	(7,932)	(9,051)	(17,684)	(41,784)

Source: Edison Investment Research, company accounts

Contact details	Revenue by geography
Level 32, 200 George St, EY Centre Sydney NSW 2000 Australia +61 (2) 9256 2571 Suite 10, 3 Brodie Hall Drive, Technology Park Bentley WA 6102 Australia +61 (8) 9362 9860 www.recce.com.au/	

Management team

Chairman: Dr John Prendergast, BSc (Hons), MSc (UNSW), PhD (UNSW), CSS (HU)	**CEO and managing director: James Graham, BCom (Entrepreneurship), GAICD**
Dr Prendergast is based in the United States. He is the current chairman and co-founder of Palatin Technologies (NYSE: PTN) and lead director of Heat Biologics (NASDAQ: HTBX) and has extensive experience in the international commercialisation of pharmaceutical technologies.	James was an executive director of Recce for five years and has extensive experience in marketing, business development and commercialisation of early-stage technologies with global potential.
CSO and executive director: Michele Dilizia, BSc (Med Sci), Grad Dip Bus (Mkting), BA (Journ), GAICD, MASM	**Executive director and principal quality chemist: Justin Ward, BSc (Chem), PhD (Chem), MRACI, CChem**
Michele is a co-inventor and qualified medical scientist, specialising in medical microbiology and regulatory affairs.	Dr Ward has extensive experience in quality control and has worked with several well-recognised pharmaceutical companies. He is working to advance Recce's research and development and manufacturing up to US FDA requirements.
Vice-president of translational sciences: Philip Sutton, BSc (Hons), PhD	**Non-executive director: Alan Dunton, BSc (BioChem) Hons, MD (NYU)**
Dr Sutton has over 30 years of research and industry experience in infectious diseases, having served as former head of immunology at CSL in Melbourne. He is he chief editor of the textbook *Helicobacter pylori in the 21st Century* and has co-authored 92 manuscripts published in peer-reviewed journals. .	Dr Dunton is based in the United States and is a director of Palatin Technologies. He has over three decades of senior pharmaceutical experience including as president and MD of Janssen Research Foundation (Johnson & Johnson). Dr Dunton has advanced a number of blockbuster antibiotics through regulatory review and commercialisation at Fortune 500 companies including J&J and Roche.

Principal shareholders	(%)
Graham Melrose and Olga Melrose	22.08
HSBC Custody Nominees (Australia)	3.61
James Graham	3.47
LDU Pty Ltd	2.65
Acuity Capital Investment Management Pty Ltd	2.59
M Rogers and A Veliss	2.30
Michele Keryn Dilizia	2.04

General disclaimer and copyright

This report has been commissioned by Recce Pharmaceuticals and prepared and issued by Edison, in consideration of a fee payable by Recce Pharmaceuticals. Edison Investment Research standard fees are £60,000 pa for the production and broad dissemination of a detailed note (Outlook) following by regular (typically quarterly) update notes. Fees are paid upfront in cash without recourse. Edison may seek additional fees for the provision of roadshows and related IR services for the client but does not get remunerated for any investment banking services. We never take payment in stock, options or warrants for any of our services.

Accuracy of content: All information used in the publication of this report has been compiled from publicly available sources that are believed to be reliable, however we do not guarantee the accuracy or completeness of this report and have not sought for this information to be independently verified. Opinions contained in this report represent those of the research department of Edison at the time of publication. Forward-looking information or statements in this report contain information that is based on assumptions, forecasts of future results, estimates of amounts not yet determinable, and therefore involve known and unknown risks, uncertainties and other factors which may cause the actual results, performance or achievements of their subject matter to be materially different from current expectations.

Exclusion of Liability: To the fullest extent allowed by law, Edison shall not be liable for any direct, indirect or consequential losses, loss of profits, damages, costs or expenses incurred or suffered by you arising out or in connection with the access to, use of or reliance on any information contained on this note.

No personalised advice: The information that we provide should not be construed in any manner whatsoever as, personalised advice. Also, the information provided by us should not be construed by any subscriber or prospective subscriber as Edison's solicitation to effect, or attempt to effect, any transaction in a security. The securities described in the report may not be eligible for sale in all jurisdictions or to certain categories of investors.

Investment in securities mentioned: Edison has a restrictive policy relating to personal dealing and conflicts of interest. Edison Group does not conduct any investment business and, accordingly, does not itself hold any positions in the securities mentioned in this report. However, the respective directors, officers, employees and contractors of Edison may have a position in any or related securities mentioned in this report, subject to Edison's policies on personal dealing and conflicts of interest.

Australia

Edison Investment Research Pty Ltd (Edison AU) is the Australian subsidiary of Edison. Edison AU is a Corporate Authorised Representative (1252501) of Crown Wealth Group Pty Ltd who holds an Australian Financial Services Licence (Number: 494274). This research is issued in Australia by Edison AU and any access to it, is intended only for "wholesale clients" within the meaning of the Corporations Act 2001 of Australia. Any advice given by Edison AU is general advice only and does not take into account your personal circumstances, needs or objectives. You should, before acting on this advice, consider the appropriateness of the advice, having regard to your objectives, financial situation and needs. If our advice relates to the acquisition, or possible acquisition, of a particular financial product you should read any relevant Product Disclosure Statement or like instrument.

New Zealand

The research in this document is intended for New Zealand resident professional financial advisers or brokers (for use in their roles as financial advisers or brokers) and habitual investors who are "wholesale clients" for the purpose of the Financial Advisers Act 2008 (FAA) (as described in sections 5(c) (1)(a), (b) and (c) of the FAA). This is not a solicitation or inducement to buy, sell, subscribe, or underwrite any securities mentioned or in the topic of this document. For the purpose of the FAA, the content of this report is of a general nature, is intended as a source of general information only and is not intended to constitute a recommendation or opinion in relation to acquiring or disposing (including refraining from acquiring or disposing) of securities. The distribution of this document is not a "personalised service" and, to the extent that it contains any financial advice, is intended only as a "class service" provided by Edison within the meaning of the FAA (i.e. without taking into account the particular financial situation or goals of any person). As such, it should not be relied upon in making an investment decision.

United Kingdom

This document is prepared and provided by Edison for information purposes only and should not be construed as an offer or solicitation for investment in any securities mentioned or in the topic of this document. A marketing communication under FCA Rules, this document has not been prepared in accordance with the legal requirements designed to promote the independence of investment research and is not subject to any prohibition on dealing ahead of the dissemination of investment research.

This Communication is being distributed in the United Kingdom and is directed only at (i) persons having professional experience in matters relating to investments, i.e. investment professionals within the meaning of Article 19(5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005, as amended (the "FPO") (ii) high net-worth companies, unincorporated associations or other bodies within the meaning of Article 49 of the FPO and (iii) persons to whom it is otherwise lawful to distribute it. The investment or investment activity to which this document relates is available only to such persons. It is not intended that this document be distributed or passed on, directly or indirectly, to any other class of persons and in any event and under no circumstances should persons of any other description rely on or act upon the contents of this document.

This Communication is being supplied to you solely for your information and may not be reproduced by, further distributed to or published in whole or in part by, any other person.

United States

Edison relies upon the "publishers' exclusion" from the definition of investment adviser under Section 202(a)(11) of the Investment Advisers Act of 1940 and corresponding state securities laws. This report is a bona fide publication of general and regular circulation offering impersonal investment-related advice, not tailored to a specific investment portfolio or the needs of current and/or prospective subscribers. As such, Edison does not offer or provide personal advice and the research provided is for informational purposes only. No mention of a particular security in this report constitutes a recommendation to buy, sell or hold that or any security, or that any particular security, portfolio of securities, transaction or investment strategy is suitable for any specific person.

London | New York | Frankfurt
20 Red Lion Street
London, WC1R 4PS
United Kingdom